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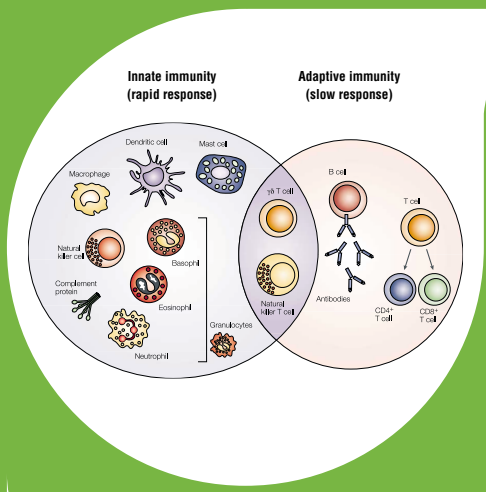
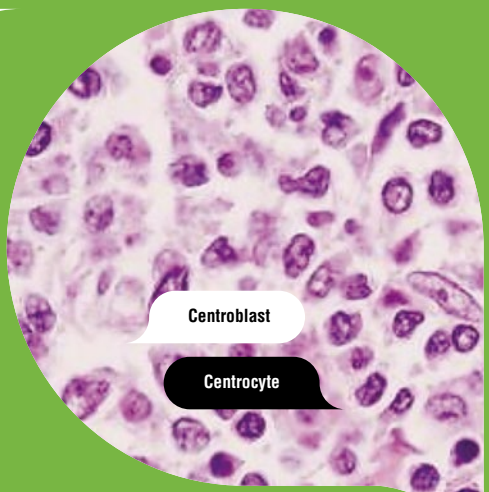
Silvia Montoto
Martin Dreyling
Veronika Ballova

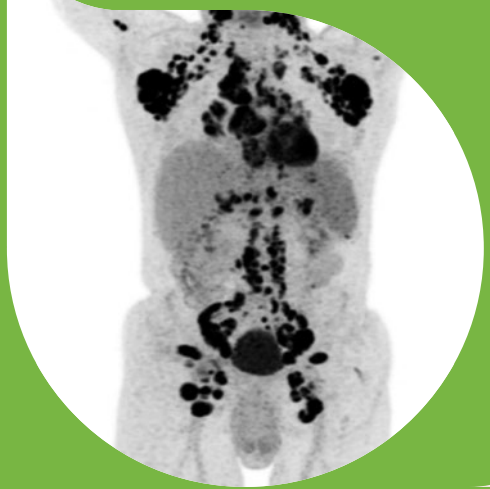
LYMPHOMAS

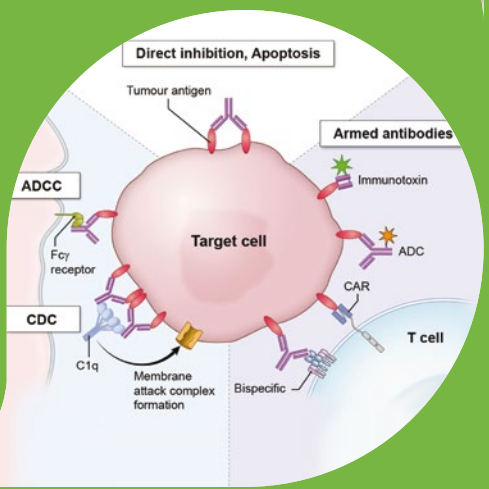
THIRD EDITION

ESSENTIALS *for* CLINICIANS









ESMO Press

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Lymphomas
Essentials for Clinicians

Third edition

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ESMO Press

Third edition published in 2024 by ESMO Press.

First published in 2012 by ESMO Press. Second edition published in 2015 by ESMO Press.

A CIP record for this book is available from the British Library.

ISBN: 978-88-944465-7-9

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6900 Lugano

Switzerland

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Email: publication_support@esmo.org

www.esmo.org

Printed through s|s|media limited, Rickmansworth, Hertfordshire, UK

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Preface

Malignant lymphomas are an especially complex group of neoplasms encompassing at least three dozen different entities with a wide variety of pathological patterns. During recent years, novel therapeutic approaches targeting distinct signalling pathways or activating the patient's immune system have proven to be superior to classical cytostatic approaches and have become the standard of care in several lymphoma subtypes, at least in relapsed disease. Thus, particularly in this fast-developing field of lymphomas, it is essential to have an up-to-date overview of the current treatment options and what future developments are on the horizon.

The format of this third edition remains true to the visual approach of all books in the *Essentials for Clinicians* series, where each figure is complemented by a succinct statement. The book is also very interactive: at the end of each page the reader can check, thanks to a few questions, whether he/she has understood the most important points. Each chapter concludes with a brief, but complete, summary as well as selective further critical readings.

Thanks to our expert authors, we are now very fortunate to provide you with an excellent overview of what we consider 'the essentials' for clinicians who are taking care of patients with lymphomas.

Professor Martin Dreyling, on behalf of all editors

Editors

Silvia Montoto, MD, PhD

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Silvia Montoto is a haemato-oncologist who trained at the Hospital Clínic de Barcelona in Spain. Since 2004, she has been working in the Department of Haemato-oncology at St Bartholomew's Hospital in London, UK as a consultant haemato-oncologist with a specific interest in lymphoma.

Dr Montoto's special fields of interest are follicular lymphoma (which was the subject of her MD(Res): 'Study of BCL2 rearrangement and other prognostic factors in follicular lymphoma'), the management of lymphoma in patients with human immunodeficiency virus (HIV) infection and the role of stem-cell transplantation and other cell therapies in patients with lymphoma. She is the author of around 200 papers published in peer-reviewed journals and is a regular reviewer for numerous peer-reviewed journals, international meetings and international funding bodies. She has also participated as a speaker in multiple educational programmes at international meetings (the European Society for Medical Oncology [ESMO], the European Hematology Association [EHA], the European Group for Blood and Marrow Transplantation [EBMT] and the American Society of Hematology [ASH]).

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Martin Dreyling is Professor of Medicine and head of the lymphoma programme in the Department of Medicine III, LMU Hospital, Munich, Germany. He studied at the Universities of Düsseldorf, Giessen, Tübingen and Würzburg, and completed his clinical training at the Universities of Bonn, Münster, Göttingen and Munich, Germany. He was also a visiting scientist at the University of Chicago, USA.

Prof. Dreyling's scientific focus is on the molecular basis of malignant transformation, cell-cycle dysregulation and secondary genetic alterations as well as biological prognostic factors in malignant lymphoma. He is also interested in innovative therapeutic approaches, including molecular targeted approaches such as inhibitors of the B-cell receptor pathway and immunological approaches.

Prof. Dreyling is a coordinator of the European MCL Network and president of the German Lymphoma Alliance as well as a member of the EHA executive board. He has co-authored numerous scientific papers, book chapters and abstracts in international peer-reviewed journals.

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Dr Veronika Ballova is a senior medical oncologist at the Onkologie Kantonsspital in Baden, Switzerland. She graduated in medicine from the Comenius University Bratislava, Slovakia, and completed her specialist training in clinical oncology at the National Cancer Institute (NCI) in Bratislava.

Dr Ballova worked as an assistant professor in the Department of Microbiology of the University of Bratislava, and as a resident at the NCI in Bratislava. In 2003 she also completed a (European Society for Medical Oncology) ESMO fellowship at the University Hospital in Cologne, Germany, with the German Hodgkin Study Group. Since then, her career has been mainly focused on haematological malignancies, working for 20 years as a medical oncologist in the Department of Lymphoproliferative Diseases & Hematologic Malignancies, Bone Marrow Transplantation Unit of the NCI in Bratislava, Slovakia. She serves as a member of the ESMO Educational Publications Working Group (Chair 2024–2025), and as a member of the Slovak Oncology Society (S.O.S), Slovak Society for Haematology (SHS) and International Extranodal Lymphoma Study Group (IELSG). She also served as chair of the Slovak Lymphoma Group (LySk) from 2012 to 2015.

Dr Ballova is the author of several papers published in peer-reviewed international journals and has been an invited speaker at several national meetings. She has also collaborated on international publications (books), as an author and editor.

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Abbreviations

^{18}F-FDG	^{18}F-fluorodeoxyglucose
Ab	Antibody
ABC	Activated B-cell-like
ABVD	Doxorubicin, bleomycin, vinblastine and dacarbazine
ADC	Antibody–drug conjugate
AE	Adverse event
Ag	Antigen
AID	Activation-induced deaminase
AIDS	Acquired immunodeficiency syndrome
AIHA	Autoimmune haemolytic anaemia
AITL	Angioimmunoblastic T-cell lymphoma
ALCL	Anaplastic large cell lymphoma
ALK	Anaplastic lymphoma kinase
alloSCT	Allogeneic stem-cell transplantation
APC	Antigen-presenting cell
AraC	Cytarabine
ART	Antiretroviral therapy
ASCT	Autologous stem-cell transplantation
BBB	blood–brain barrier
BCL	B-cell lymphoma
BCL2	B-cell lymphoma 2
BCL2i	B-cell lymphoma 2 inhibitor
BCL6	B-cell lymphoma 6
BCL10	B-cell lymphoma 10
BCR	B-cell receptor
BEACOPP	Bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone
BL	Burkitt lymphoma
BM	Bone marrow
BMB	Bone marrow biopsy
BMT	Bone marrow transplant
B-R	Bendamustine-rituximab
BsAb	Bispecific antibody
BTK	Bruton tyrosine kinase
BTKi	Bruton tyrosine kinase inhibitor
BV	Brentuximab vedotin
C	Concentration
C-ALCL	Cutaneous anaplastic large cell lymphoma
CAR	Chimeric antigen receptor
CAR-T	Chimeric antigen receptor T cell
CB	Centroblast
CBCL	Cutaneous B-cell lymphoma
CC	Centrocyte
CD	Cluster of differentiation
CDK6	Cyclin-dependent kinase 6
CECT	Contrast-enhanced computed tomography
CEUS	Contrast-enhanced ultrasound
cHL	Classical Hodgkin lymphoma
CHOEP	Cyclophosphamide, doxorubicin, etoposide, vincristine and prednisone
CHOP	Cyclophosphamide, doxorubicin, vincristine and prednisone
CHP	Cyclophosphamide, doxorubicin and prednisone
Chr	Chromosome
ChT	Chemotherapy
CIT	Chemoimmunotherapy
CK	Cytokine
CLL	Chronic lymphocytic leukaemia
CNS	Central nervous system
CODOX-M	Cyclophosphamide, vincristine, doxorubicin and high-dose methotrexate
COO	Cell of origin
CR	Complete response
CRS	Cytokine release syndrome
CSF	Cerebrospinal fluid
CT	Computed tomography
CTCL	Cutaneous T-cell lymphoma
ctDNA	Circulating tumour DNA
D	Diversity
DA	Dose adjusted
DA-EPOCH-R	Dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin plus rituximab
DHAP	Dexamethasone, high-dose cytarabine and cisplatin
DLBCL	Diffuse large B-cell lymphoma
Dmax	Tumour distance
DRC	Dexamethasone, rituximab and cyclophosphamide
DS	Deauville score
EBER	Epstein–Barr early RNA
EBV	Epstein–Barr virus
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free survival
EFS24	Event-free survival at 24 months
ENKTCL	Extranodal natural killer/T-cell lymphoma
EOT	End-of-treatment
EPOCH	Etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin
EPOCH-R	Etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin and rituximab
ESMO	European Society for Medical Oncology
EUS	Endoscopic ultrasound
EZH2	Enhancer of zeste homologue 2
Fab	Fragment antigen-binding
FACS	Fluorescence-activated cell sorting
Fc	Fragment crystallisable
FCM	Flow cytometry
FDA	Food and Drug Administration
FDC	Follicular dendritic cell
FFPE	Formalin-fixed paraffin-embedded
FISH	Fluorescent *in situ* hybridisation
FL	Follicular lymphoma
FLEX	Follicular Lymphoma Evaluation Index
FLIPI	Follicular Lymphoma International Prognostic Index
GC	Germinal centre
GCB	Germinal centre B-cell like
G-CSF	Granulocyte colony-stimulating factor
GEP	Gene expression profiling
GI	Gastrointestinal
GVD	Gemcitabine, vinorelbine and liposomal doxorubicin
GvHD	Graft-versus-host disease
GWAS	Genome-wide association studies
GZL	Grey zone lymphoma
H chain	Heavy chain
H. pylori	*Helicobacter pylori*
HAART	Highly active antiretroviral therapy
Hb	Haemoglobin
HCLv	Hairy cell leukaemia variant
HCV	Hepatitis C virus
HD	High dose
HDAC	Histone deacetylase
HD-AraC	High-dose cytarabine
HD--IFO	High-dose ifosfamide
HD-MTX	High-dose methotrexate
HDT	High-dose therapy
HE	Haematoxylin and eosin
HHV8	Human herpes virus 8
HIV	Human immunodeficiency virus
HL	Hodgkin lymphoma
HLA	Human leukocyte antigen
HPLL	Haemoglobin, Platelets, Lactate dehydrogenase and extrahilar Lymphadenopathy
HPS	Haemophagocytic syndrome
H-RS	Hodgkin and Reed–Sternberg
HTLV-1	Human T-lymphotropic virus 1
HVS	Hyperviscosity syndrome
Hyper-CVAD	Cyclophosphamide, vincristine, doxorubicin, methotrexate, cytarabine and dexamethasone
i.v.	Intravenous
ICC	International Consensus Classification
ICE	Ifosfamide, carboplatin and etoposide
ICI	Immune checkpoint inhibitor
ICOS	Inducible T-cell costimulator
IDH2	Isocitrate dehydrogenase 2
IELSG	International Extranodal Lymphoma Study Group
IFN-α	Interferon alpha
Ig	Immunoglobulin
IGH	Immunoglobulin heavy chain
IGHV	Immunoglobulin heavy-chain variable
IgM	Immunoglobulin M
IHC	Immunohistochemistry
IMiD	Immunomodulatory imide drug

IPCG	International Primary Central Nervous System Lymphoma Collaborative Group
iPET	Interim positron emission tomography
IPI	International Prognostic Index
IPS	International Prognostic Score
IPSID	Immunoproliferative small intestinal disease
ISH	*In situ* hybridisation
ISRT	Involved-site radiotherapy
ISSWM	International Prognostic Scoring System for Waldenström Macroglobulinaemia
IVAC	Ifosfamide, etoposide and high-dose cytarabine
iwCLL	International Workshop on Chronic Lymphocytic Leukemia
J	Joining
JAK	Janus kinase
L chain	Light chain
LBCL	Large B-cell lymphoma
LDH	Lactate dehydrogenase
LMB	Lymphomes Malins B
LN	Lymph node
LP	Lymphocyte predominant
LPD	Lymphoproliferative disorder
LT	Lymphoid tissue
LTI	Local tumour invasiveness
mAb	Monoclonal antibody
MAG	Myelin-associated glycoprotein
MALT	Mucosa-associated lymphoid tissue
MALT-IPI	MALT lymphoma International Prognostic Index
MATRix	Methotrexate, cytarabine, thiotepa and rituximab
MBL	Monoclonal B-cell lymphocytosis
MCL	Mantle cell lymphoma
MCL1	Myeloid cell leukaemia 1
MF	Mycosis fungoides
MGUS	Monoclonal gammopathy of undetermined significance
MGZL	Mediastinal grey zone lymphoma
MH	Metabolic heterogeneity
MHC	Major histocompatibility complex
MIPI	Mantle Cell Lymphoma International Prognostic Index
MIPI-c	Combined MIPI
MM	Multiple myeloma
MR	Magnetic resonance
MRD	Minimal residual disease
MRI	Magnetic resonance imaging
mRNA	Messenger RNA
mTOR	Mammalian target of rapamycin
MTV	Metabolic tumour volume
MTX	Methotrexate
MZL	Marginal zone lymphoma
NCCN	National Comprehensive Cancer Network
NF-κB	Nuclear factor-kappa B
NGS	Next-generation sequencing
NHL	Non-Hodgkin lymphoma
NK	Natural killer
NKTCL	Natural killer/T-cell lymphoma
NLPHL	Nodular lymphocyte-predominant Hodgkin lymphoma
NMZL	Nodal marginal zone lymphoma
NNKTCL	Nodal natural killer/T-cell lymphoma
NOS	Not otherwise specified
NRI	Nomogram-revised risk index
ORR	Overall response rate
OS	Overall survival
PAS	Periodic acid-Schiff
PB	Peripheral blood
PCL	Primary cutaneous lymphoma
PCNSL	Primary central nervous system lymphoma
PCR	Polymerase chain reaction
PD-1	Programmed cell death protein 1
PD-L1/2	Programmed death-ligand 1/2
PET	Positron emission tomography
PFS	Progression-free survival
PI3K	Phosphoinositide 3-kinase
PI3Ki	Phosphoinositide 3-kinase inhibitor
PINK	Prognostic Index of Natural Killer Lymphoma
PIT	Prognostic Index for T-cell Lymphoma
PLHIV	People living with human immunodeficiency virus
PMBCL	Primary mediastinal large B-cell lymphoma
POD24	Progression of disease within 2 years
Pola	Polatuzumab vedotin
PPI	Proton pump inhibitor
PS	Performance status
PTCL	Peripheral T-cell lymphoma
PTCL-NOS	Peripheral T-cell lymphoma not otherwise specified
PTLD	Post-transplant lymphoproliferative disorder
PUVA	Psoralen plus ultraviolet-A
R	Rituximab
R^2 regimen	Rituximab and lenalidomide
R-ACVBP	Rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin and prednisone
R-CAP	Rituximab, cyclophosphamide, doxorubicin and prednisone
R-CHOEP	Rituximab, cyclophosphamide, doxorubicin, vincristine, etoposide and prednisone
R-CHOP	Rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone
R-CHP	Rituximab, cyclophosphamide, doxorubicin and prednisone
R-CODOX-M	Rituximab, cyclophosphamide, doxorubicin, vincristine and methotrexate
R-CVP	Rituximab, cyclophosphamide, vincristine and prednisone
R-FM	Rituximab, fludarabine and mitoxantrone
RI	Reduction of immunosuppression
RIC	Reduced intensity conditioning
RIT	Radioimmunotherapy
R-IVAC	Rituximab, ifosfamide, etoposide and cytarabine
R-MACOP-B	Rituximab, methotrexate, leucovorin, doxorubicin, cyclophosphamide, vincristine, prednisone and bleomycin
RR	Response rate
R/R	Relapsed/refractory
RS	Richter syndrome
RT	Radiotherapy
sALCL	Systemic anaplastic large cell lymphoma
SDT	Skin-directed therapy
SKY	Spectral karyotyping
SLL	Small lymphocytic lymphoma
SMILE	Steroid, methotrexate, ifosfamide, L-asparaginase, etoposide
SMZL	Splenic marginal zone lymphoma
SOT	Solid organ transplant
SS	Staging system
STAT	Signal transducer and activator of transcription
SUV	Standardised uptake value
T	Time
Tc	T-cytotoxic
TCL	T-cell lymphoma
TCR	T-cell receptor
TFH	T-follicular helper
Th	T-helper
TKI	Tyrosine kinase inhibitor
TLG	Total lesion glycolysis
TLS	Tumour lysis syndrome
TME	Tumour microenvironment
TMTV	Total metabolic tumour volume
TRM	Transplantation-related mortality
ULN	Upper limit of normal
UVB	Ultraviolet-B
V	Variable
VR-CAP	Bortezomib, rituximab, cyclophosphamide and doxorubicin/prednisone
W+W	Watch and wait
WBRT	Whole-brain radiotherapy
WHO	World Health Organization
WHO-HAEM5	WHO Classification of Haematolymphoid Tumours, 5th edition
WM	Waldenström macroglobulinaemia
XPO-1	Exportin 1

Acknowledgements

The editors would like to thank the members of the Educational Publications Working Group and the Educational Committee for their support in this initiative. The editors also wish to thank Claire Bramley, Aude Galli, Matthew Hillier and Nicki Peters for their support in preparing this publication.

Silvia Montoto, Martin Dreyling and Veronika Ballova

A

What every oncologist/haematologist should know

1 The immune system

The immune response

The immune system comprises two arms functioning cooperatively to provide a comprehensive protective response: the innate and the adaptive immune systems.

The innate immune system is primitive, does not require the presentation of an antigen (Ag) and does not lead to immunological memory.

Its effector cells are neutrophils, macrophages and mast cells, reacting within minutes to hours with the help of complement activation and cytokines (CKs).

Innate and adaptive immunity

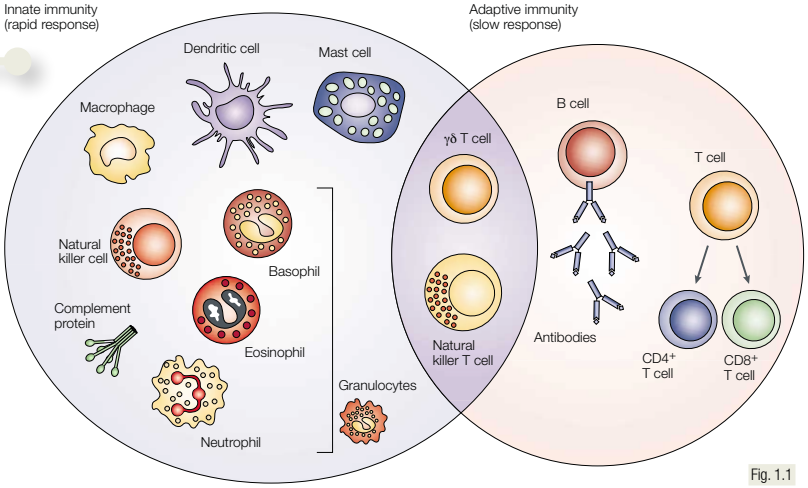
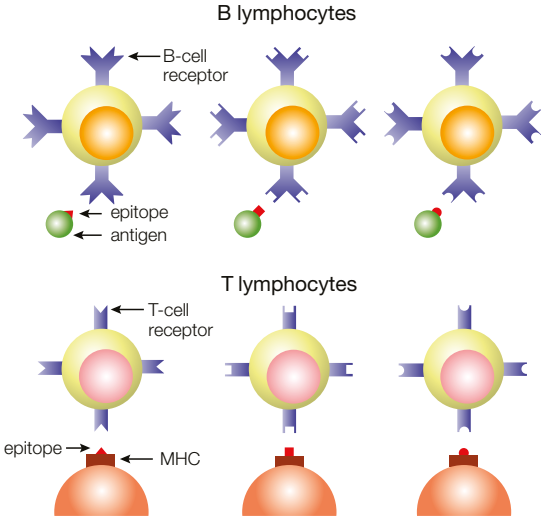


Fig. 1.1

B and T lymphocytes



MHC, major histocompatibility complex.

Fig. 1.2

The adaptive immune response is provided by the lymphocytes, which precisely recognise unique Ags through cell-surface receptors.

Receptors are produced in billions of variations through cut and splicing of genes and subsequent negative selection: thus, self-recognising lymphocytes are eradicated.

Immunological memory after an Ag encounter permits a faster and heightened state of response on a subsequent exposure.

Lymphocytes develop in primary lymphoid tissue (bone marrow [BM], thymus) and circulate towards secondary lymphoid tissue (lymph nodes [LNs], spleen, mucosa-associated lymphoid tissue [MALT]).

The Ag reaches the LN carried by lymphocytes or dendritic cells. Lymphocytes enter the LN from blood transiting through specialised endothelial cells.

The Ag is processed within the LN by lymphocytes, macrophages and other immune cells in order to mount a specific immune response.

Primary and secondary lymphoid tissues

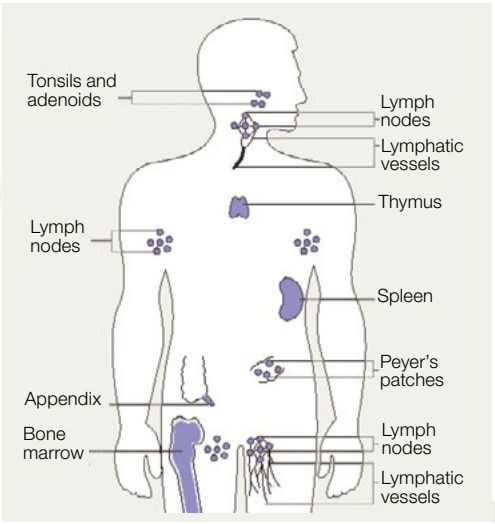


Fig. 1.3

REVISION QUESTIONS

1. What are the effector cells of the innate immune system?
2. Which cells are responsible for immune memory?
3. In which anatomical structure are the Ags processed by lymphocytes?

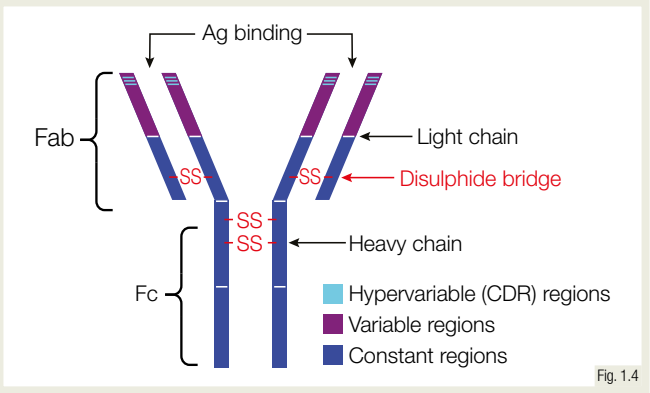
Immunoglobulins (Igs) and B-cell development

The final task of the lymphocytes (B cells) developed in the BM is the production of Ag-specific Igs, which function as antibodies (Abs).

Igs are proteins secreted by or present on the surface of B cells, assembled from identical pairs of heavy (H) and light (L) chains.

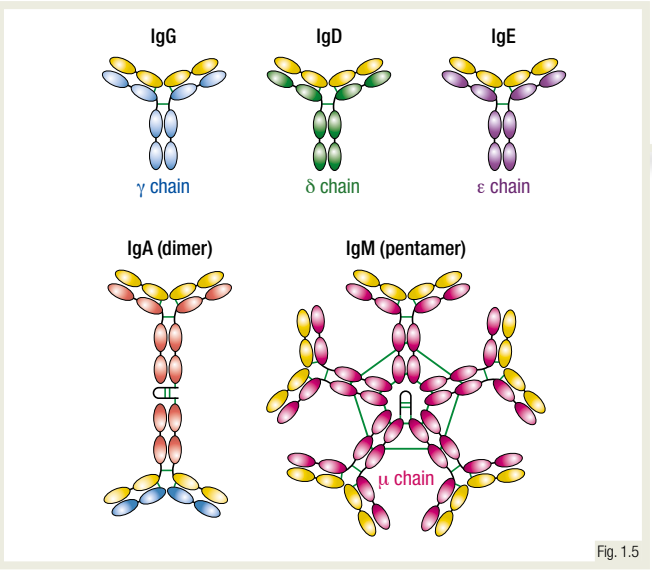
The highly variable N-terminal regions are the fragment antigen-binding (Fab) portion. The constant domains interact with the fragment crystallisable (Fc) receptors on the effector cells.

Antibody structure



Ag, antigen; CDR, complementary-determining region; Fab, fragment antigen-binding; Fc, fragment crystallisable.

Immunoglobulin classes



Ig, immunoglobulin.

There are five classes of Igs: M, G, A, E and D, distinguished by different H chains. B cells can change the class of Ig produced: class switching.

Before being capable of producing Ag-specific Ig, B cells must undergo a number of transformations, first in the BM and subsequently in the LNs.

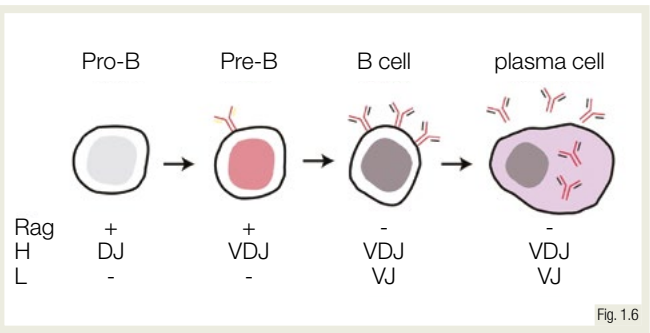
In the rest of the cells in the body (not B cells), the genes encoding the H and L chains of the Ig are distributed in many segments, thus they cannot be expressed.

These gene segments must be rearranged within the chromosome in the B cells so the final gene structure allows the expression of a functional protein.

The first stages of B-cell development occur in the BM, where pro-B cells first rearrange the Ig H chain gene to become pre-B cells.

Pre-B cells continue this somatic recombination process by rearranging the L chain to become immature B cells, expressing IgM on their surface.

B-cell development



D, diversity; H, heavy; L, light; J, joining; Rag, recombinase activating gene; V, variable.

REVISION QUESTIONS

1. What are the Fab and the Fc portions of an Ig?
2. What distinguishes a pre-B from a pro-B from an immature B cell?
3. What is meant by the term 'somatic recombination'?

B-cell diversity

In B cells, the variable regions of the Ig L chains are encoded by the random joining of one of many variable (V) and joining (J) segment genes.

In addition to the above, for the H chain gene, a diversity (D) gene must also be rearranged.

The result of this random process is the expression on any individual naïve B-cell surface of a unique Ig with Ag specificity: the B-cell receptor (BCR).

V(D)J recombination

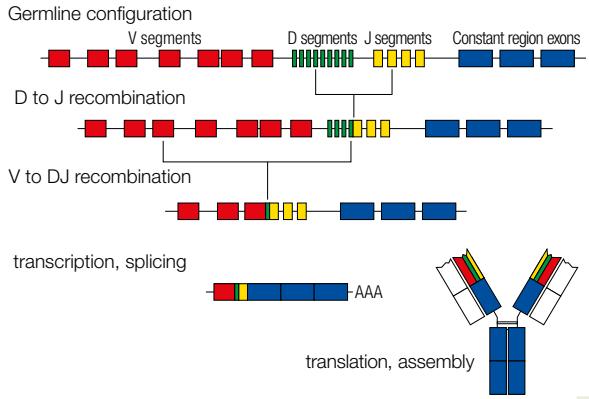


Fig. 1.7

VDJ, variability, diversity and joining.

Germinal centre

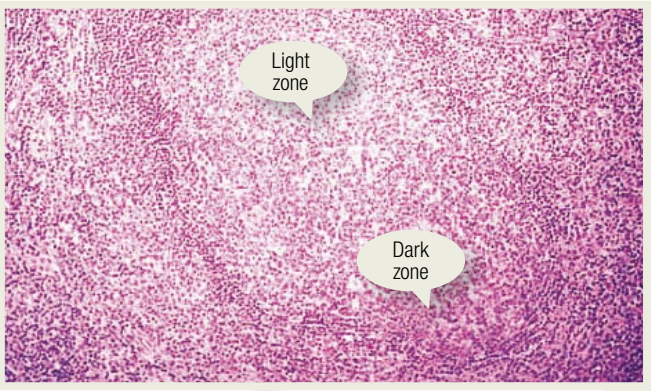


Fig. 1.8

Naïve B cells exit the BM and circulate between blood, LNs and secondary lymphoid tissue in search of an Ag that will match the randomly determined BCR.

When naïve B cells encounter an Ag within the germinal centre (GC) of a LN they undergo further variation and selection.

Binding of an Ag to the BCR, with the help of T cells and antigen-presenting cells (APCs), initiates Ag-dependent GC reaction.

In the peripheral dark zone of the GC, rapidly dividing B cells (centroblasts [CBs]) introduce random mutations in the H and L chains (somatic hypermutation).

In the central light zone, CBs mature to centrocytes (CCs) and are selected for affinity with the help of T-follicular helper cells and dendritic cells.

High-affinity CCs mature to either plasma cells or memory B cells and leave the GC. They may undergo Ig class switching by changing the Ig H chain.

Somatic hypermutation and class-switch recombination

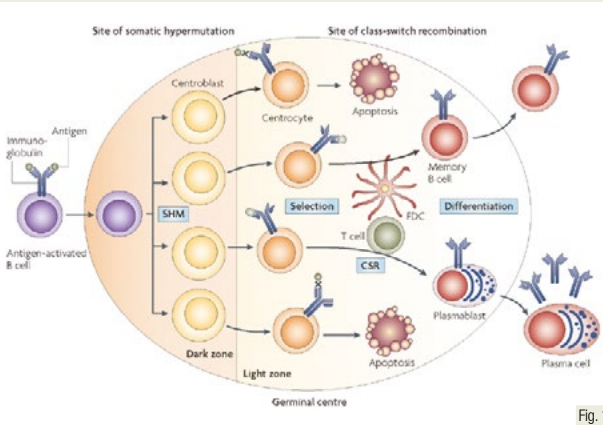


Fig. 1.9

CSR, class-switch recombination; FDC, follicular dendritic cell; SHM, somatic hypermutation.

REVISION QUESTIONS

1. What are the phases of B-cell development and where do they take place?
2. How is the diversity of Ig specificity derived?
3. What is meant by 'somatic hypermutation'?

T cells and natural killer (NK) cells

T lymphocytes arise in the BM but soon migrate to the thymus, where they mature to express the Ag-binding T-cell receptor (TCR) on their membrane.

The TCR is a dimer composed of two chains, usually α and β. Similar to the BCR, each one of these chains includes a variable and a constant domain.

T cells are able to recognise Ags (through their TCR) only when the Ag is bound to a major histocompatibility complex (MHC) molecule.

T-cell receptor structure

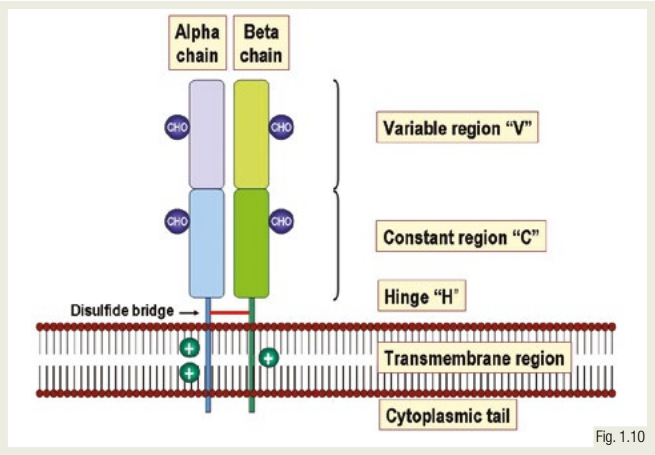


Fig. 1.10

T-cell maturation

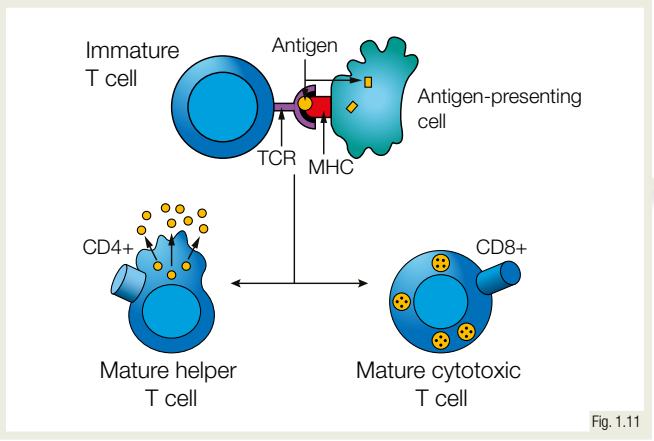


Fig. 1.11

MHC, major histocompatibility complex; TCR, T-cell receptor.

After migrating to the secondary lymphoid organs, naïve T cells are exposed to Ags which bind to the TCR. TCR activation induces proliferation and differentiation.

T cells mature to distinct T-helper (Th) and T-cytotoxic (Tc) populations characterised by expression of CD4 and CD8, respectively.

There are two classes of MHC molecules: class I and class II. Th cells recognise Ags in the context of class II MHC, whereas Tc cells recognise Ags bound to class I MHC.

Activated Th cells divide and produce a clone of effector cells, which in turn secrete CKs, activating other components of the immune response.

Once activated, Tc cells induce apoptosis of dysfunctional cells (i.e. infected) by enzymatic or signalling processes. NK cells have a similar function.

Memory T cells are produced after Ag exposure. They remain quiescent and provide an enhanced response after repeated exposure to the Ags.

Natural killer cell activation

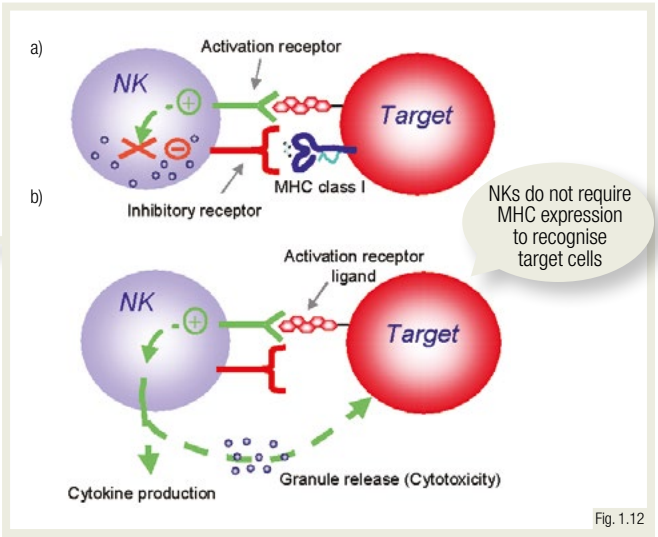


Fig. 1.12

MHC, major histocompatibility complex; NK, natural killer.

REVISION QUESTIONS

1. What is the structure of the TCR?
2. How can Th and Tc cells be easily distinguished from one another?
3. What is the main function of Tc cells?

Immune system activity

CKs are low molecular weight proteins that play a key role in the induction and regulation of the immune response.

Produced by a variety of cells, their actions are mediated through their receptive receptors; they exert autocrine, paracrine and endocrine effects.

CKs regulate the intensity and duration of both the innate and adaptive immune response.

Cytokines

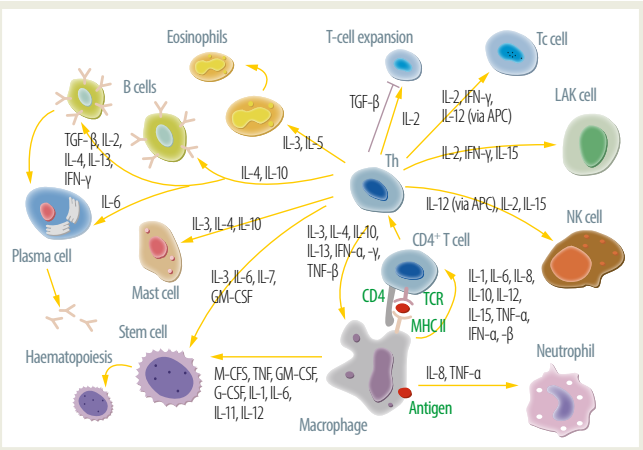


Fig. 1.13

APC, antigen-presenting cell; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon; IL, interleukin; LAK, lymphokine-activated killer; M-CFS, macrophage colony-stimulating factor; MHC, major histocompatibility complex; NK, natural killer; Tc, T cytotoxic; TCR, T-cell receptor; TGF, transforming growth factor; TNF, tumour necrosis factor.

Antigen processing and presentation

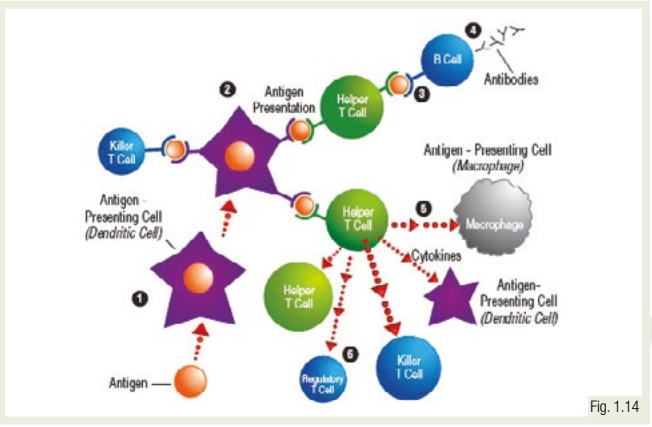


Fig. 1.14

The various individual facets of the immune response interact in a complex fashion to result in a coordinated response.

Following a rapid response by the cells of the innate system, the cells of the adaptive immune system recognise Ags, expanding and activating effectors.

APCs, present throughout the body, internalise and process Ags, displaying part of them on their surface bound to a class II MHC molecule.

This way APCs carry cargos of foreign Ags to lymphoid organs, where they are recognised by Th cells that initiate the adaptive response.

All aspects of the adaptive response are initiated and controlled by T cells. They recruit immunological effector mechanisms by direct contact or through CKs.

Abs may cause direct cytotoxicity by activation of the complement cascade or by recruiting effector cells (NK, macrophages, etc.) that cause cell death.

Antibody-mediated cytotoxicity

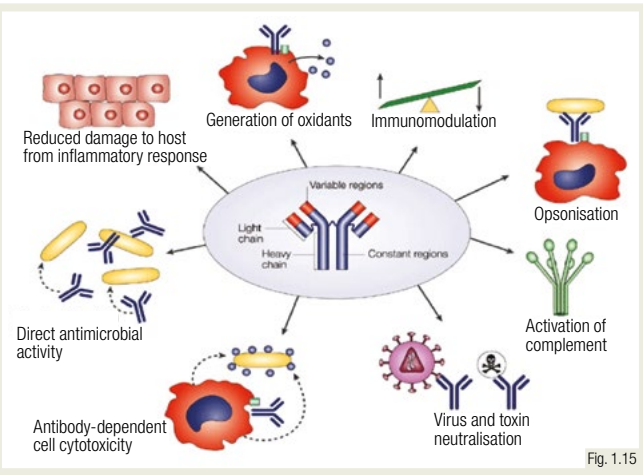


Fig. 1.15

REVISION QUESTIONS

1. What are CKs and how do they exert their function?
2. What is the role of APCs?
3. Which mechanisms are employed by Abs to cause dysfunctional cell death?

Summary: The immune system

- Cells of the primitive innate immune system and the Ag-specific adaptive immune system act as a cooperative network to bring about a coordinated and tightly regulated immune response to foreign Ags
- The primitive innate immune system uses a limited pattern of recognition molecules and, although it retains no memory, is able to mount a rapid response
- The Ag-specific adaptive immune system recognises a huge diversity of different specific Ags and elicits a response that is highly specific and retains memory
- Diversity and Ag specificity in both the TCR and BCR result from somatic recombination and the random splicing of a selected number of gene segments
- When naïve B cells encounter an Ag, further Ag specificity is added by somatic hypermutation in the GC of secondary lymphoid organs
- Only the most avid Ag-binding cells mature to become either Ab-producing plasma cells or memory B cells
- Abs may switch to different classes with differing effector functions and tissue locations while retaining the same Ag specificity in their variable regions
- In response to Ags, T cells differentiate to effector T cells that may augment the immune response, cytotoxic T cells that destroy altered self-cells, or regulatory T cells
- CKs regulate the immune response by autocrine, paracrine and endocrine mechanisms
- Cooperative interactions of both facets of the immune response result in efficient effector mechanisms that clear foreign Ags with residual immunological memory

Further Reading

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2 Diagnosing lymphomas

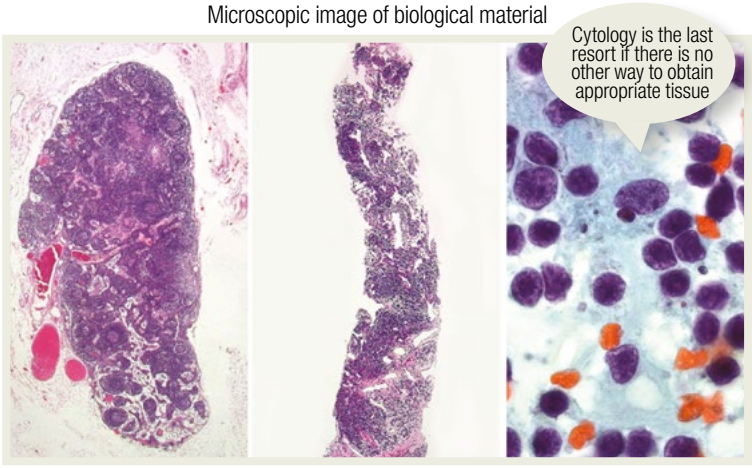
Introduction – Cytology and histology

Pathology (from 'logos', study, and 'pathos', suffering) is a discipline devoted to studying the changes associated with disease in cells, tissues and organs.

When lymphoma is suspected, the affected biological tissue is examined microscopically and with the aid of immunophenotypic and, optionally, genetic studies.

Excisional biopsies of lymphoid tissue are preferred to core needle biopsies or cytology-based analysis as they generally allow higher diagnostic accuracy.

Microscopic image of biological material



Excisional biopsy | Core needle biopsy | Cytology smear

Fig. 2.1

Fine-needle aspiration and staining of cytological material

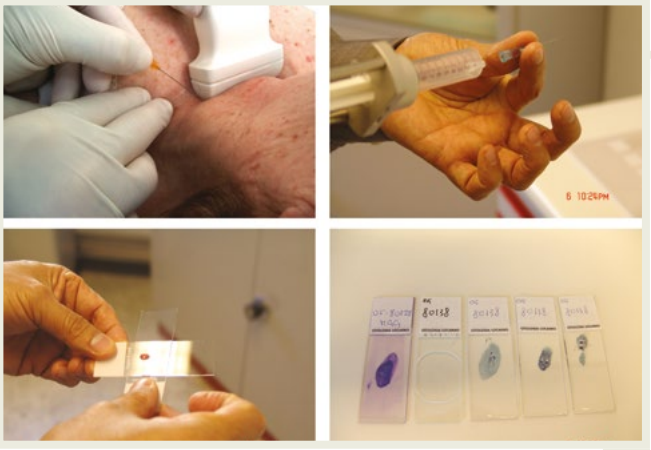


Fig. 2.2

Cytological preparations can be obtained from touch and scrape imprints of fresh material or from fine-needle aspirates.

Slides are either fixed (alcohol or formalin) or air-dried. These are then stained, usually with Wright-Giemsa-type staining (e.g. Diff-Quick) or Papanicolaou.

In addition to morphological examination, cytological material allows immunophenotypic (flow cytometry, immunocytochemistry) and genetic studies.

Histology requires biopsy material to be submitted to the pathologist. If fresh material is available, a portion can be used for immunophenotypic and genetic studies.

Specimens are sectioned by the pathologist into slices for fixation, usually in buffered formalin. After processing, paraffin-embedded material is cut in 2 µm sections.

Sections are stained with haematoxylin and eosin (HE) and Giemsa for morphological assessment. Other useful stains are Periodic Acid-Schiff (PAS) and Gomori.

Preparation of specimen into paraffin blocks and stained slides

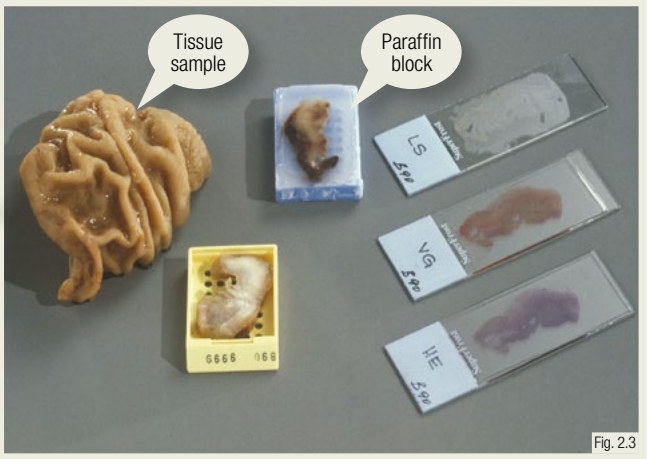


Fig. 2.3

REVISION QUESTIONS

1. How is pathology defined?
2. What is the best material for an accurate lymphoma diagnosis?
3. Which stains are commonly used in cytology and histology?

Histopathology and cytology of lymphoid tissue

Lymphoid tissues (LTs) are divided into primary LT (bone marrow [BM] and thymus) and secondary LT (lymph nodes [LNs], mucosa-associated LT and spleen).

LNs present B-cell rich (cortex) and T-cell rich (paracortex) areas. A plasma cell-rich area, fibrous capsule and sinuses further characterise LNs.

In reactive conditions, each component can be increased or diminished, which can lead to an alteration of the whole structure, however, without effacing it.

Anatomy of a lymph node

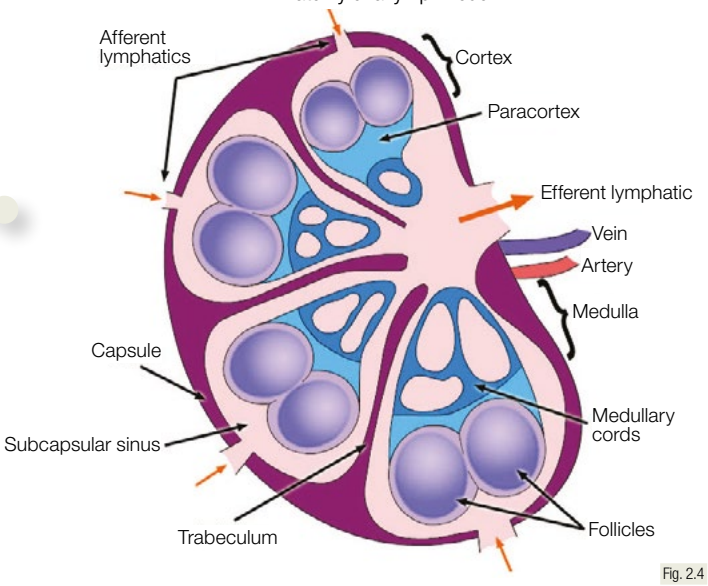


Fig. 2.4

Different histological features in lymphoma

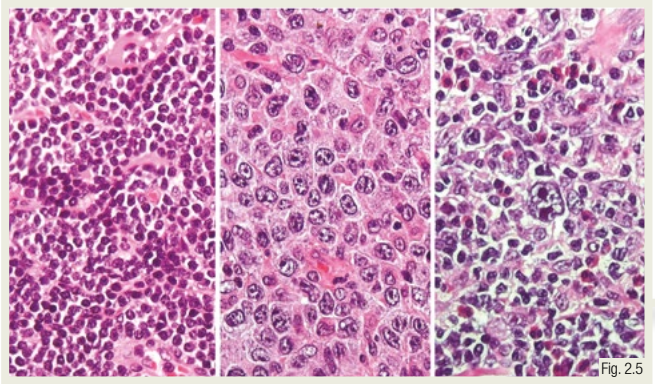


Fig. 2.5

Small cells in small lymphocytic lymphoma | Large cells in diffuse large B-cell lymphoma | Hodgkin cell with inflammatory background

Histology of lymphoma: the neoplastic cell population effaces the structure of LT, at least focally. Occasionally, it impinges on the non-neoplastic LT.

In addition, the neoplastic cell population shows signs of invasion (e.g. tissue surrounding LT, vessel walls) and cytological atypia (cell size, nuclear morphology).

Once a diagnosis of malignancy is made, the lymphoma has to be classified according to growth pattern and cytological features, with the aid of ancillary studies.

Cytological specimens may be of value in special situations, such as for staging or in case of relapse, being rapid, accurate and safe.

For the initial diagnosis of lymphoma, however, histological material is preferred and ancillary studies (immunophenotype, molecular studies) are required.

In contrast to reactive conditions, cytological specimens of neoplastic LNs show limited range of maturation of the neoplastic cells.

Different cytological features in lymphoma

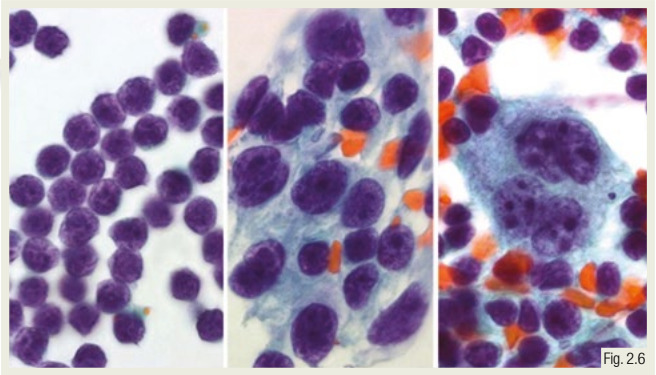


Fig. 2.6

Small cells in small lymphocytic lymphoma | Large cells in diffuse large B-cell lymphoma | Hodgkin cell with inflammatory background

REVISION QUESTIONS

1. Recapitulate the structure of a non-neoplastic LN.
2. What are the three key histological characteristics of a neoplastic LN?
3. When would you try to obtain a cytological sample instead of a histological sample?

Immunophenotype – Immunohistochemistry and flow cytometry

Immunohistochemistry (IHC) represents the most important method for immunophenotyping lymphocytes on formalin-fixed paraffin-embedded (FFPE) material.

It allows the visualisation of an antigen (Ag) by means of primary monoclonal or polyclonal antibodies (Abs) and a detection system.

Monoclonal primary Abs specific for the same Ag are assigned cluster of differentiation (CD) numbers at International Leukocyte Typing Workshops.

The most widely used antibodies in immunohistochemistry

Lymphoma	Characteristic antigen
Mature B-cell lymphomas	
CLL/SLL	CD20, CD79a, CD5, CD23
Mantle cell lymphoma	CD20, CD79a, CD5, Cyclin D1
Follicular lymphoma	CD20, CD79a, BCL2, CD10, BCL6
Burkitt lymphoma	CD20, CD79a, CD10, BCL6
Mature T- and NK-cell lymphomas	
Peripheral T-cell lymphoma	CD2, CD3, CD4>CD8
Anaplastic large cell lymphoma	CD2, CD30, ALK, CD4>CD8, EMA
Angioimmunoblastic T-cell lymphoma	CD2, CD3, CD5, CD4>CD8
Extranodal NK/T-cell lymphoma, nasal type	CD2, CD56
Hodgkin lymphomas (HLs)	
Classical HL	CD15, CD30
Nodular lymphocyte-predominant HL	CD20, CD79a, CD45

Fig. 2.7

ALK, anaplastic lymphoma kinase; BCL2/6, B-cell lymphoma 2/6; CLL, chronic lymphocytic leukaemia; EMA, epithelial membrane antigen; NK, natural killer; SLL, small lymphocytic lymphoma.

Plasma cell myeloma CD38+ with kappa (κ) light chain restriction

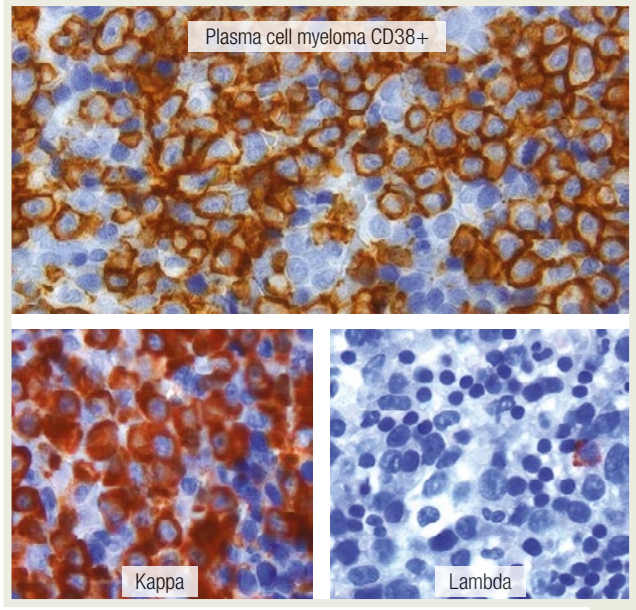


Fig. 2.8

IHC staining requires a careful correlation with the morphological findings to define lineage and immunophenotype of the neoplastic cells.

Staining for immunoglobulin (Ig) light chain κ (kappa) and λ (lambda) is useful in B-cell lymphomas (BCLs) to assess clonality (light chain restriction). In T-cell lymphomas (TCLs), staining for CD4 and CD8 is relevant.

In addition, the aberrant or lost expression of a specific Ag may be suggestive of lymphoma (such as CD5 expression in chronic lymphocytic leukaemia [CLL] or loss of CD7 in TCL).

Flow cytometry represents an alternative technique to IHC for immunophenotyping lymphocytes. However, it requires fresh tissue to produce cell suspensions.

Cells are incubated with multiple fluorochrome-labelled Abs and passed through a laser light beam in the fluorescence-activated cell sorting (FACS) machine.

When the light beam hits the fluorochrome it produces a photon that, detected by a sensor, results in a 'dot' representing each individual cell on the scattergram.

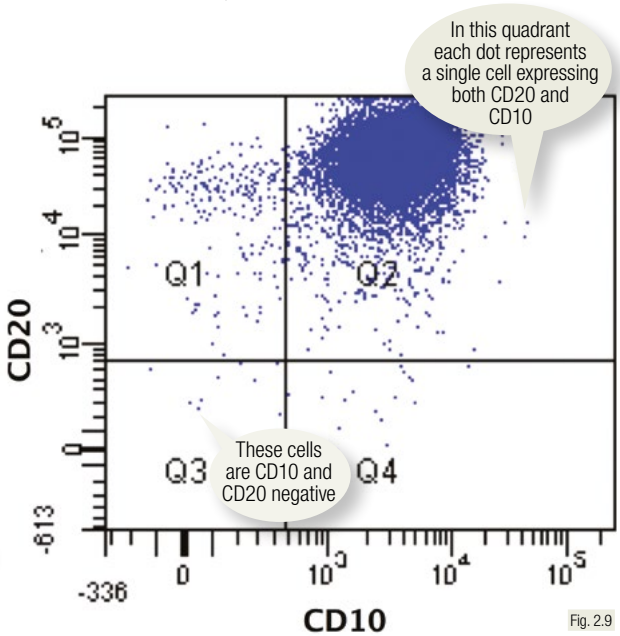


Fig. 2.9

Follicular lymphoma: co-expression of CD10 and CD20

REVISION QUESTIONS

1. Why is IHC very useful in the diagnostic work-up of lymphomas?
2. What are the most important lineage-specific markers?
3. What are the advantages of flow cytometry over IHC?

Molecular diagnostics – Cytogenetics and FISH (fluorescent *in situ* hybridisation)

Conventional cytogenetics requires dividing cells. In contrast, FISH is a commonly used alternative molecular method applicable on fresh and FFPE tissue.

Fluorophore-labelled DNA probes hybridise to specific DNA sequences. They are used to detect non-random chromosomal translocations in lymphoma.

Translocation results either in the juxtaposition of a gene with a regulatory region (e.g. Ig) or in the fusion of two genes encoding a chimeric protein.

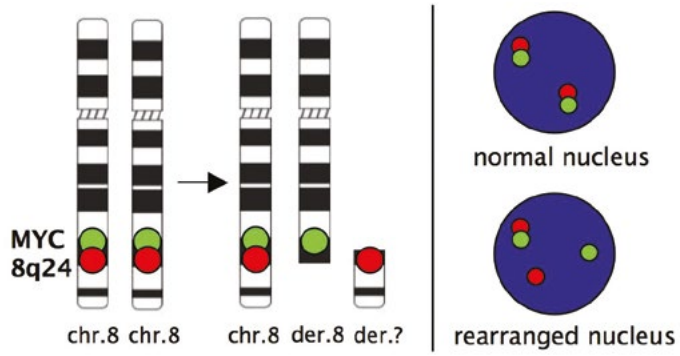
Common translocations found in B- and T-cell lymphomas

Genetic abnormality	Oncogene	Lymphoma
t(8;14)(q24;q32)	*MYC*	BL, DLBCL
t(8;22)(q24;q11)	*MYC*	BL, DLBCL
t(2;8)(p12;q24)	*MYC*	BL, DLBCL
t(14;18)(q32;q21)	*BCL2*	FL, DLBCL
t(11;14)(q13;q32)	*CCND1* (Cyclin D1)	MCL
t(11;18)(q21;q21)	*API2-MALT1* fusion gene	MALT lymphoma
t(14;18)(q32;q21)	*MALT1*	MALT lymphoma
t(3;14)(p14.1;q32)	*FOXP1*	MALT lymphoma
t(1;14)(p22.1;q32)	*BCL10*	MALT lymphoma
t(2;5)(p23;q35)	*NPM-ALK* fusion gene	ALCL ALK+
t(1;2)(q25;p23)	*TPM3-ALK* fusion gene	ALCL ALK+

Fig. 2.10

ALCL, anaplastic large cell lymphoma; ALK, anaplastic lymphoma kinase; BCL2/10, B-cell lymphoma 2/10; BL, Burkitt lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MALT, mucosa-associated lymphoid tissue; MCL, mantle cell lymphoma; NPM, nucleophosmin; TPM3, tropomyosin 3.

Translocation detected on chromosome 8 using break-apart FISH probes



chr, chromosome; der, derivative; FISH, fluorescent *in situ* hybridisation.

Fig. 2.11

In lymphomas, two FISH strategies are commonly used: break-apart (or split-signal) and dual-colour dual-fusion.

FISH with break-apart strategy is used to detect rearrangements in the investigated gene, without knowing the partner involved in the translocation.

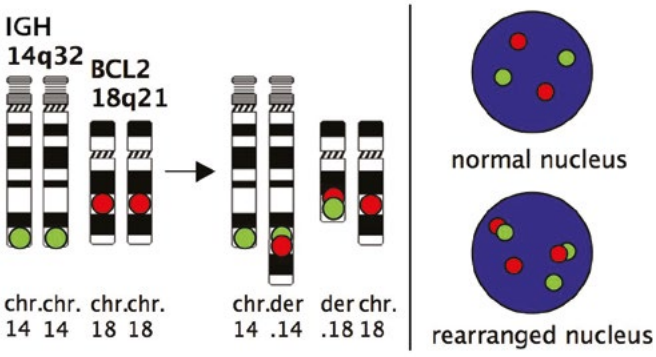
In case of gene rearrangement, separated signals (1 red and 1 green) indicate translocation, whereas juxtaposed probes represent the normal chromosome.

FISH with dual-colour dual-fusion strategy is used to detect the presence of a reciprocal translocation between the investigated gene and a known partner.

In case of translocation, both gene sequences are rearranged: 2 juxtaposed probes (translocation), 1 red and 1 green signal (normal chromosomes), are visualised.

FISH on interphase nuclei requires tailored handling procedures and interpretation of FISH results should be carried out by trained personnel.

Fusion of chromosome 14 and 18 detected using dual-colour dual-fusion FISH probes



BCL2, B-cell lymphoma 2; chr, chromosome; der, derivative; FISH, fluorescent *in situ* hybridisation; IGH, immunoglobulin heavy chain.

Fig. 2.12

REVISION QUESTIONS

1. What is the advantage of FISH over conventional cytogenetics?
2. What are the two most important FISH strategies in lymphomas?
3. Using the break-apart method, what information do you obtain by detecting a separation of the two probes?

Molecular diagnostics – *In situ* hybridisation (ISH), polymerase chain reaction (PCR), others

ISH uses labelled probes (complementary DNA or RNA strands) to localise specific DNA or RNA sequences in tissue specimens.

In situ studies for Ig light chain κ and λ are useful in the diagnosis of BCL, when IHC gives high background or light-chain proteins are not expressed.

Epstein–Barr early RNA (EBER) ISH is the most sensitive method to detect an Epstein–Barr virus (EBV) infection (e.g. in angioimmunoblastic T-cell lymphoma).

Detection of EBV infection in Hodgkin lymphoma using ISH and IHC

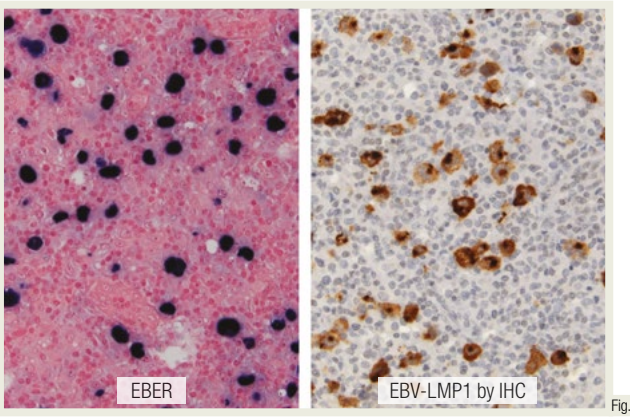


Fig. 2.13

EBER, Epstein–Barr early RNA; EBV, Epstein–Barr virus; IHC, immunohistochemistry; ISH, *in situ* hybridisation; LMP1, latent membrane protein 1.

PCR clonality study in reactive and neoplastic lymph node

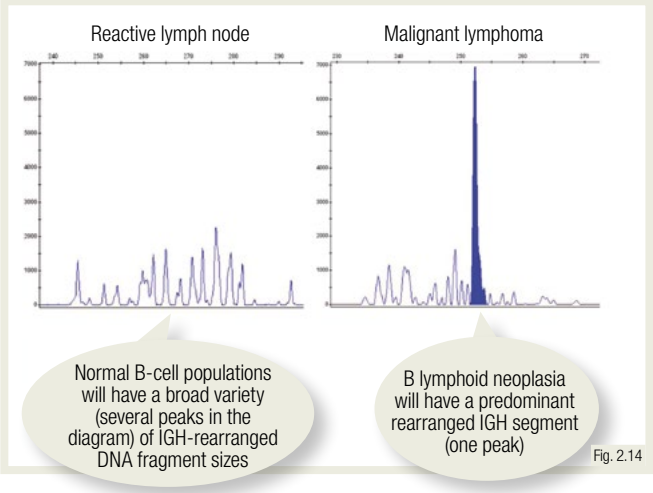


Fig. 2.14

IGH, immunoglobulin heavy chain; PCR, polymerase chain reaction.

PCR is a very sensitive method to detect clonality on fresh or FPE material. It can also be used to detect specific chromosomal translocations.

PCR enables detection of rearrangements in the *Ig* gene in BCL and of the T-cell receptor (*TCR*) gene in TCL, therefore suggesting clonality.

Clonality should be assessed only if specimens are highly suspicious for lymphoma. As results can be misleading, priority must be given to morphology/IHC.

Next-generation sequencing (NGS) technologies are based on the fragmentation and amplification of DNA and RNA combined with in-parallel sequencing.

NGS is rapidly improving our knowledge of lymphomas due to its high speed, relative low cost and versatility to detect all types of genomic alterations.

Several markers can be routinely studied using NGS technologies, which carry important diagnostic and prognostic values for individual patients (precision medicine).

Precision cancer medicine utilising NGS-based gene panel testing

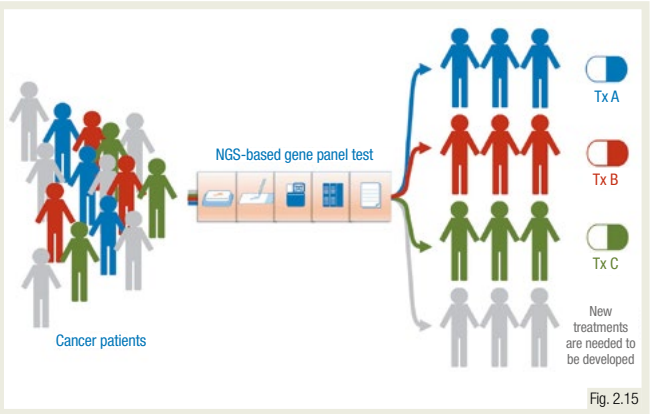


Fig. 2.15

NGS, next-generation sequencing, Tx, treatment.

REVISION QUESTIONS

1. What are the main applications of ISH?
2. When are clonality studies by PCR indicated?
3. What are the advantages of NGS technologies?

Summary: Diagnosing lymphomas

- Lymphoma diagnosis requires microscopic examination of biological material
- Excisional biopsies represent the best-suited material for diagnostic purposes. In special cases (when it is difficult to obtain a biopsy) cytological samples can be an option
- When specimens are suspicious for lymphoma, ancillary studies are required in addition to conventional morphology
- Immunophenotypic characterisation of the specimen (IHC, FACS) is necessary for the correct diagnosis
- IHC is performed on cytological and histological fixed material
- Flow cytometry is a very useful technique in the diagnosis of lymphoma, but requires fresh material
- FISH represents the most widely used cytogenetic technique for lymphoma diagnosis
- FISH allows visualisation of chromosomal translocations associated with specific lymphomas
- High throughput technologies, such as NGS, allow study of all types of genomic alterations

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Image sources: **Fig. 2.4.** Adapted from hematologyoutlines.com; **2.15.** Nagahashi M, et al. Cancer Sci 2019;110:6-15. All other figures courtesy of the authors.

3 Basis for lymphoma classification

Basic principles

Two classifications were proposed in 2022: the International Consensus Classification of Mature Lymphoid Neoplasms (ICC) and the 5th edition of the World Health Organization (WHO) Classification of Haematolymphoid Tumours (WHO-HAEM5).

These classifications recognise non-overlapping entities with well-defined pathological and clinical features. They are therefore biologically solid and clinically useful.

Each entity has its specific clinical course: some grow slowly but are incurable (e.g. follicular lymphoma [FL]), while others are clinically aggressive but curable (e.g. diffuse large B-cell lymphoma [DLBCL]).

Schematic structure of lymphoma classification

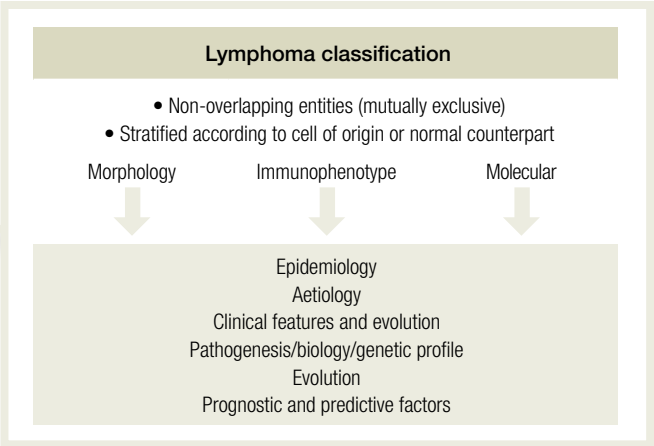
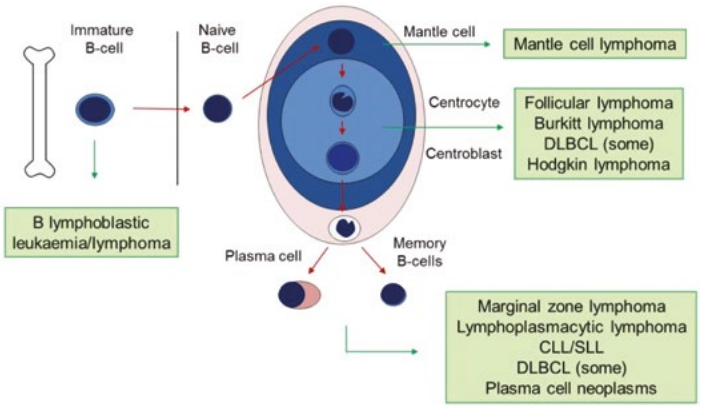


Fig. 3.1

Normal B-cell differentiation and its relationship to major B-cell neoplasms



CLL, chronic lymphocytic leukaemia; DLBCL, diffuse large B-cell lymphoma; SLL, small lymphocytic lymphoma.

Fig. 3.2

The basic conceptual framework to classify lymphoid neoplasms is the putative normal cell counterpart from which they arise.

The ICC/WHO-HAEM5 recognise the relevance of the anatomical site (such as the central nervous system [CNS], testis, skin, etc.) in the identification of specific lymphoma entities.

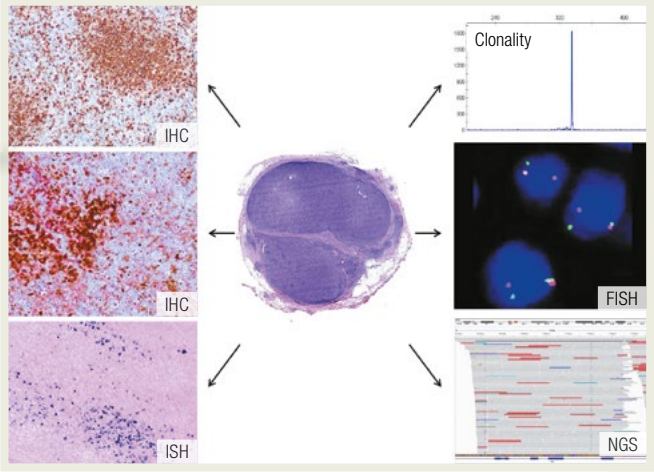
Clinical aspects such as age or immunodeficiency are also a distinct feature in some entities, e.g. paediatric-type FL or post-transplant lymphoproliferative disorders.

Histopathological diagnosis relies on morphology, immunophenotype and molecular data. Having sufficient tissue for this multiparameter approach is critical.

Excisional biopsies are preferred over core needle biopsies for the primary diagnosis of lymphoma. Fine-needle aspiration is generally inadequate for this purpose.

The diagnosis of lymphoid neoplasms requires the integration of histopathological data in the context of a complete clinical history.

Multiparametric approach to the diagnosis of lymphomas



IHC, immunohistochemistry; ISH: *in situ* hybridisation; FISH, fluorescent *in situ* hybridisation; NGS, next-generation sequencing.

Fig. 3.3

REVISION QUESTIONS

1. What are the basic principles in lymphoma classification?
2. Which lymphomas are presumed to derive from a germinal centre B cell?
3. What is one of the major limitations facing lymphoma diagnosis?

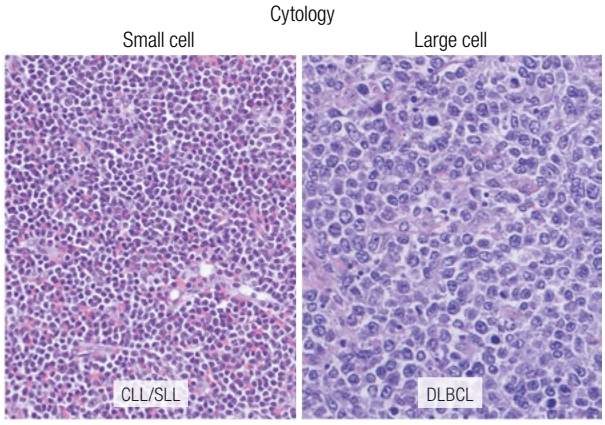
Cytological and histological diagnostic criteria

Cytological features are a mainstay of lymphoid neoplasms classification, with the size of the neoplastic cell being a fundamental diagnostic feature.

Mature small B-cell lymphoid neoplasms (e.g. FL, marginal zone lymphoma [MZL] or others) usually have a better prognosis than large B-cell lymphomas, which generally have a more aggressive course.

Mature T-cell lymphomas are usually composed of a heterogeneous population of small, medium-sized and large neoplastic T cells.

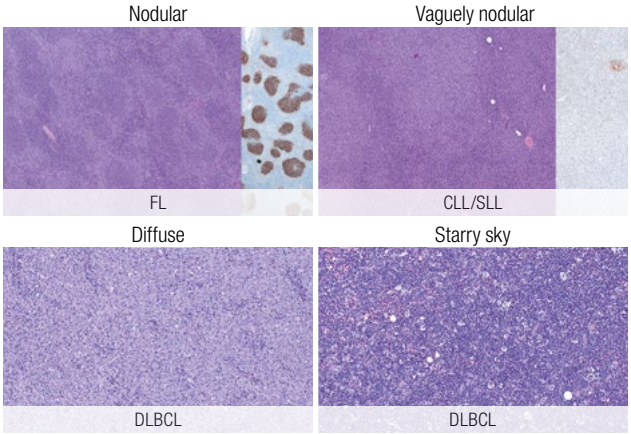
Cytological features of lymphoid neoplasms



CLL, chronic lymphocytic leukaemia; DLBCL, diffuse large B-cell lymphoma; SLL, small lymphocytic lymphoma.

Fig. 3.4

Architectural patterns of lymphoid neoplasms



CLL, chronic lymphocytic leukaemia; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; SLL, small lymphocytic lymphoma.

Fig. 3.5

The histological architecture is also an important feature for the diagnosis. For example, FL shows most frequently a nodular growth pattern.

The relationship between the neoplastic cells and the normal tissue can provide valuable information, such as lymphoepithelial lesions in mucosa-associated lymphoid tissue (MALT) lymphoma.

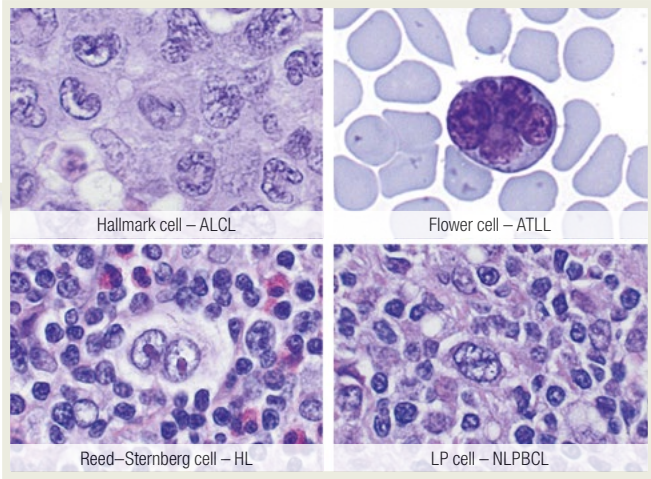
Regarding bone marrow infiltration, certain lymphomas have characteristic infiltration patterns: paratrabecular lymphoid nodules suggest infiltration by FL.

Certain lymphomas display characteristic cells with very distinctive features, such as 'hallmark' cells in anaplastic large cell lymphoma (ALCL) or Reed–Sternberg cells in Hodgkin lymphoma (HL).

The importance of the microenvironment in the pathogenesis and evolution of lymphomas is increasingly being recognised.

While B-cell lymphomas tend to be more monotonous, T-cell lymphomas and HL tend to be accompanied by a rich inflammatory 'milieu'.

Characteristic cell types of certain lymphoma entities



ALCL, anaplastic large cell lymphoma; ATLL, adult T-cell leukaemia/lymphoma; HL, Hodgkin lymphoma; LP, lymphocyte predominant; NLPBCL, nodular lymphocyte-predominant B-cell lymphoma.

Fig. 3.6

REVISION QUESTIONS

1. How does cytology help in distinguishing different lymphoma entities?
2. What are the main growth patterns of lymphoid neoplasms?
3. Name one lymphoma characterised by a rich inflammatory microenvironment.

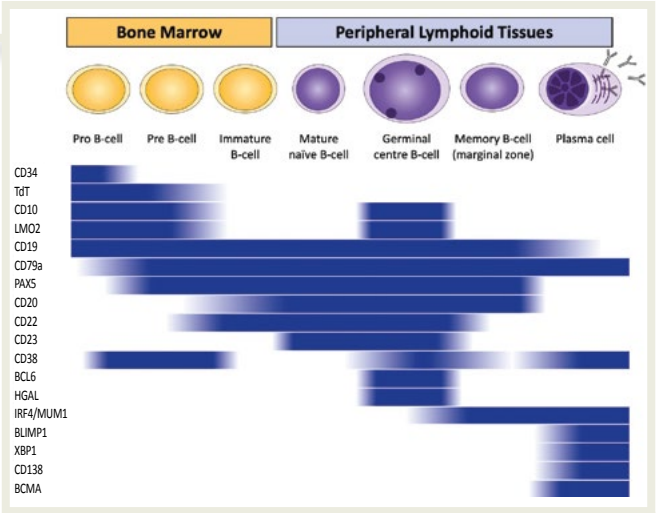
Immunophenotypic criteria for diagnosis

The stage of differentiation of lymphocytes may be recognised by their different surface antigen expression patterns (immunophenotype).

Lymphoid neoplasms can be characterised by their immunophenotype, which reflects that of their normal counterpart.

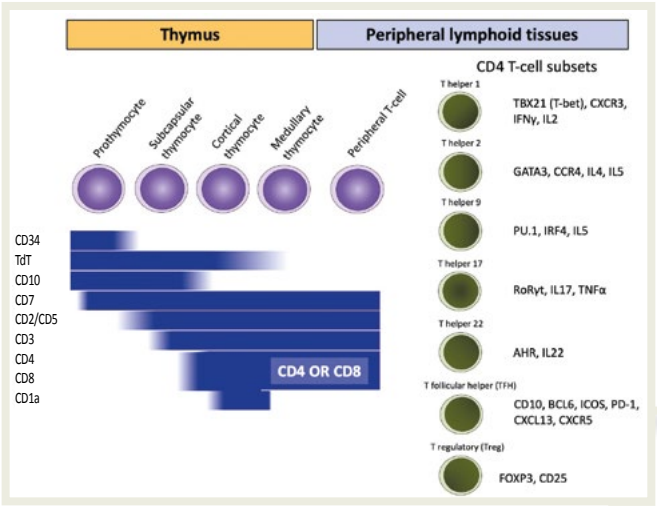
CD10 and B-cell lymphoma 6 (BCL6) are expressed by centrocytes and centroblasts, and are positive in germinal centre-derived lymphomas, such as FL or Burkitt lymphoma (BL).

B-cell antigen expression according to stage of development



BCL6, B-cell lymphoma 6. Fig. 3.7

T-cell antigen expression according to stage of development and to T-cell subsets



BCL6, B-cell lymphoma 6; IFNγ, interferon gamma; IL, interleukin; PD-1, programmed cell death protein 1; TNFα, tumour necrosis factor alpha. Fig. 3.8

TdT, CD34 and CD10 are expressed by B- and T-cell lymphoblasts and thus may be useful in recognising lymphoblastic leukaemia/lymphomas.

CD2, CD3, CD5 and CD7 recognise virtually all mature T cells and are useful in the diagnostic work-up of T-cell lymphomas.

T-follicular helper (TFH) lymphomas express Tfh cell markers such as CD10, programmed cell death protein 1 (PD-1), CXCL13 and inducible T-cell costimulator (ICOS).

Aberrant expression of CD5 (a T-cell marker) is a common feature of some B-cell lymphomas such as small lymphocytic lymphoma/chronic lymphocytic leukaemia (SLL/CLL) or mantle cell lymphoma (MCL).

Loss of T-cell markers (especially CD7) is common in mature T-cell lymphomas. Other common aberrant phenotypes include double expression or double negativity of CD4 and CD8.

Natural killer (NK) cells and NK-cell lymphomas have a specific immunophenotype with negativity for surface CD3 and positivity for CD16, CD56, CD57 and cytotoxic markers.

Aberrant immunophenotype or loss of expression of CD markers is an immunophenotypic feature suggesting the diagnosis of lymphoma

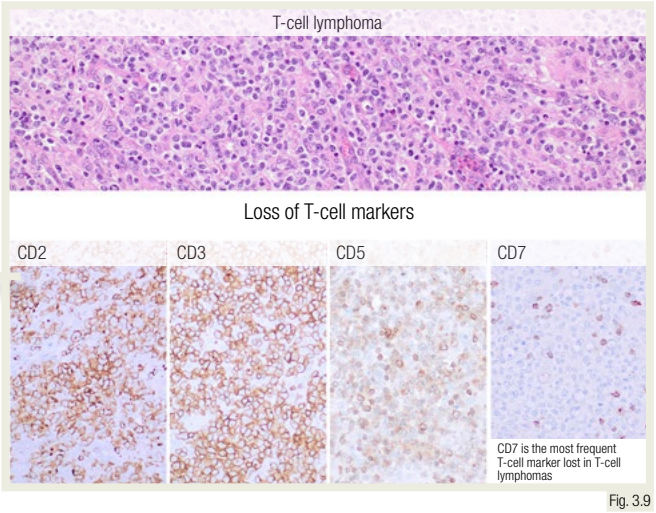


Fig. 3.9

REVISION QUESTIONS

1. List three typical markers of B cells.
2. Name two B-cell lymphomas that typically express the T-cell marker CD5.
3. Which lymphomas express Tfh markers?

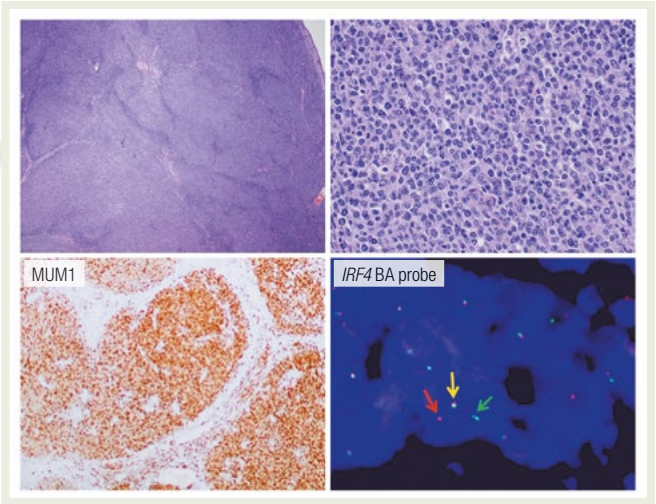
Molecular criteria for diagnosis

Molecular data is required for the diagnosis of some entities since some lymphomas are defined by a specific genetic abnormality.

Examples of this are large B-cell lymphoma with *IRF4* rearrangement or ALCL, anaplastic lymphoma kinase (*ALK*)-positive.

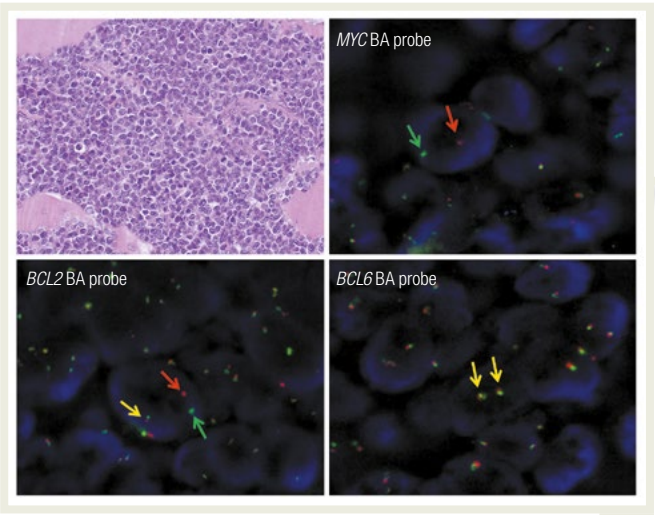
Some genetic aberrations can be recognised by surrogate immunohistochemistry (IHC) studies (e.g. *ALK* rearrangement detected by ALK protein expression).

Large B-cell lymphoma with *IRF4* rearrangement



BA, break-apart. Fig. 3.10

High-grade B-cell lymphoma, with *MYC* and *BCL2* rearrangements



BA, break-apart; BCL2/6, B-cell lymphoma 2/6. Fig. 3.11

Cytogenetic studies (both karyotype and fluorescent *in situ* hybridisation [FISH]) are important for the identification of specific genomic alterations.

FISH studies may aid in the diagnosis of FL (*BCL2*), MCL (*CCND1*), MALT lymphomas (*MALT1*), BL (*MYC*) and DLBCL (*MYC*, *BCL2* and *BCL6*).

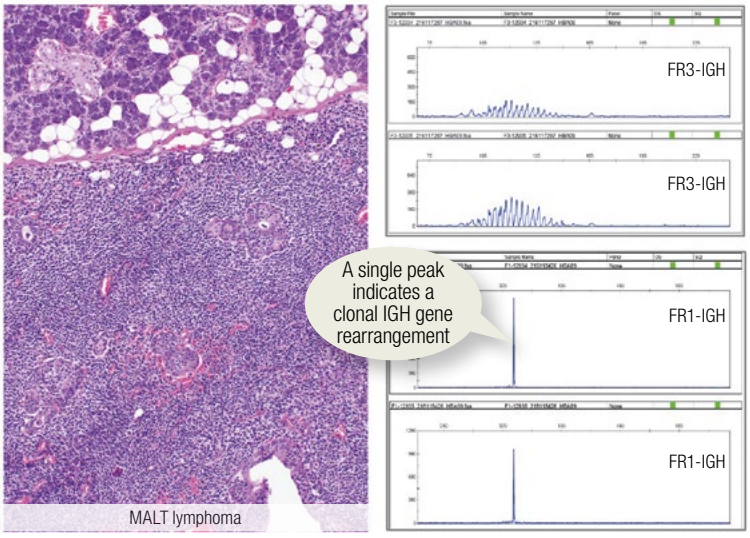
In contrast, most molecular abnormalities (such as *MYC*, *CCND1* or *BCL2* rearrangements), while characteristic of one entity, are not specific.

A monoclonal rearrangement of the immunoglobulin heavy chain (IGH) or T-cell receptor genes proves clonality. This is shown by a single peak in a polymerase chain reaction (PCR) analysis.

B- and T-cell clonality help in the differential diagnosis between some lymphomas and reactive processes or in determining the clonal relation of relapses/transformations.

Genomic studies have unveiled specific mutational signatures for different lymphomas. Targeted next-generation sequencing (NGS) panels have a role in diagnosis.

MALT lymphoma of the salivary gland displaying a clonal IGH rearrangement



IGH, immunoglobulin heavy chain; MALT, mucosa-associated lymphoid tissue. Fig. 3.12

REVISION QUESTIONS

1. Describe the role of cytogenetics in the diagnosis of lymphoid neoplasms.
2. How do NGS panels help in the routine diagnosis of lymphoid neoplasms?
3. In which cases is B- and T-cell clonality assessment helpful?

Emerging concepts

Molecular profiling studies have identified five to seven new functional genetic subgroups of DLBCL that may provide more precise patient stratification in the future.

It has been suggested that some of these DLBCL subgroups may represent transformations from different low-grade B-cell lymphomas.

The category of 'high-grade B-cell lymphoma with *MYC* and *BCL2* rearrangements' includes tumours with very aggressive behaviour.

Genetic subtypes of DLBCL

COO	HMRN	Harvard	LymphGen	Genetic Similarities with Other Lymphoma Entities
ABC	*MYD88*	C5	*MCD*	Primary extranodal (CNS, testis, skin) Lymphoplasmacytic lymphoma
	NEC	C2	*A53*	
		C0		
UNC	*NOTCH1*		*N1*	*NOTCH1*-mutant CLL
	NOTCH2	C1	*BN2*	Marginal zone lymphoma
	SOCS1/SGK1	C4	*ST2*	Primary mediastinal large B-cell lymphoma
	SOCS1/TET2			Nodular lymphocyte-predominant B-cell lymphoma T-cell histiocyte rich large B-cell lymphoma
GCB	*BCL2*	C3	*EZB*	Follicular lymphoma
	BCL2-MYC		*EZB-MYC*	Burkitt lymphoma

ABC, activated B cell; BCL2, B-cell lymphoma 2; CLL, chronic lymphocytic leukaemia; CNS, central nervous system; COO, cell-of-origin; DLBCL, diffuse large B-cell lymphoma; GCB, germinal centre B cell; HMRN; Haematological Malignancy Research Network; UNC, unclassified. Fig. 3.13

Clinical, biological and pathological features of GZL and related entities

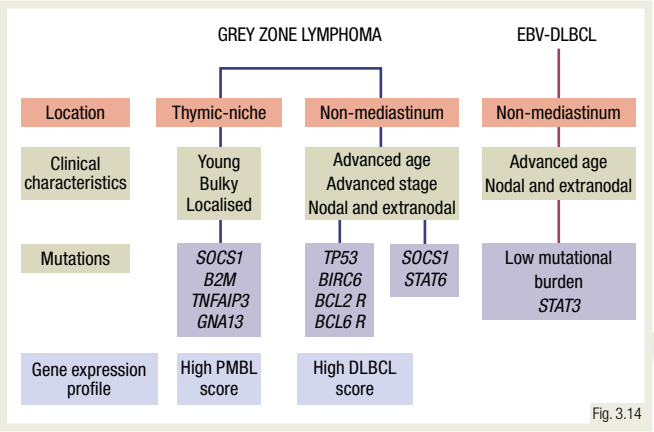


Fig. 3.14

BCL2/6 R, B-cell lymphoma 2/6 rearrangement; DLBCL, diffuse large B-cell lymphoma; EBV, Epstein–Barr virus; GZL, grey zone lymphoma; PMBL, primary mediastinal large B-cell lymphoma.

HL is characterised by the presence of a variable number of tumour cells, with a prominent inflammatory microenvironment.

The term nodular lymphocyte-predominant B-cell lymphoma replaces nodular lymphocyte-predominant HL in the ICC, recognising major clinical and biological differences from classical HL

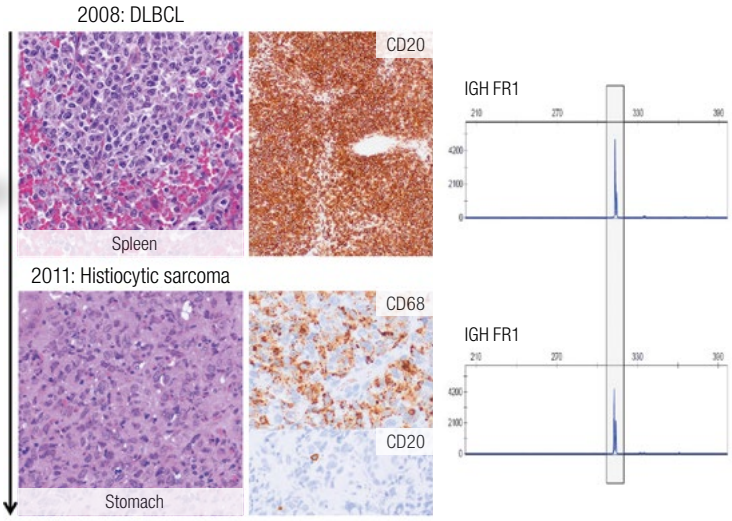
The term grey zone lymphoma (GZL) is restricted to mediastinal tumours (MGZL). Extramediastinal tumours are similar to DLBCL and should be diagnosed as DLBCL, not otherwise specified (NOS).

Transdifferentiation phenomena, such as the transformation from low-grade B-cell lymphomas to histiocytic sarcoma, highlight the plasticity of the haematopoietic system.

The emergence of novel biological treatments such as chimeric antigen receptor (CAR)-T-cell therapy encourages the incorporation of new markers in the work-up of some lymphomas.

The increasing biological knowledge of the entities allows for a greater refinement, and the emergence of new subtypes with clinical implications.

Example case of transdifferentiation



DLBCL, diffuse large B-cell lymphoma; IGH, immunoglobulin heavy chain. Fig. 3.15

REVISION QUESTIONS

1. What has been the impact of genomic studies in DLBCL?
2. How has genomic profiling helped in refining the classification of GZLs?
3. Name a phenomenon that highlights the plasticity of the haematopoietic system.

Summary: Basis for lymphoma classification

- Lymphomas are non-overlapping diseases stratified according to cell lineage
- Lymphoma entities are considered to be the malignant counterpart of a specific stage of lymphocyte differentiation
- Cytology, growth pattern and microenvironment are important morphological features for the diagnosis of lymphoid neoplasms
- Age, site and clinical features such as immunodeficiency are relevant aspects of some entities. Clinicopathological correlation is of utmost importance
- Immunophenotypic profiling determined by immunohistochemical staining or flow cytometry allows the characterisation of lymphocytes
- Aberrant or loss of expression of markers are features suggesting the diagnosis of lymphoid neoplasms
- Ancillary molecular techniques can be helpful in the diagnosis of certain entities, and are necessary for the diagnosis of others
- Different entities have different mutational profiles, whose identification with NGS gene panels may aid in the diagnosis
- The increasing biological knowledge allows a better subclassification of entities. Further research is needed to shed more light on some entities
- Given that the histological pattern may not be represented in core needle biopsies and the increase of the number of techniques necessary to reach a diagnosis, excisional biopsies are encouraged over needle biopsies

Further Reading

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Image sources: **Fig. 3.14.** Campo E, Jaffe ES. Blood 2021;137:1703-1704. All other figures courtesy of the authors.

4 Staging and response assessment in lymphoma patients

Clinical and biological evaluation

The standard initial assessment procedures include physical examination, performance status, blood tests with haemogram, proteinogram, renal and liver function tests and lactase dehydrogenase (LDH) measurement.

Imaging procedures include contrast-enhanced computed tomography (CECT) and positron emission tomography/computed tomography (PET–CT) in a single imaging session.

The above-mentioned investigations will allow the staging of the lymphoma according to the Ann Arbor classification and the most updated Lugano Classification.

PET–CT images

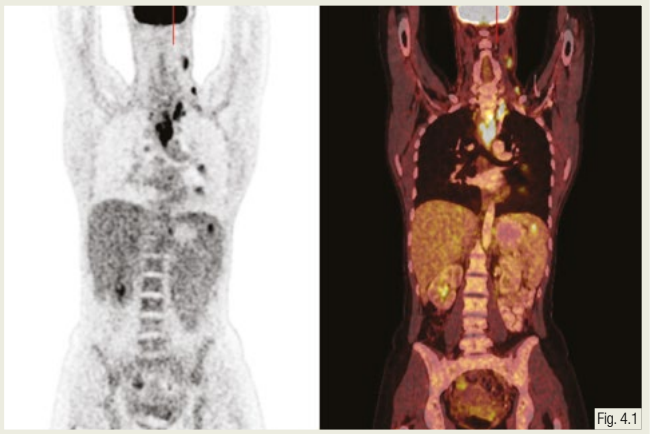


Fig. 4.1

CT, computed tomography; PET, positron emission tomography.

Tonsils and Waldeyer ring

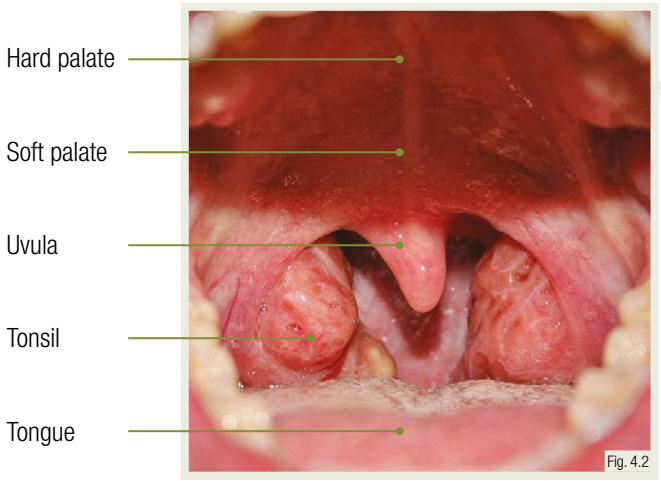


Fig. 4.2

Detailed medical history and physical examination are mandatory. Special attention is required for all superficial lymph nodes (LNs), Waldeyer ring, liver and spleen. Skin lesions should never be omitted.

B symptoms may not always be present. In Hodgkin lymphoma (HL) 25%-30% of patients present with fever (>38°C), night sweats, weight loss (>10% of body weight) and itching is also frequent.

Routine bone marrow biopsy (BMB) does not add relevant diagnostic or prognostic value over PET–CT in diffuse large B-cell lymphoma (DLBCL) and HL but remains mandatory in low-grade lymphoma.

Lumbar puncture should be done in high-risk DLBCL; endoscopic ultrasound (EUS) for staging gastric wall invasion and contrast-enhanced ultrasound (CEUS) for assessing lymphoma spread in the spleen.

Laboratory tests must include blood count, chemistry, protein electrophoresis, LDH, erythrocyte sedimentation rate, beta-2-microglobulin, albumin and a pregnancy test in women of childbearing potential.

Patients should also be checked for human immunodeficiency virus (HIV), viral hepatitis and *Helicobacter pylori* in gastric MALT (mucosa-associated lymphoid tissue).

MRI of MALT lymphoma of orbit

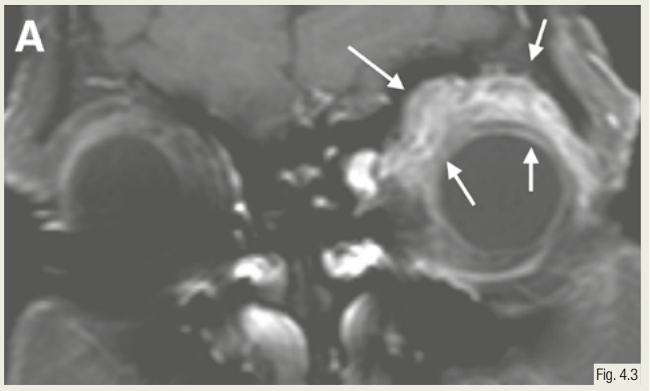


Fig. 4.3

MALT, mucosa-associated lymphoid tissue; MRI, magnetic resonance imaging.

REVISION QUESTIONS

1. Which lymphoma subtypes still require BMB?
2. Is there any role for other invasive diagnostic tools in lymphoma staging?
3. What is the role of clinical examination?

Clinical and biological evaluation (continued), PET–CT in lymphoma staging

Next-generation sequencing (NGS) to detect cell-free DNA in patients' blood was recently proven to be a very sensitive tool for minimal residual disease (MRD) assessment in HL and DLBCL.

Whole-body CECT is done to detect occult nodal and extranodal disease. Cranial magnetic resonance imaging (MRI) is required for patients with central nervous system lymphoma.

A 'bulky nodal lesion' is defined as a single nodal mass of 10 cm or greater than a third of the transthoracic diameter determined by CT.

Mediastinal bulky lesion

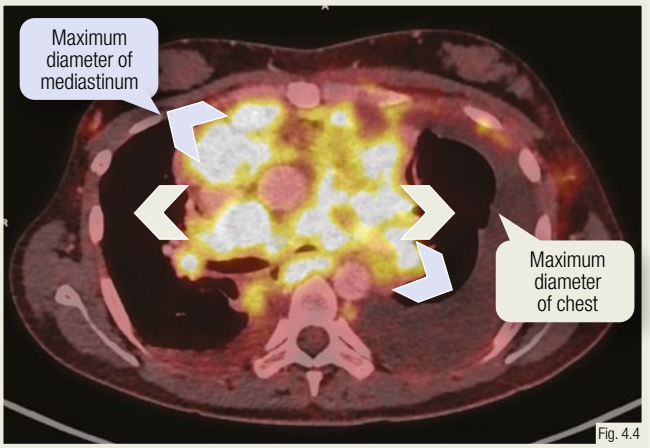
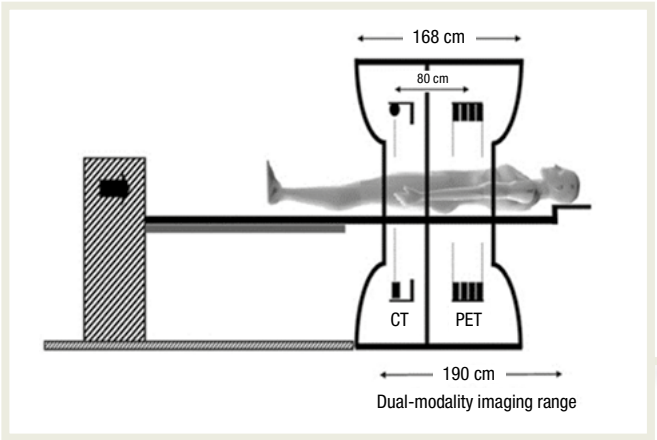


Fig. 4.4

Integrated PET–CT scanner



CT, computed tomography; PET, positron emission tomography.

Fig. 4.5

^{18}F-fluorodeoxyglucose (FDG)–PET has become the main imaging tool for tumour staging and restaging in lymphoma, with some exceptions, such as chronic lymphocytic lymphoma (CLL), small lymphocytic lymphoma and cutaneous lymphoma.

PET can detect more nodal and extranodal areas than CT; 10%-25% of patients are upstaged by PET, sometimes resulting in a change in management.

In modern PET–CT scanners, PET and CT are performed in a single imaging session, using CT for attenuation correction of PET.

The limit of resolution of current PET systems to detect tumours generally ranges between 0.5 and 1 cm, which translates into an estimated 10^8-10^9 cells.

In the PET era, trephine BMB has been proven unnecessary in HL since very few patients were upstaged by BMB, but none had their treatment changed.

In HL, only focal FDG uptake is considered a harbinger of BM invasion by lymphoma, while diffuse uptake portrays an unspecific reaction to inflammatory cytokines.

Focal lesion in bone marrow in HL

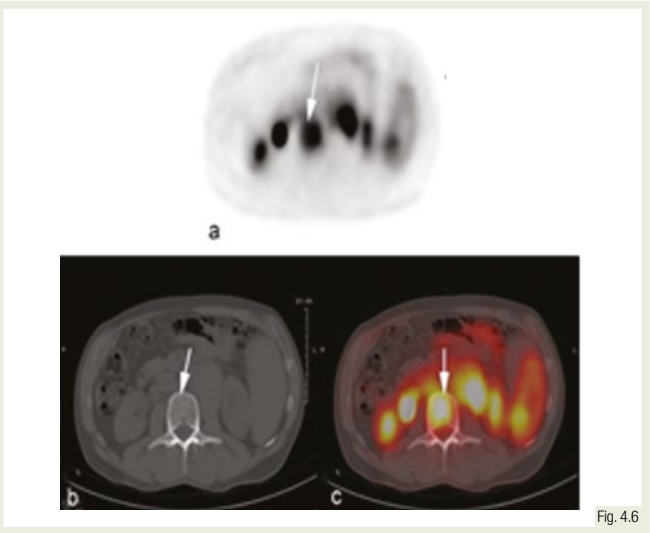


Fig. 4.6

HL, Hodgkin lymphoma.

REVISION QUESTIONS

1. What is the 'gold standard' imaging test in lymphoma?
2. What imaging modality is required for patients with central nervous system lymphoma?
3. What is the meaning of a diffuse BM FDG uptake in HL?

PET–CT in lymphoma staging (continued)

In DLBCL staged by PET–CT, BMB proved useful to detect BM invasion by lymphoma only in discordant cases with a low-grade component spread in BM.

PET image interpretation is based on qualitative visual assessment. Pathological uptake is defined as a focal or diffuse FDG uptake with a higher intensity compared with background.

SUV mathematical formula

$$SUV\ (g/ml) = \frac{C_{(T)}}{Dose\ (MBq)/weight\ (kg)}$$

C, concentration; SUV, standardised uptake value; T, time.

Fig. 4.7

SUV (standardised uptake value) is a semi-quantitative interpretation of a PET scan: ratio of tissue radioactivity concentration (C; kBq/mL) at time (T) and administered dose (MBq) at the time of injection divided by body weight (kg).

Tumour segmentation

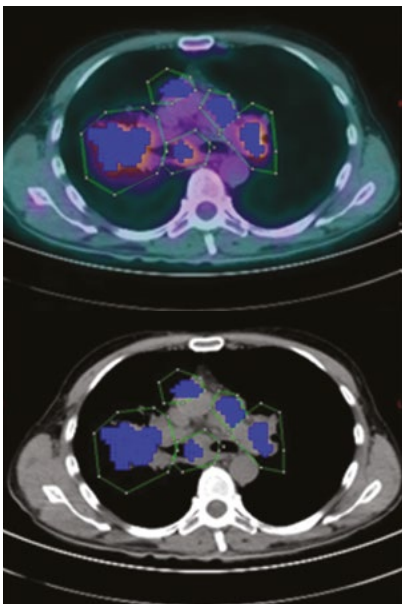


Fig. 4.8

SUV is the starting metric to measure total metabolic tumour volume (TMTV). To calculate MTV, all tumour masses should be manually contoured by an expert imaging physician, or automatically by dedicated software.

An algorithm to compute MTV starts with tumour segmentation, drawing a 3D map of every single voxel measured inside the contoured mass.

Thresholding: only voxels with a SUV comprised between the SUVmax and a given SUV threshold are computed to correct the spatial partial volume effect.

The threshold could be a fixed percentage of SUV, for instance 41%, or an absolute value, i.e. SUV >2.5. The physiological sites of FDG uptake are manually removed.

The sum of all the computed voxels in all the MTV sites allows the calculation of TMTV (cm^3). Total lesion glycolysis is computed by multiplying TMTV x SUVmean.

TMTV, which behaves as a continuous variable, proved to be a powerful and independent predictive tool of treatment outcome in different lymphoma subtypes such as DLBCL, HL and others.

Total metabolic tumour volume (TMTV)

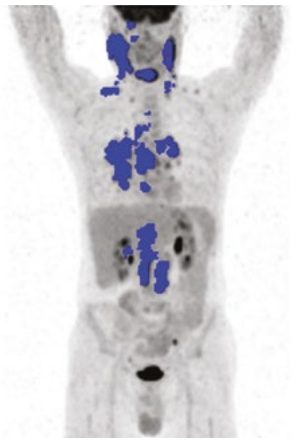


Fig. 4.9

REVISION QUESTIONS

1. What is the standard PET reading: qualitative or quantitative?
2. What is the standard unit of measurement for quantitative PET?
3. Does TMTV predict outcome in patients with lymphoma?

PET in lymphoma treatment monitoring and restaging

Another interesting prognostic index calculated in the baseline PET–CT is 'tumour distance' (Dmax).

Dmax is the longest distance (in cm) measured between pixels belonging to any two sites (nodal or extranodal) detected upon tumour segmentation among all the paired lesions of lymphoma spread.

Dmax, in advanced-stage HL and in negative interim PET (iPET) patients with International Prognostic Score (IPS) ≥2, is the only predictive marker of disease relapse in a multivariate analysis.

Tumour distance (Dmax)

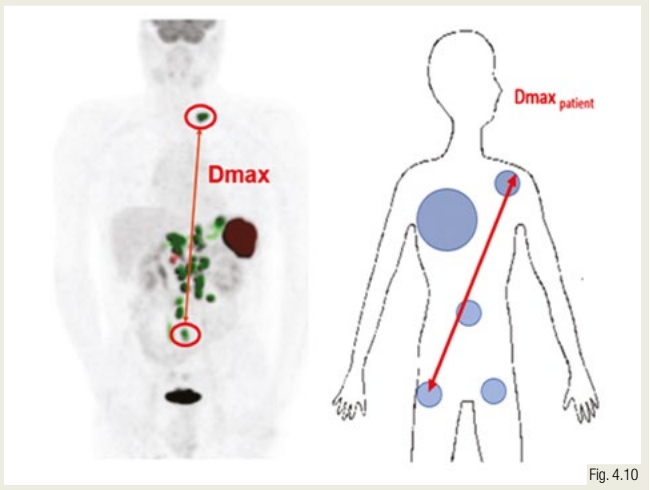


Fig. 4.10

Deauville 5-point scale

1. No uptake
2. Uptake ≤ mediastinum
3. Uptake > mediastinum but ≤ liver
4. Uptake moderately increased above liver at any site
5. Markedly increased uptake at any site including new sites of disease

Fig. 4.11

In 2014, during the 12th International Congress on Malignant Lymphoma, PET–CT was proposed as a standard imaging technique for lymphoma treatment monitoring and response assessment.

The interpretation key proposed for residual uptake grading was the Deauville 5-point scale, in which residual uptake is compared with standard uptake of mediastinum and of liver parenchyma.

The Deauville score (DS) was proposed as the interpretation key both for interim and end-of-treatment (EOT) PET scans, with a score ≤3 identifying patients in complete metabolic response.

iPET is performed after 2 chemotherapy (ChT) cycles in HL, peripheral T-cell lymphoma (PTCL) and follicular lymphoma (FL); and after 2 or 4 cycles in DLBCL (PET-2, PET-4).

In advanced-stage HL, iPET after 2 courses of ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) was the most important independent prognostic factor for progression-free survival (PFS).

In HL, iPET is considered a surrogate test for chemosensitivity allowing to guide subsequent treatment.

Interim PET in stage IIA (adverse)-IVB HL (n=260)

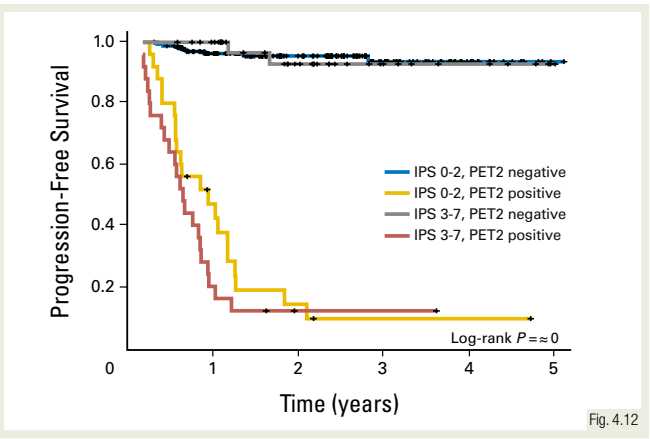


Fig. 4.12

HL, Hodgkin lymphoma; IPS, International Prognostic Score; PET, positron emission tomography.

REVISION QUESTIONS

1. What is the aim of measuring Dmax in lymphoma spread?
2. What is the clinical impact of iPET in HL?
3. What are the lymphoma subsets in which an iPET-adapted therapy is clinically useful?

PET in lymphoma treatment monitoring and restaging (continued)

In DLBCL, iPET showed a lower predictive value for treatment outcome, up to 40% of PET-2-positive patients experiencing long-term disease control.

Both qualitative evaluation by DS and semi-quantitative evaluation by SUVmax readings have been proposed for iPET in DLBCL.

In DLBCL, the best response criterion at iPET was ΔSUVmax (SUVmax reduction) with higher discriminative power and predictive values than currently used DS criteria.

Probability of EFS estimation according to PET status at mid-therapy (A) visual analysis, (B) SUVmax reduction

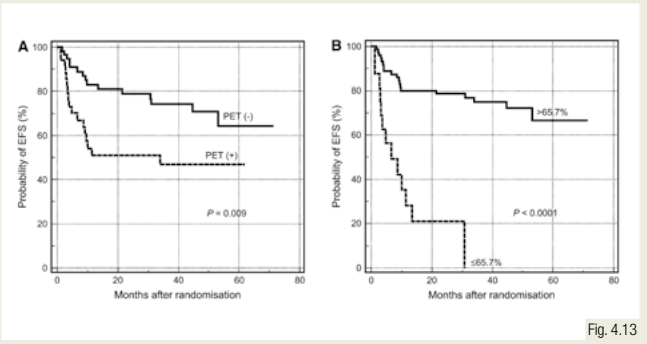


Fig. 4.13

EFS, event-free survival; PET, positron emission tomography; SUVmax, maximum standardised uptake volume.

End-of-treatment PET-CT DLBCL

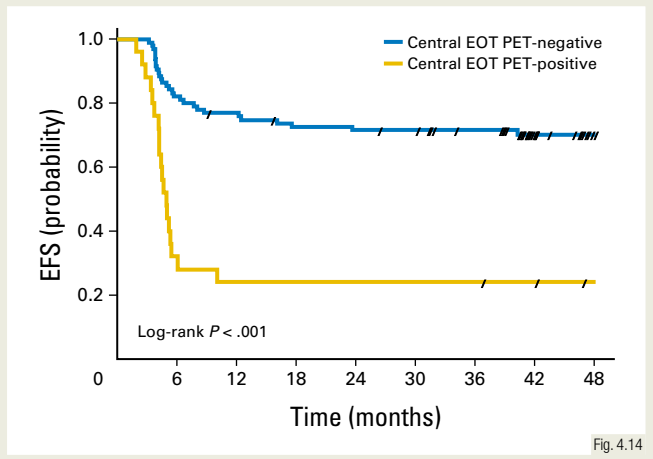


Fig. 4.14

CT, computed tomography; DLBCL, diffuse large B-cell lymphoma; EFS, event-free survival; EOT, end of treatment; PET, positron emission tomography.

In DLBCL, EOT PET showed a much higher predictive value on treatment outcome compared with iPET after 2 cycles of CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone).

Notably, PET-2 also proved to be predictive of treatment outcome in FL and PTCL.

Additionally, EOT PET was shown to be useful to guide consolidation radiotherapy for PET-positive residual masses persisting after ChT.

In patients with primary mediastinal large B-cell lymphoma (PMBCL), standard EOT PET has proven to be the most powerful predictor of treatment outcome.

However, new metrics extracted from baseline PET, such as metabolic heterogeneity (MH) and total lesion glycolysis (TLG), have also shown to be useful in predicting outcome.

High TLG combined with high MH at presentation identifies patients at high risk for progression after conventional therapy.

PFS according to a prognostic score based on the combination of MH and TLG at baseline

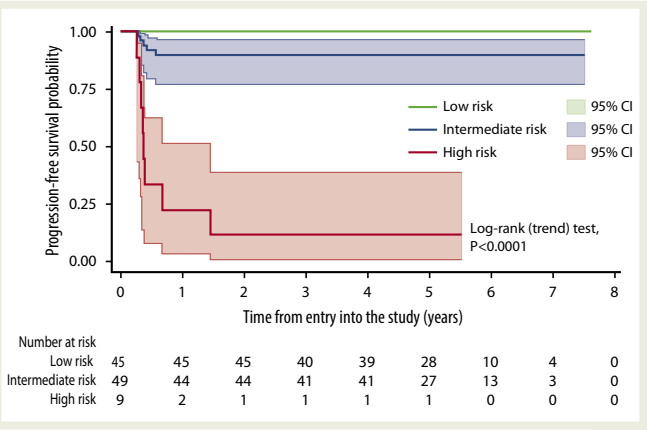


Fig. 4.15

CI, confidence interval; MH, metabolic heterogeneity; PFS, progression-free survival; TLG, total lesion glycolysis.

REVISION QUESTIONS

1. In DLBCL, what is the preferred time point for a PET-adapted therapeutic strategy?
2. What is the most accurate interpretation key for interim PET in DLBCL?
3. What are the strongest predictors of treatment outcome in PMBCL?

Summary: Staging and response assessment in lymphoma patients

- The standard procedures for lymphoma staging rely on physical examination, laboratory tests, imaging procedures and cytological/histological sampling. Special procedures should be reserved for specific lymphoma subtypes
- Lymphoma staging according to Ann Arbor classification is still mandatory, but new imaging techniques are currently being explored to measure the tumour burden
- Trephine BMB is no longer needed in HL and DLBCL, but it remains the only invasive tool needed to detect tumour spread in BM for FL, mantle cell lymphoma, PTCL and marginal zone lymphoma
- PET–CT remains the most accurate imaging tool for nodal and extranodal detection of disease spread in most lymphoma subtypes, except for lymphocytic lymphoma/CLL
- Semi-quantitative PET reading by SUVmax is used for MTV measurement. Lack of procedure standardisation still hampers its use in clinical practice, but harmonisation programmes are underway
- PET–CT is also the best tool to assess lymphoma treatment response both early during treatment and at EOT, as recommended by the 2014 Lugano Classification rules
- DS is the preferred interpretation key, but a semi-quantitative reading by ΔSUVmax is also used

Further Reading

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Image sources: **Fig. 4.1.** courtesy of Martin Hutchings, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark; **4.2.** https://emedicodiary.com/images/queimg/a6ad6c4e4585f2d8298f1e5d69ffe6d9.jpg; **4.3.** Ferreri AJ, et al. J Clin Oncol 2012;30:2988-2994; **4.4.** courtesy of David Chardin, Centre Antoine Lacassagne, Nice, France; **4.5. & 4.7.** courtesy of Nuclear Medicine Dept., Cuneo Hospital, Cuneo, Italy; **4.6.** courtesy of Anne Segolène Cottereau, Cochin Hospital, Paris, France; **4.8. & 4.9.** courtesy of Michel Meignan, Henri-Mondor University Hospital, Créteil, France; **4.10.** courtesy of Stephane Chauvie, S. Croce e Carle Hospital, Cuneo, Italy; **4.11.** courtesy of the authors; **4.12.** Gallamini A, et al. J Clin Oncol 2007;25:3746-3752; **4.13.** Lin C, et al. J Nucl Med 2007;48:1626-1632; **4.14.** Mamot C, et al. J Clin Oncol 2015;33:2523-29; **4.15.** Ceriani L, et al. Blood 2018;132:179-186.

5 Cytostatic treatments for lymphoma

Cytotoxic agents

Chemotherapy (ChT) and corticosteroids are the mainstay of lymphoma treatment, used either as single agents or in combination.

Alkylating agents were the first agents to show activity against lymphomas, which are very frequently treated with corticosteroids.

Doxorubicin revolutionised lymphoma treatment: diffuse large B-cell lymphoma (DLBCL) became curable with CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) and Hodgkin lymphoma (HL) with ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine), with lower risk of secondary leukaemia compared with previous regimens.

Cytotoxic agents and toxicities

Drug class	Drugs	Specific toxicity
Corticosteroids	Prednisone, methylprednisolone, etc.	Hyperglycaemia, osteonecrosis, osteoporosis, gastric ulcer
Alkylating agents	Chlorambucil, cyclophosphamide, ifosfamide, melphalan, DTIC, procarbazine, thiotepa, carmustine	Bone marrow failure, male oligospermic infertility, female anovulatory infertility, acute leukaemia, myelodysplasia
Anthracyclines	Doxorubicin, epirubicin	Cardiomyopathy
Cytotoxic antibodies	Bleomycin	Pulmonary fibrosis
Vinca alkaloids	Vincristine, vinorelbine, etc.	Peripheral neuropathy
Platinum derivatives	Cisplatin, carboplatin, oxaliplatin	Renal failure, peripheral neuropathy
Antimetabolites	Methotrexate, cytarabine, gemcitabine, fludarabine	Bone marrow failure, acute leukaemia, myelodysplasia
Topoisomerase inhibitor	Etoposide	Bone marrow failure, acute leukaemia, myelodysplasia

DTIC, dacarbazine.

Fig. 5.1

Anthracycline-induced cardiotoxicity

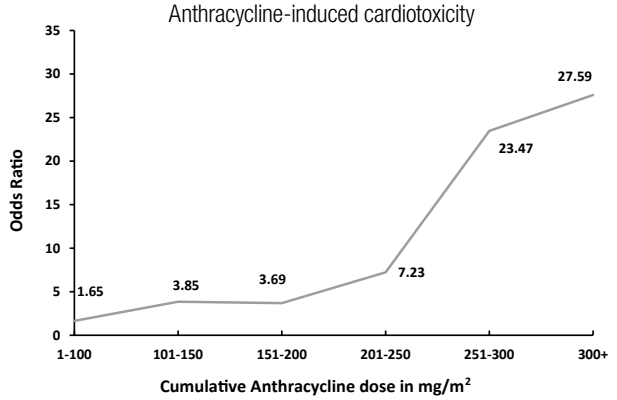


Fig. 5.2

Other drugs are usually added to the alkylating-anthracycline backbone, the choice of agents depending on single-agent anti-lymphoma activity and absence of cross-toxicities.

Due to the multiple treatments that these patients will receive, it is mandatory to know the maximum doses of each drug administered to prevent treatment-related toxicities.

Cumulative doses of >400 units of bleomycin are associated with increased risk for pulmonary toxicity, and cumulative doses of >450 mg/m² of doxorubicin with increased risk for cardiotoxicity.

Some lymphomas tend to relapse in the central nervous system (CNS) or cerebrospinal fluid (CSF), but the majority of cytotoxic drugs do not pass the blood–brain barrier (BBB).

To circumvent this problem, cytotoxic drugs such as steroids, methotrexate (MTX) or cytarabine (AraC), can be administered by direct intrathecal injection through a lumbar puncture.

Another possibility is to administer drugs that partly pass the BBB systemically at high doses (such as steroids, MTX, AraC, etoposide or thiotepa).

Intrathecal administration of cytostatics

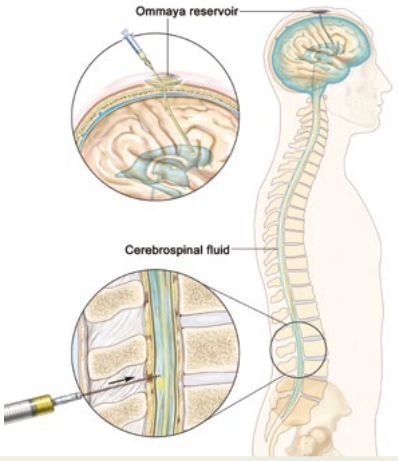


Fig. 5.3

REVISION QUESTIONS

1. Which drug has made aggressive lymphomas curable?
2. What is the maximum dose of anthracyclines and bleomycin to avoid/minimise toxicity?
3. How can ChT drugs reach therapeutic concentrations in the CNS?

Combination (immuno)chemotherapy

A combination of several cytotoxic drugs is used mainly for treatments with curative intent or to treat patients in whom a rapid and sustained response is desired.

When administering the first cycle to rapidly growing or bulky lymphomas, tumour lysis syndrome should be prevented with hydration and allopurinol or rasburicase.

To cure aggressive non-Hodgkin lymphomas (NHLs), appropriate dose intensity is essential. Doses and planned schedules should be maintained, if necessary, with the use of granulocyte colony-stimulating factor (G-CSF).

Effect of chemotherapy dose intensity and density on tumour cell kill and regrowth between cycles

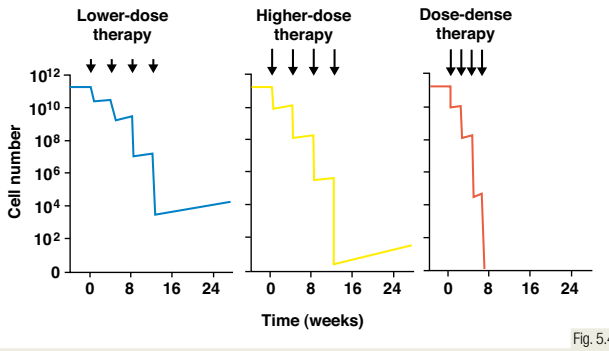


Fig. 5.4

CHOP given intravenously (i.v.) every 3 weeks is the most classical regimen for aggressive NHL. By adding rituximab, the regimen (R-CHOP) becomes more active for B-cell NHL.

How to improve on CHOP

Increasing the dose
Adding further cytotoxic drugs
Adding monoclonal antibodies
Continuous infusions
Reducing the intervals between cycles

Fig. 5.5

CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone.

R-MACOP-B (rituximab, MTX, leucovorin, doxorubicin, cyclophosphamide, vincristine, prednisone and bleomycin), R-CHOEP (rituximab, cyclophosphamide, doxorubicin, vincristine, etoposide and prednisone) and R-ACVBP (rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin and prednisone) are examples of more active but also more toxic regimens which were developed by adding further drugs.

The intensity can also be enhanced with the aid of G-CSF by administering cycles every 2 weeks (CHOP-14) or increasing the dose of some drugs (Mega-CHOP).

Finally, the activity of CHOP could be improved by administering some of the drugs as continuous infusion (as in the EPOCH [etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin] or hyper-CVAD [cyclophosphamide, vincristine, doxorubicin, methotrexate, cytarabine and dexamethasone] regimens).

Some of the more active regimens increase the response rate and the duration of responses, but they result in a higher toxicity so they do not improve overall survival (OS).

Bendamustine combinations with rituximab (B-R) are mainly used for indolent NHL and are generally well tolerated. Fludarabine combinations can also be used in this setting.

Response rate of first-line treatment in indolent lymphomas

Response	B-R	R-CHOP	R-FM
Overall	91.3%	92.7%	100%
Complete	40.1%	30.8%	90%
Partial	29%	20%	10%

Fig. 5.6

B-R, bendamustine-rituximab; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; R-FM, fludarabine, mitoxantrone and rituximab.

REVISION QUESTIONS

1. How can the efficacy of CHOP be increased?
2. Does a more active and more toxic regimen always improve survival?
3. How can tumour lysis syndrome be prevented?

High-dose therapy (HDT) and stem-cell transplantation

Some lymphoma clones respond to ChT in a dose-dependent way. In these cases, the administration of very high-dose drugs can be curative.

As some cytotoxic drugs and radiotherapy (RT) have myelosuppression as the main limiting toxicity, they can be given at very high doses (HDT) provided bone marrow (BM) toxicity is rescued.

Reinfusion of the patient's haematopoietic stem cells (autologous stem-cell transplantation [ASCT]) after the administration of the HDT results in BM rescue.

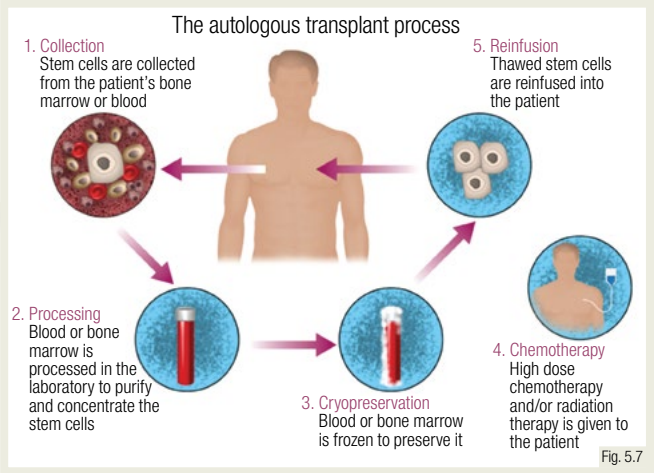


Fig. 5.7

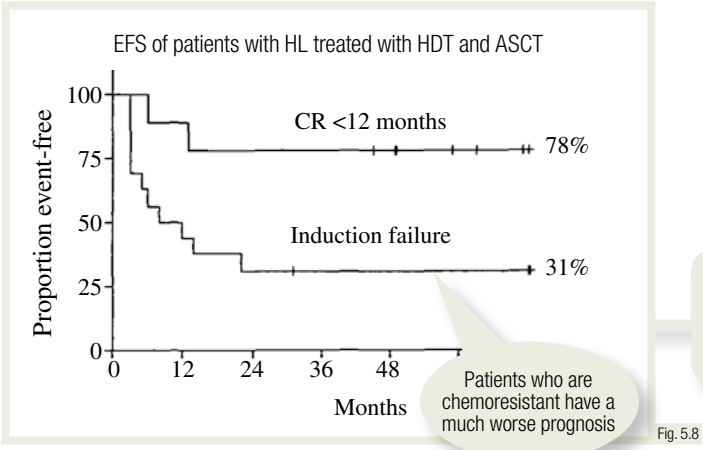


Fig. 5.8

ASCT, autologous stem-cell transplantation; CR, complete response; EFS, event-free survival; HDT, high-dose therapy; HL, Hodgkin lymphoma.

Stem cells used to be collected directly from the BM. At present, they are usually collected from the peripheral blood (PB) following mobilisation with G-CSF ± ChT.

HDT with ASCT is rarely used as part of the initial treatment of lymphoma, but mostly to consolidate a second or subsequent remission.

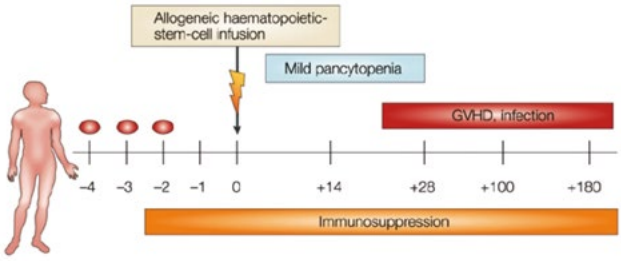
An essential condition for the success of HDT with ASCT is the chemosensitivity of the lymphoma, demonstrated by a response to salvage therapy.

The effect of allogeneic stem-cell transplantation (alloSCT) is based on a combination of cytotoxic and immune therapy. It requires the availability of a human leukocyte antigen (HLA)-compatible donor.

Conditioning cytotoxic regimens can be myeloablative (increased toxicity, only for younger patients) or reduced intensity conditioning (RIC), allowing an expansion of the indications.

RIC regimens rely on the immune effect of the donor graft mounting an anti-lymphoma response (graft-versus-lymphoma effect) rather than on its cytotoxicity.

Non-myeloablative allogeneic haematopoietic stem-cell transplantation



GVHD, graft-versus-host disease.
Fig. 5.9

REVISION QUESTIONS

1. What are the necessary conditions to proceed to HDT with ASCT?
2. What is the therapeutic effect of HDT with ASCT based on?
3. What is the therapeutic effect of alloSCT based on?

Summary: Cytostatic treatments for lymphoma

- Single-agent ChT can result in palliation, but curative treatment requires the use of multi-agent chemo(immuno)therapy, sometimes with the addition of monoclonal antibodies
- The most frequently used ChT regimens are CHOP for NHL and ABVD for HL
- Their efficacy can be increased by adding drugs, increasing doses, shortening intervals or by administration as continuous infusion
- ChT regimens should be given at their original dose and schedule, if necessary with the help of G-CSF
- It is mandatory to know the maximum doses of each drug administered to prevent treatment-related toxicities
- For rapidly-growing tumours or bulky disease, prevention of tumour lysis syndrome is mandatory
- In some situations, ChT can be given at high, myeloablative doses, with the support of autologous stem-cell rescue
- AlloSCT can be used in very selected cases to exploit the graft-versus-lymphoma effect

Further Reading

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6 Targeted treatment strategies in lymphoma

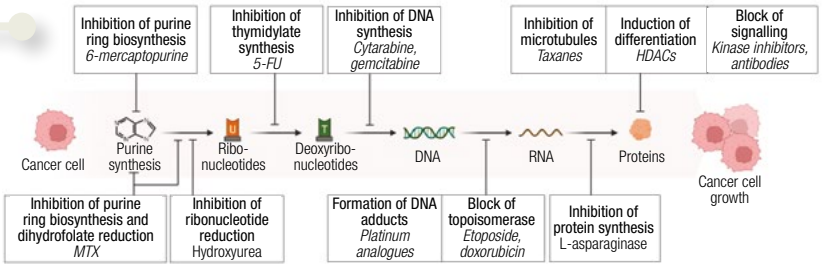
Development of targeted strategies

Conventional cytotoxic drugs work by unspecific inhibition of general functions of the cell machinery (e.g. DNA replication or mitotic spindle formation).

Their efficacy is based on the pronounced dependency of tumour cells over normal tissue but limited by a small therapeutic window and a high rate of adverse events (AEs).

Therefore, targeting specific and selective structures of the tumour cell may increase efficacy and reduce AEs.

Principles of cytotoxic chemotherapy



5-FU, 5-fluorouracil; HDAC, histone deacetylase; MTX, methotrexate. Fig. 6.1

Bispecific antibody mechanism of action as an example of targeted therapy for the treatment of B-cell lymphomas

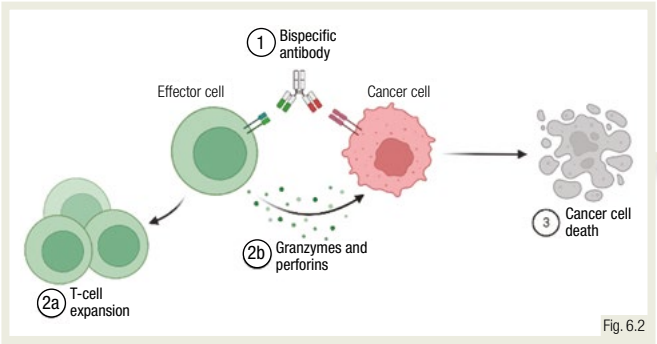


Fig. 6.2

The ideal target is characterised by its relevance for the survival of the tumour cell, dominant or exclusive presence in the pathological tissue, stable expression and drugability.

Targets may be restricted physiological structures, such as antigens or kinases, or tumour-specific targets, e.g. unphysiologically overexpressed proteins, or *de novo* targets caused by genetic rearrangements.

Tumour cells have shrunken signalling pathways, which limit the number of potential targets, and typically not all tumours of one entity depend on the same mechanism.

Currently, there are two major categories of targeted agents: monoclonal antibodies (mAbs) against surface antigens and small molecules interacting with kinases.

mAbs bind tumour antigens to activate the immune system or engage secondary mechanisms (drug delivery, radioisotopes or T-cell binding).

Small molecules interact with members of the signalling pathway; the most relevant among these are Bruton tyrosine kinase inhibitors (BTKis), B-cell lymphoma 2 inhibitors (BCL2is) and phosphoinositide 3-kinase inhibitors (PI3Kis).

Mechanism of antibody-based cancer therapies

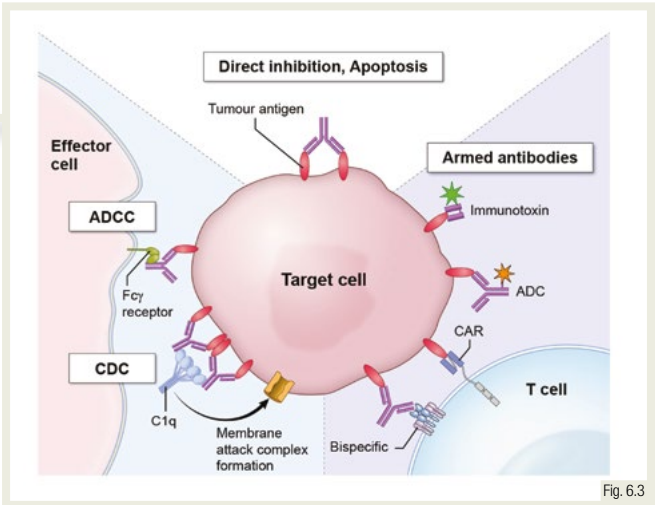


Fig. 6.3

ADC, antibody–drug conjugate; ADCC, antibody-dependent cell-mediated cytotoxicity; CAR, chimeric antigen receptor; CDC, complement-dependent cytotoxicity; Fcγ, fragment crystallisable gamma.

REVISION QUESTIONS

1. What disadvantages are related to conventional chemotherapies?
2. What are the requirements for an ideal therapeutic target?
3. Which categories of treatment are currently relevant in lymphoma treatment?

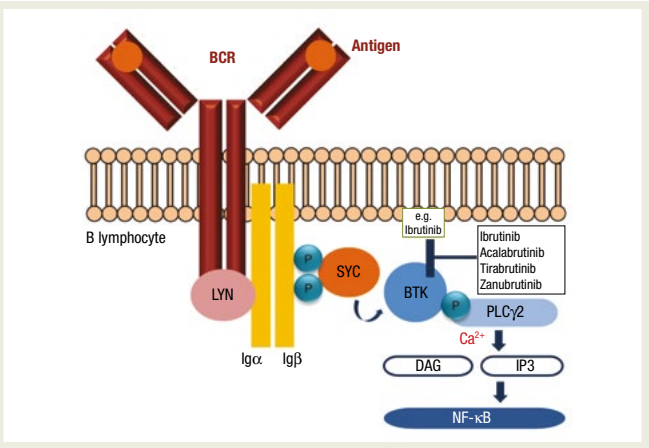
Signalling inhibitors

The B-cell receptor pathway is of particular importance and can be attacked at different levels; the inhibition of BTK is therefore currently the most relevant target.

BTK inhibition is effective in many but not all B-cell malignancies, as in chronic lymphocytic leukaemia (CLL), mantle cell lymphoma (MCL), Waldenström macroglobulinaemia (WM) and, recently, marginal zone lymphoma (MZL), with conflicting results in large B-cell lymphomas (LBCLs).

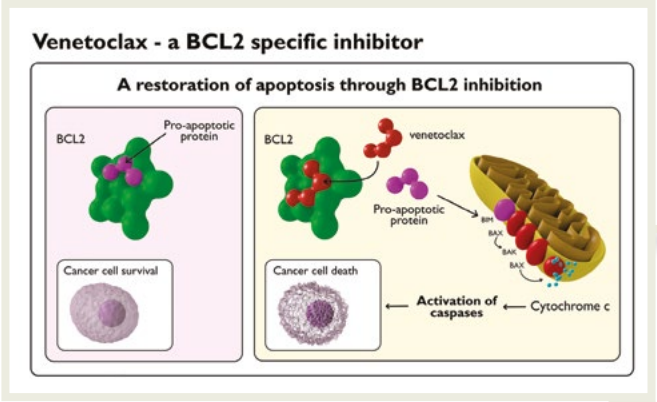
Ibrutinib was the first-in-class BTKi, with second- and third-generation BTKis showing better tolerability and maybe higher efficacy, e.g. acalabrutinib, zanubrutinib or pirtobrutinib.

B-cell receptor pathway inhibition by BTK



BCR, B-cell receptor; BTK, Bruton tyrosine kinase; Igα/β, immunoglobulin alpha/beta; NF-κB, nuclear factor-kappa B. Fig. 6.4

Targeting BCL2 – antiapoptotic pathway inhibition in lymphoma



BCL2, B-cell lymphoma 2. Fig. 6.5

BCL2 is a key protein regulator of apoptosis and is expressed in many lymphatic malignancies to abrogate apoptotic signals, as in CLL, MCL and WM or follicular lymphoma (FL).

Venetoclax is a first-in-class oral inhibitor of this pathway by mimicking BH3 activity and may be especially attractive in combination with BTKis.

The drug has been approved for CLL, is promising and still under evaluation in MCL, WM and MZL, while failing to show activity in LBCLs and FL.

PI3K is key in many intracellular signalling cascades, comprising four isoforms (alpha, beta, gamma, delta), with delta being the most relevant target for lymphoma treatment.

Idelalisib (alpha, delta) was the first drug to be approved in CLL and FL; however, it is associated with severe treatment-emergent AEs, predominantly infections.

Second-generation PI3Kis have been developed for better selectivity and improved tolerability, such as copanlisib (alpha, delta), duvelisib (delta) and umbralisib (delta).

Signalling pathways activated by different isoforms of Class I PI3K and PI3K inhibitors that target specific components of these pathways

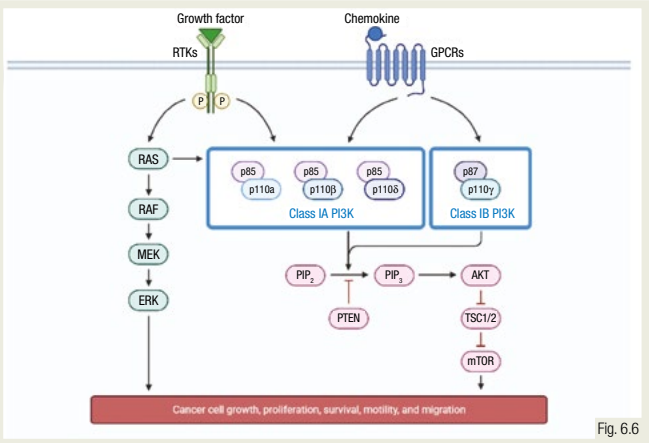


Fig. 6.6

GPCR, G protein-coupled receptor; mTOR, mammalian target of rapamycin; PI3K, phosphoinositide 3-kinase; PTEN, phosphatase and tensin homologue; RTK, receptor tyrosine kinase; TSC 1/2, tuberous sclerosis complex 1/2.

REVISION QUESTIONS

1. In which diseases do BTKis play a major role?
2. Which protection mechanism of tumour cells is neutralised by BCL2is?
3. What limits the usability of PI3Kis?

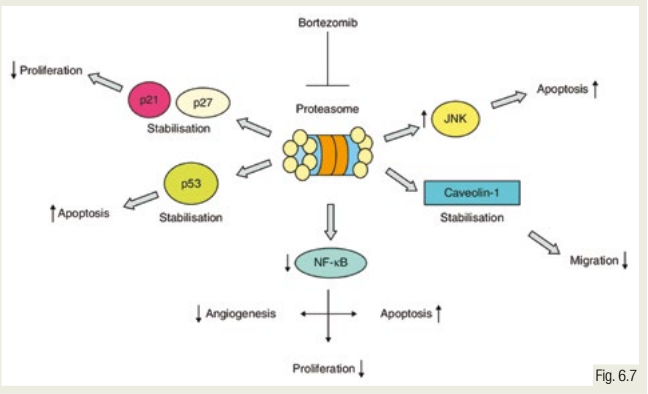
Signalling inhibitors (continued)

Proteasome inhibitors interfere with the protein haemostasis of the cell; bortezomib is approved for MCL and has demonstrated efficacy in WM and MZL.

Mammalian target of rapamycin (mTOR) inhibitors interact downstream of PI3K and have been used especially in MCL (temsirolimus and everolimus), but due to their toxicity profile have a limited role today.

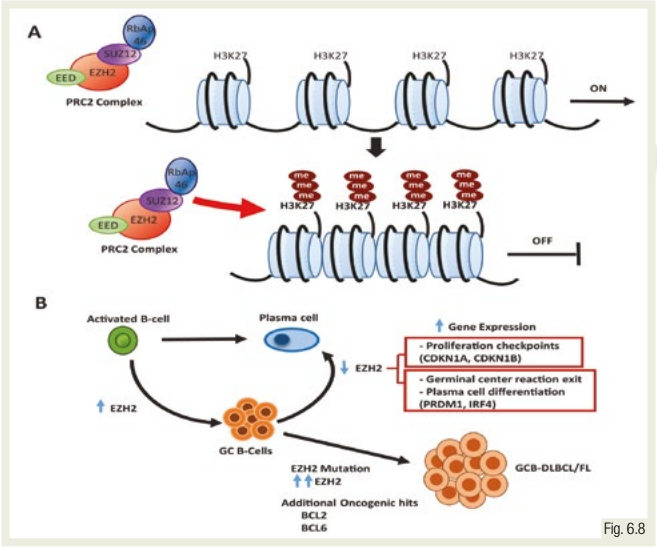
Exportin 1 (XPO-1) is a nuclear transporter protein, affected in lymphoid malignancies; it is inhibited by selinexor, which has been approved by the Food and Drug Administration (FDA).

Effects of proteasome inhibition by bortezomib. Alteration of several proteins leads to apoptosis, reduction of angiogenesis, migration and cellular proliferation



JNK, Jun N-terminal kinase; NF-κB, nuclear factor-kappa B.

EZH2 is an epigenetic regulator of B-cell identity in the germinal centre



BCL2/6, B-cell lymphoma 2/6; DLBCL, diffuse large B-cell lymphoma; EED, embryonic ectoderm development; EZH2, enhancer of zeste homologue 2; FL, follicular lymphoma; GC, germinal centre; GCB, germinal centre B-cell like; PRC2, polycomb repressive complex 2; RbAp 45, retinoblastoma-associated protein 46; SUZ12, suppressor of zeste 1.

Tazemetostat blocks EZH2 (enhancer of zeste homologue 2), a histone methyltransferase regulating germinal cell formation in normal B-cell biology; mutations can lead to oncogenic transformation by preventing B-cell differentiation.

Myeloid cell leukaemia 1 (MCL1) is an antiapoptotic protein of the BCL2 family with high expression in many lymphoid malignancies.

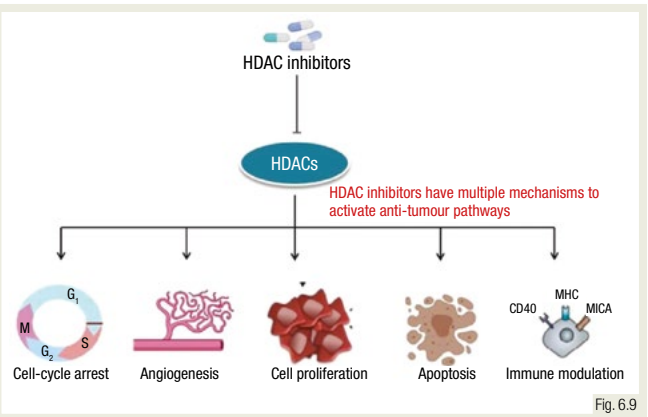
Mucosa-associated lymphoid tissue 1 (MALT1) plays a critical role in suppressing immune reactions against tumour cells; inhibition results in reprogramming of regulatory T cells and reactivation of immune responses.

Histone deacetylase (HDAC) inhibitors represent an epigenetic treatment, which has been tested in a variety of lymphomas, namely T-cell malignancies, with limited activity and substantial toxicity.

NOTCH inhibitors have been tested to inhibit gamma-secretase activity, but also demonstrated substantial toxicity and limited activity.

Cyclin-dependent kinase 6 (CDK6) inhibitors have been explored in MCL and diffuse large B-cell lymphoma (DLBCL) but did not provide substantial benefit.

Mechanisms of HDAC inhibition



HDAC, histone deacetylase; MHC, major histocompatibility complex.

REVISION QUESTIONS

1. Which additional targeted agents have been approved for lymphoid malignancies?
2. Which targets are being addressed in current research?
3. Which drugs failed to prove benefit in lymphoid malignancies?

Summary: Targeted treatment strategies in lymphoma

- Targeted therapies interact with key pathways of cell proliferation and the tumour microenvironment
- Among the so-called small molecules, BTKis and BCL2is are already established in clinical routine, whereas PI3K, mTOR and proteasome inhibitors play only limited roles
- Currently, novel BTKis, PI3Kis and inhibitors of EZH2, MALT1 and MCL1 are in clinical development
- Combinations of different targeted therapies (to establish chemotherapy-free approaches) or addition of targeted therapies to chemotherapy are currently being studied in clinical trials in a variety of lymphoid malignancies
- Targeted therapies harbour a differential side effect profile, basically due to off-target effects or interaction with physiological mechanisms, which underlines the necessity for optimally designed agents

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Image sources: **Fig. 6.1, 6.2 & 6.6** Created with BioRender.com; **6.3.** Ho M. Antib Ther 2018;1:1-5; **6.4.** Kim HO. Arch Pharm Res 2019;42:171-181; **6.5.** Mihalyova J, et al. Exp Hematol 2018;61:10-25; **6.7.** Russo A, et al. Expert Opin Ther Targets 2007;11:1571-1586; **6.8.** Gulati N, et al. Leuk Lymph 2018;59:1574-1585; **6.9.** Shanmugam G, et al. Transl Oncol 2022;16:101312.

7 Immunotherapy

Monoclonal antibodies

Lymphoma immunotherapy comprises various treatments including monoclonal antibodies (mAbs), bispecific antibodies (BsAbs), adoptive cellular therapies and immune checkpoint inhibitors (ICIs), which harness the power of the immune system to fight disease.

These drugs or procedures stimulate the immune system to recognise and attack lymphoma cells.

Depending on definitions, allogeneic stem-cell transplantation can also be regarded as an immunotherapy.

The main classes of immunotherapy in lymphoma

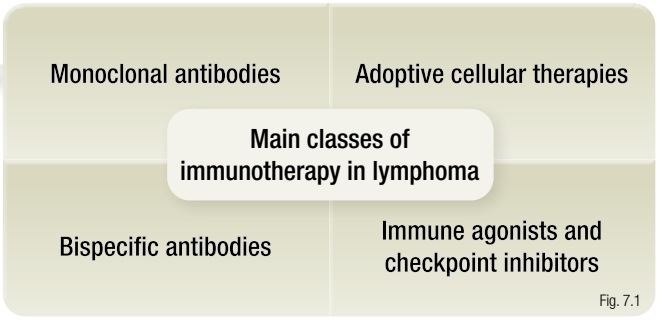

Fig. 7.1

Cytotoxicity of unconjugated monoclonal antibodies

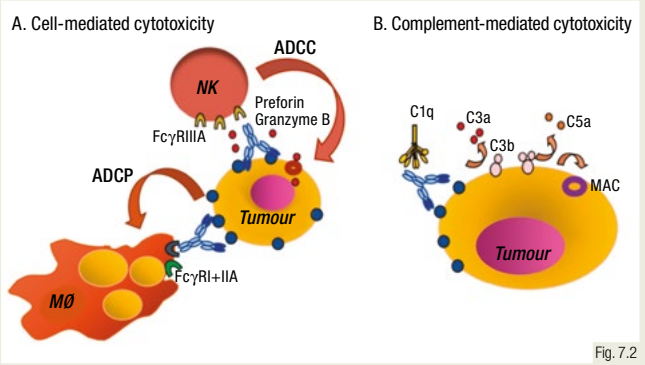

Fig. 7.2

ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; MØ, macrophage; MAC, membrane attack complex; NK, natural killer.

mAbs are most often reserved for those immunotherapies where the antibody binds only to a cancer cell and not to an immune effector cell.

mAbs bind to antigens stably expressed on the lymphoma cell and specific to the tumour. Unconjugated mAbs act via antibody-dependent cytotoxicity, complement-dependent cytotoxicity or by induction of phagocytosis.

Examples of unconjugated ('naked') mAbs used in lymphomas are rituximab and obinutuzumab (anti-CD20), tafasitamab (anti-CD19) and mogamulizumab (anti-CCR4).

Conjugated mAbs direct the attached effectors to the lymphoma cells. Such effectors can be radioisotopes or cytotoxic drugs resulting in antibody–drug conjugates (ADCs).

Upon binding to the lymphoma cell, the ADC is internalised into the cell via endocytosis. Once inside the cell, the ADC is broken down by lysosomal enzymes, releasing the cytotoxic drug.

ADCs function independently of the lymphoma's immune microenvironment. In lymphoma, ADCs are brentuximab vedotin (anti-CD30), loncastuximab tesirine (anti-CD19) and polatuzumab vedotin (anti-CD79b).

Mechanism of antibody–drug conjugates

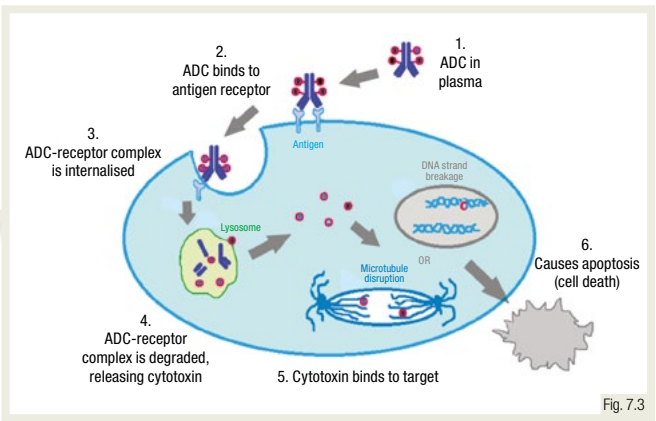

Fig. 7.3

ADC, antibody–drug conjugate.

REVISION QUESTIONS

1. Which are the four main types of immunotherapy in lymphoma?
2. What characterises an ideal target for antibody-based immunotherapy?
3. Is the activity of ADCs dependent on the immune cells in the lymphoma microenvironment?

BsAbs and chimeric antigen receptor (CAR)-T-cell therapy

BsAbs are designed to simultaneously target two different antigens, one on the lymphoma cell and another on an immune effector cell (typically a T cell but can also be natural killer [NK] cells or macrophages).

The formation of a tight immunological synapse between the lymphoma cell and the T cell leads to T-cell activation and cell kill using cytotoxic granules and to local T-cell proliferation and the release of cytokines/chemokines, resulting in enhanced T-cell recruitment.

There are many BsAbs under development, as well as trispecific antibodies.

Mechanism of action of the bispecific T-cell engaging antibodies

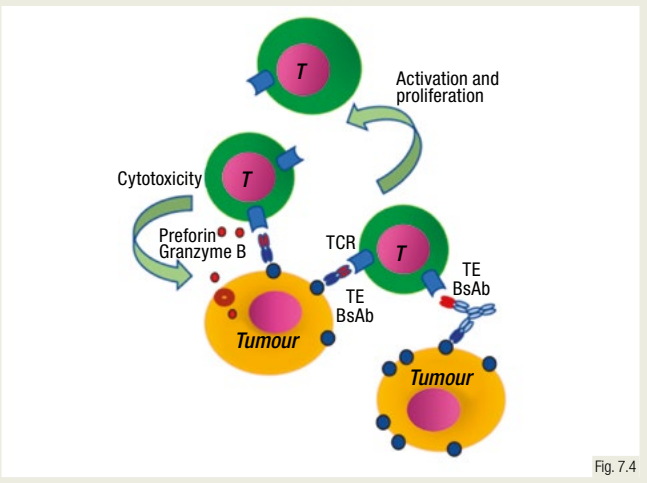

Fig. 7.4

T, T cell; TCR, T-cell receptor; TE BsAb, T-cell engaging bispecific antibody.

Production of CAR-T cells for lymphoma treatment

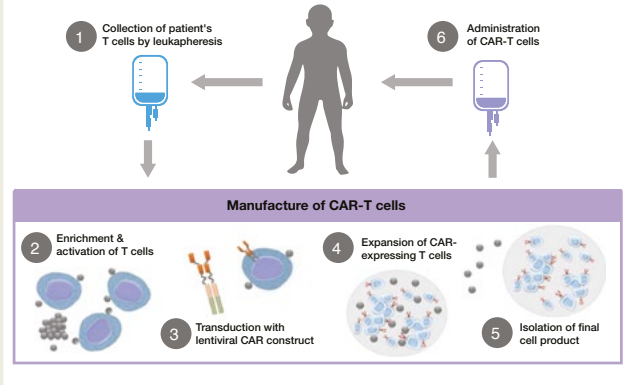

Fig. 7.5

CAR, chimeric antigen receptor.

CAR-T cell therapy is an adoptive cellular therapy which involves modifying a patient's T cells to attack cancer cells.

T cells are collected from the patient's blood and transfected via a genetically engineered viral vector to give them a new sequence of DNA which codes for the new receptor (the CAR). Once the CAR-T cells have been produced, they are infused back into the patient's bloodstream.

Other CAR therapies are under development, including CAR-NK cells, bispecific CARs targeting two different lymphoma antigens and allogeneic CAR-T cells.

CAR-T cells express a CAR on their surface.

The CAR has an extracellular domain that recognises a specific antigen on the surface of cancer cells, a transmembrane domain that anchors the receptor to the T-cell membrane, and an intracellular domain that activates, stimulates and enhances the function of the T cell when the CAR binds to its target.

The binding of the CAR-T cells to the target antigen on the lymphoma cells triggers a series of events inside the T cells, which lead to the destruction of the cancer cell by a mechanism related to that of the bispecific T-cell engaging antibodies.

Basic structure of the chimeric antigen receptor

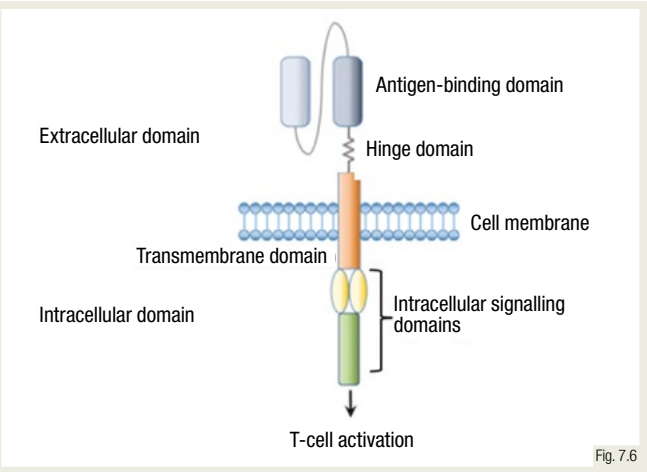

Fig. 7.6

REVISION QUESTIONS

1. Which cells are most commonly the effector cells activated by BsAbs in lymphoma?
2. What is the difference between BsAbs and CAR-T cells?
3. Is a CAR a mAb?

Other immunotherapies: ICIs, allograft, immunomodulatory drugs

Immune checkpoints prevent the immune system from attacking healthy cells. The survival of some cancer cells, including lymphomas, relies on the activation of checkpoints, the most well-known being programmed cell death protein 1 (PD-1).

PD-1 is expressed on T cells and interacts with its ligands, programmed death-ligand 1/2 (PD-L1/2), expressed on some lymphoma cells, leading to T-cell exhaustion and downregulation of immune response (Fig. 7.7a).

When these checkpoints are inhibited by specific drugs (anti-PD-1/PD-L1 mAbs), T cells are reactivated and can recognise and attack the lymphoma (Fig. 7.7b).

Mechanism of anti-PD-1 immune checkpoint inhibition

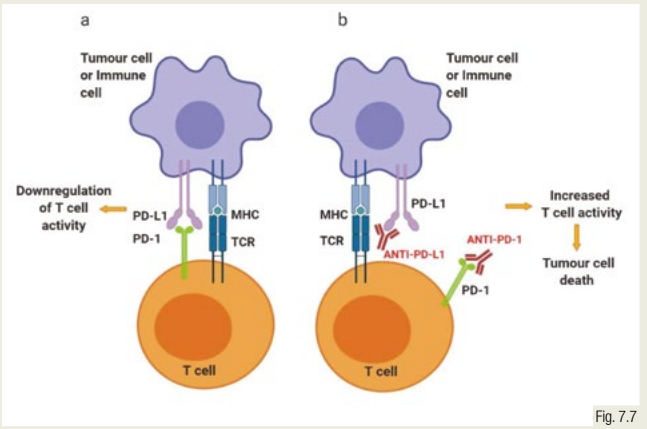

Fig. 7.7

MHC, major histocompatibility complex; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; TCR, T-cell receptor.

Allograft principle

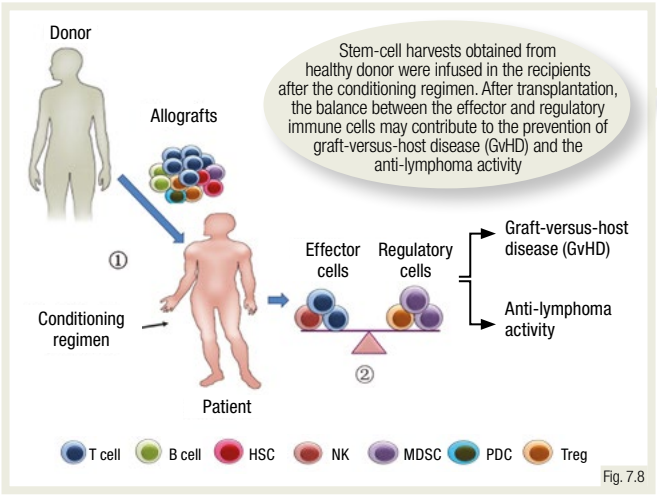

Fig. 7.8

HSC, haematopoietic stem cell; MDSC, myeloid-derived suppressor cell; NK, natural killer; PDC, plasmacytoid dendritic cell; Treg, regulatory T cell.

Allograft or allogeneic progenitor cell transplantation is a potentially curative treatment affording long-term remission for patients in whom conventional therapy for lymphoma has failed.

Several series have reported the benefit of allograft in indolent and aggressive lymphomas, particularly T-cell lymphomas, as well as in Hodgkin lymphoma.

However, the high transplantation-related mortality (TRM) rate, 20%-40%, makes this procedure difficult to recommend.

Immunotherapy combinations represent an appealing strategy in the treatment of B-cell non-Hodgkin lymphomas.

These combinations will explore how to synergise the activities of each drug, without them competing against one another. This will include (A) ICIs; (B) tyrosine kinase inhibitors (TKIs); (C) immunomodulatory imide drugs (IMiDs); (D) chemotherapy; (E) ADCs; and (F) costimulatory BsAbs.

Toxicities will have to be closely monitored in this context.

Potential treatment combinations including T-cell redirecting treatment

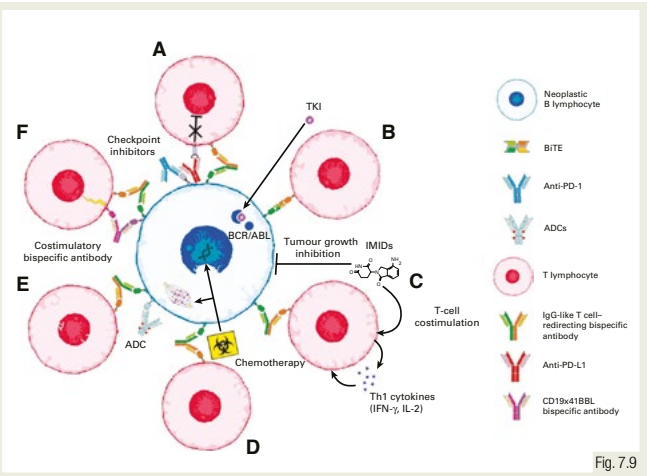

Fig. 7.9

ADC, antibody–drug conjugate; BiTE, bispecific T-cell engager; IFN-γ, interferon gamma; IgG, immunoglobulin G; IL-2, interleukin 2; IMiD, immunomodulatory imide drug; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; TKI, tyrosine kinase inhibitor.

REVISION QUESTIONS

1. Is PD-1 expressed on lymphoma cells?
2. What is the TRM rate reported in patients with relapsed/refractory lymphoma when treated by allograft?
3. Is the best strategy in B-cell lymphoma a combined strategy?

Summary: Immunotherapy

- Lymphoma immunotherapy stimulates the immune system to recognise and attack lymphoma cells, thus enhancing the body's natural defence mechanism against the disease
- These immunotherapies include mAbs, BsAbs, CAR-T cell therapy and ICIs
- Ideal antigens ('targets') for lymphoma immunotherapy should be highly expressed on the lymphoma cells, lack a soluble form, be specific to the tumour and should not be too highly expressed on normal cells
- Unconjugated mAbs act through antibody-dependent cytotoxicity, complement-dependent cytotoxicity or induction of phagocytosis
- ADCs are cytotoxic drugs attached to mAbs; upon binding to the lymphoma cell, the conjugate is internalised into the cell and degraded, leading to release of the cytotoxic drugs
- BsAbs bind to an antigen on the lymphoma cell and to an antigen on an immune effector cell, leading to direct cytotoxic killing of the lymphoma cell
- CAR-T-cell therapy is an adaptive cellular therapy which involves modifying a patient's T cells to attack cancer cells
- ICIs are mAbs targeting certain cell-cell interactions which prevent the immune cells from attacking the cancer cells
- Allograft or allogeneic progenitor cell transplantation is a potentially curative treatment. However, in the context of novel immunotherapies and of the high TRM rate, this procedure is difficult to recommend
- Combined use of immunotherapies represents an appealing strategy in the treatment of B-cell non-Hodgkin lymphomas

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Image sources: **Fig 7.1.** courtesy of the authors; **7.2. & 7.4.** Golay J, Andrea AE. Antibodies (Basel) 2020;9:17; **7.3.** Jain N, et al. Pharm Res 2015;32:3526-3540; **7.5.** Hucks G, et al. Blood Cancer Journal 2019;9:10; **7.6.** Han S, et al. Cancer Lett 2017;390:188-200; **7.7.** Alard E, et al. Cancers (Basel) 2020;12:1826; **7.8.** modified from Chang YC, et al. Front Immunol 2018;9:3041; **7.9.** Lussana F, et al. J Clin Oncol 2021;39:444-455.

8 Diffuse large B-cell lymphoma

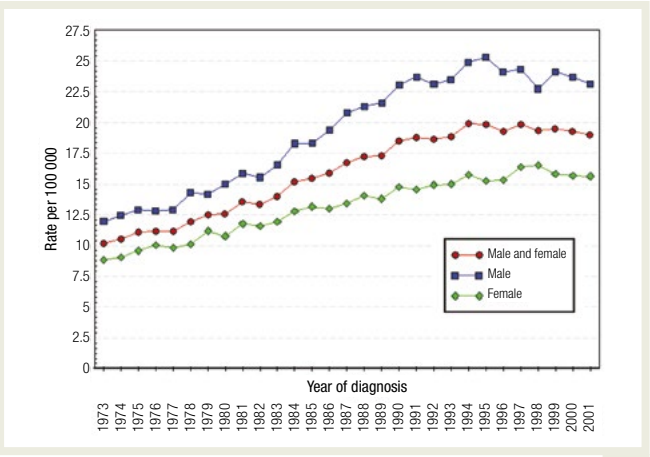
Epidemiology, aetiology, clinical presentation and staging

Diffuse large B-cell lymphomas (DLBCLs) represent 30% of all non-Hodgkin lymphomas, with an incidence of ~150 000 new cases per year.

Median age at diagnosis is 60-69 years, with one third of patients >75 years old at the time of diagnosis.

DLBCL is more frequent in immunodeficient patients; some DLBCLs have a *de novo* origin, in other cases they derive from the transformation of an indolent lymphoma.

Incidence of DLBCL 1973-2001



DLBCL, diffuse large B-cell lymphoma. Fig. 8.1

Lugano modification of Ann Arbor staging

Stage	Involvement	Extranodal (E) status
Limited		
Stage I	One node or a group of adjacent nodes	Single extranodal lesions without nodal involvement
Stage II	Two or more nodal groups on the same side of the diaphragm	Stage I or II by nodal extent with limited contiguous extranodal involvement
Stage II bulky	II as above with 'bulky' disease	Not applicable
Advanced		
Stage III	Nodes on both sides of the diaphragm Nodes above the diaphragm with spleen involvement	Not applicable
Stage IV	Additional non-contiguous extralymphatic involvement	Not applicable

Fig. 8.2

Disease presentation is usually a rapidly growing mass in a lymph node (LN) or an extranodal organ; B symptoms may be present.

At diagnosis, 60% of cases present at an advanced stage (Ann Arbor stage III or IV), with extranodal organ involvement in 40% of cases, and bone marrow (BM) infiltration in 11%-27%.

Common involved extranodal sites are the gastrointestinal tract (e.g. stomach) and, less frequently, bone, breast, testis, central nervous system (CNS), thyroid, liver and kidney.

An excisional LN biopsy is mandatory at diagnosis for histological definition; BM biopsy is useful but not mandatory if ^{18}F-fluorodeoxyglucose–positron emission tomography (^{18}F-FDG–PET) is carried out.

Standard staging includes computed tomography (CT) scan and ^{18}F-FDG–PET; endoscopy or ultrasound are useful in selected cases.

Brain magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) examination with cytology and flow cytometry are mandatory in the presence of neurological signs or in patients at high risk.

^{18}F-FDG–PET uptake in DLBCL

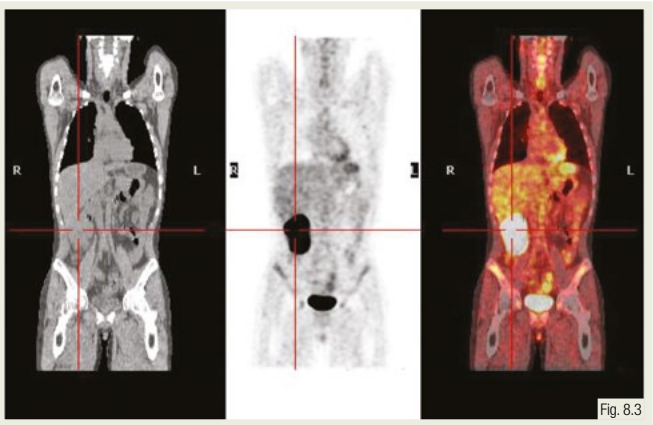


Fig. 8.3

^{18}F-FDG–PET, ^{18}F-fluorodeoxyglucose-positron emission tomography; DLBCL, diffuse large B-cell lymphoma.

REVISION QUESTIONS

1. What is the median age at diagnosis in DLBCL?
2. Describe the clinical presentation at diagnosis.
3. List the examinations required at diagnosis for complete staging of the disease.

Pathology and prognosis

DLBCL is characterised by a diffuse proliferation of atypical irregular large cells, with vesicular nuclei, prominent nucleoli and basophilic cytoplasm.

With immunohistochemistry (IHC), DLBCL cells typically express pan-B-cell markers: CD19, CD20, CD22 and CD79a.

Fluorescent *in situ* hybridisation (FISH) is recommended to identify poor-prognosis subtypes of DLBCL, such as high-grade B-cell lymphoma with rearrangement of *MYC* and B-cell lymphoma 2 (*BCL2*).

DLBCL subgroups, by FISH

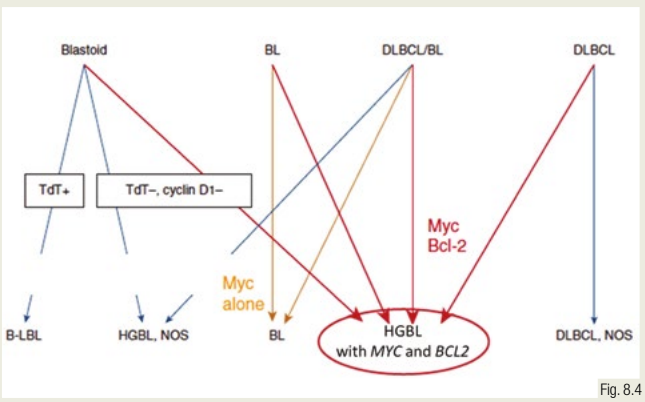


Fig. 8.4

BCL2, B-cell lymphoma 2; BL, Burkitt lymphoma; B-LBL, B-lymphoblastic leukaemia/lymphoma; DLBCL, diffuse large B-cell lymphoma; FISH, fluorescent *in situ* hybridisation; HGBL, high-grade B-cell lymphoma; NOS, not otherwise specified.

Genetically distinct DLBCL subsets are predictive of outcome

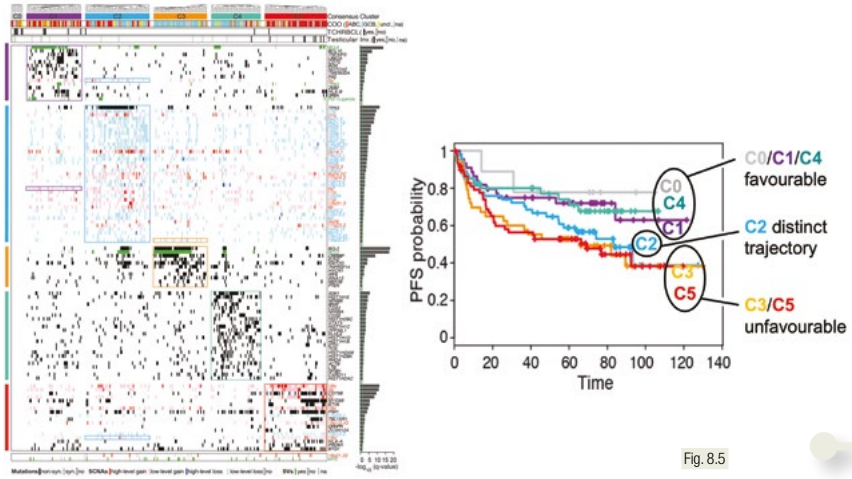


Fig. 8.5

DLBCL, diffuse large B-cell lymphoma; PFS, progression-free survival.

Gene expression profiling (GEP) distinguishes DLBCL subtypes based on the cell of origin (COO) profile: germinal centre B-cell-like (GCB) DLBCL, activated B-cell-like (ABC) DLBCL and unclassified.

The GCB subtype arises from centroblasts, whereas the ABC subtype arises from a plasmablastic cell just prior to germinal centre exit.

Detailed analyses of molecular aberrations have led to proposals of new taxonomies for DLBCL, with a classification that includes genetically defined subtypes beyond the COO.

Age >60 years, Ann Arbor stage III–IV, performance status (PS) >1, elevated lactate dehydrogenase (LDH) and extranodal sites >2 are risk factors according to the International Prognostic Index (IPI).

A better instrument to discriminate among high-risk DLBCL patients is the 2014-dated National Comprehensive Cancer Network IPI (NCCN-IPI).

The CNS-IPI is used to predict CNS recurrence; some biological features, such as *MYC* and/or *BCL2* rearrangement, ABC profile and *TP53* mutation, are associated with poor prognosis.

Risk stratification according to the IPI, in the rituximab era

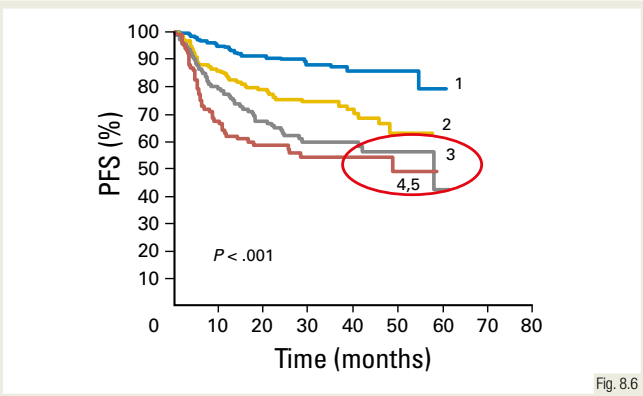


Fig. 8.6

IPI, International Prognostic Index; PFS, progression-free survival.

REVISION QUESTIONS

1. List the morphological and immunohistochemical characteristics of DLBCL.
2. What are the main DLBCL subgroups according to COO profile?
3. What are the risk factors defined in the IPI?

First-line treatment

The backbone of DLBCL treatment in the first line is R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone).

R-CHOP cures 60% of elderly DLBCL patients, with a 10-year progression-free survival (PFS) of 37%, compared with 20% in those treated with CHOP alone.

6 cycles of R-CHOP every 21 days ± 2 doses of rituximab is the standard treatment in advanced-stage DLBCL patients, aged 18 to 80 years old.

Overall survival of 1476 DLBCL patients treated with R-CHOP at the British Columbia Cancer Agency

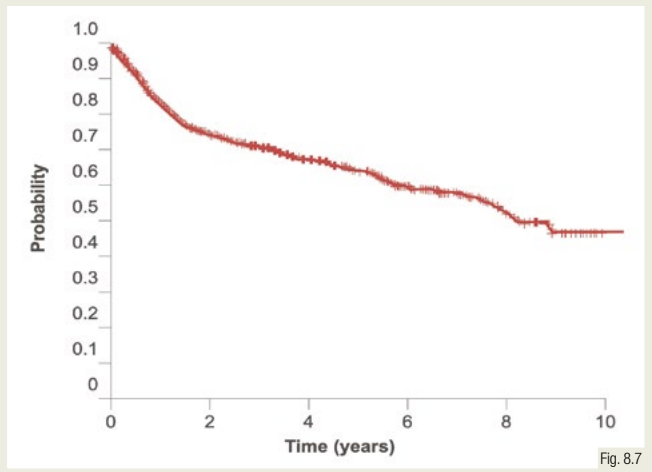


Fig. 8.7

DLBCL, diffuse large B-cell lymphoma; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone.

PFS of 524 DLBCL patients: R-CHOP vs DA-EPOCH-R

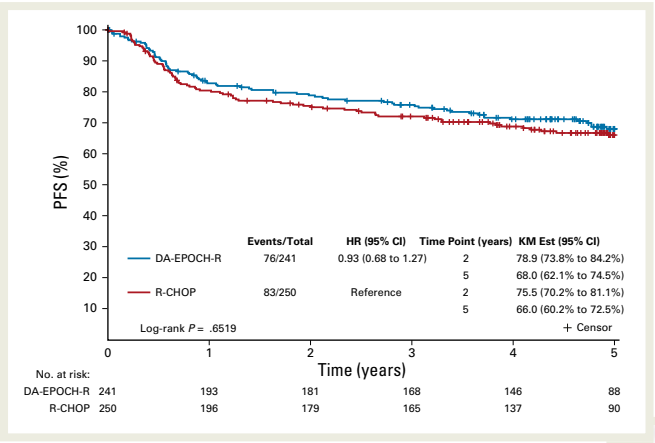


Fig. 8.8

CI, confidence interval; DA-EPOCH-R, dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin plus rituximab; DLBCL, diffuse large B-cell lymphoma; HR, hazard ratio; KM Est, Kaplan–Meier estimate; PFS, progression-free survival; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone.

R-CHOP is inadequate for the treatment of aggressive lymphoma with rearrangement of *MYC* and *BCL2* and/or *BCL6*, requiring a more intensive scheme (DA-EPOCH-R [dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin plus rituximab] or Burkitt-like regimens).

Treatment intensification in responding intermediate-high and high IPI risk patients showed no advantage when compared with standard chemotherapy (ChT).

DA-EPOCH-R in advanced-stage DLBCL has the same outcome as R-CHOP.

In non-bulky limited-stage disease with low IPI, brief chemoimmunotherapy (4-R-CHOP) ± 2 doses of rituximab ± radiotherapy (RT) is recommended.

In patients at risk of CNS recurrence, CNS prophylaxis with systemic CNS-penetrating agents (methotrexate) ± prophylactic intrathecal ChT should be considered.

According to comprehensive geriatric assessment scales, in selected cases the doses of anthracycline and vincristine should be reduced (R-mini-CHOP), mainly in patients >80 years.

PFS in 149 elderly unfit DLBCL patients treated with R-mini-CHOP

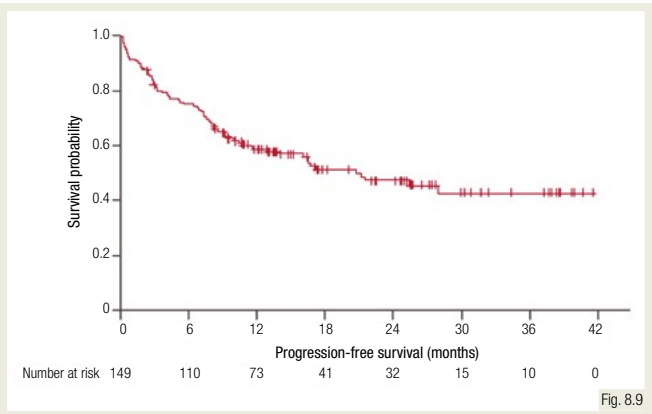


Fig. 8.9

DLBCL, diffuse large B-cell lymphoma; PFS, progression-free survival; R-mini-CHOP, rituximab plus decreased dose of CHOP (doxorubicin, cyclophosphamide, vincristine and prednisone)

REVISION QUESTIONS

1. What is the standard treatment in first-line DLBCL?
2. Is R-CHOP adequate for the treatment of all biological subtypes?
3. List the cases in which it is possible to reduce the dose of R-CHOP ChT.

First-line treatment: novel agent combinations

Obinutuzumab, a glycoengineered, type II humanised anti-CD20 monoclonal antibody (mAb), has been tested in first-line treatment.

A randomised phase III trial in untreated DLBCL patients showed no advantage in using obinutuzumab plus CHOP compared with standard R-CHOP.

Clinical trials are ongoing to test the feasibility of adding bispecific antibodies (BsAbs) to standard ChT in first-line treatment.

Progression-free survival by treatment arm in the GOYA trial

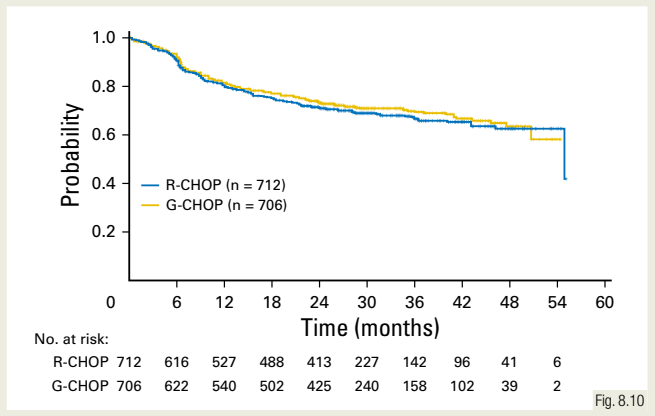


Fig. 8.10

CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone; G-CHOP, obinutuzumab + CHOP; R-CHOP, rituximab + CHOP.

Progression-free survival by treatment arm in the ROBUST trial

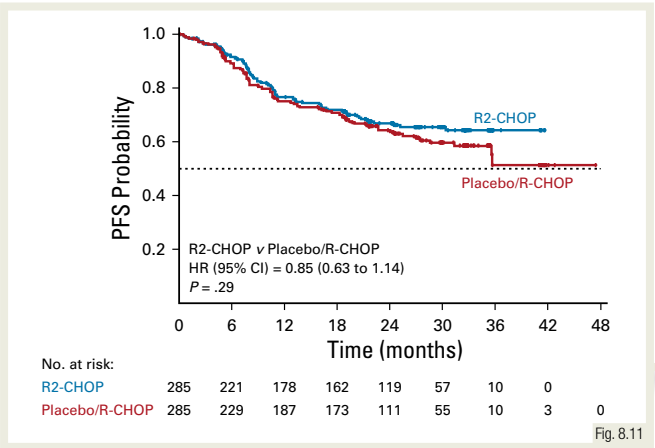


Fig. 8.11

CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone; CI, confidence interval; HR, hazard ratio; PFS, progression-free survival; R-CHOP, rituximab + CHOP; R2-CHOP, lenalidomide + R-CHOP.

In order to ameliorate the prognosis in COO-activated B-cell profiles, some combinations with targeted therapies have been tested.

Bortezomib, ibrutinib and lenalidomide have all shown activity in ABC-DLBCL subgroups and were safely combined with standard R-CHOP.

However, the randomised phase III trials combining these drugs to R-CHOP, compared with R-CHOP alone, did not meet their primary endpoints and R-CHOP remains the standard treatment.

Polatuzumab vedotin (Pola) is an antibody–drug conjugate targeting CD79b, which is ubiquitously expressed on the surface of B cells.

Pola may be combined with standard R-CHOP without vincristine, in the combination Pola-R-CHP, with no toxicity increase.

The phase III randomised Polarix trial showed, in previously untreated intermediate-risk or high-risk DLBCL patients, a benefit from adding Pola to R-CHP, compared with standard R-CHOP.

Progression-free survival by treatment arm in the Polarix trial

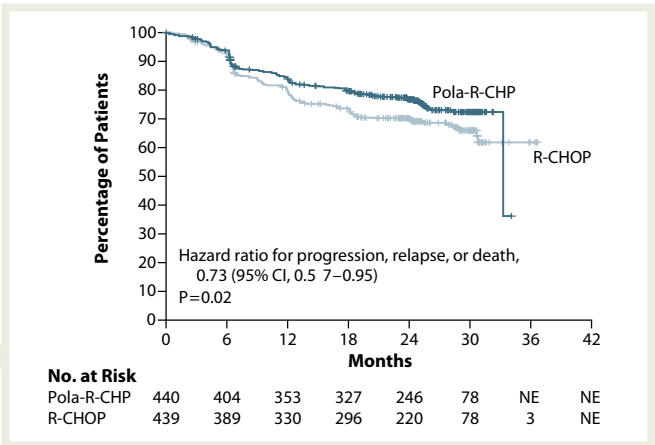


Fig. 8.12

CI, confidence interval; NE, not evaluated; Pola-R-CHP, polatuzumab vedotin + rituximab, cyclophosphamide, doxorubicin and prednisone; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone.

REVISION QUESTIONS

1. List some drugs tested in combination with R-CHOP in clinical trials.
2. List some negative phase III randomised trials.
3. What is the target for Pola?

Salvage treatment at relapse/progression

An intensive platinum-containing regimen ± cytarabine plus high-dose ChT and autologous stem-cell transplantation (ASCT) was previously considered the standard treatment in relapsed/refractory (R/R) DLBCL patients.

In the rituximab era, in chemosensitive patients who achieve a complete response with salvage therapy, consolidation with ASCT is recommended.

In selected cases with poor prognosis, consolidation with allogeneic stem-cell transplantation (alloSCT) may be considered.

Coral study, R-ICE vs R-DHAP + high-dose ChT and ASCT: OS by salvage treatment

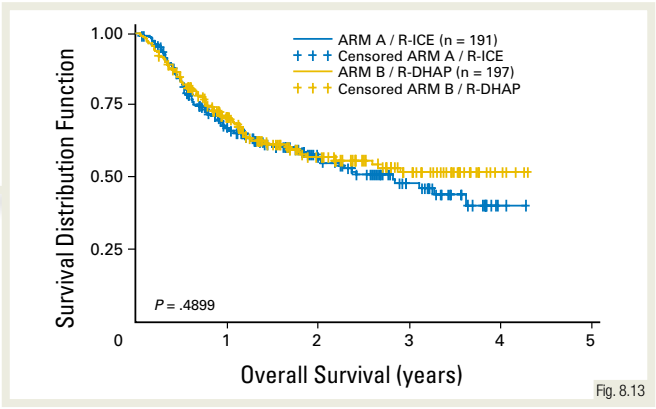


Fig. 8.13

ASCT, autologous stem-cell transplantation; ChT, chemotherapy; OS, overall survival; R-ICE, rituximab, ifosfamide, carboplatin and etoposide; R-DHAP, rituximab, cisplatin, cytarabine and dexamethasone.

Event-free survival in refractory diffuse large B-cell lymphoma

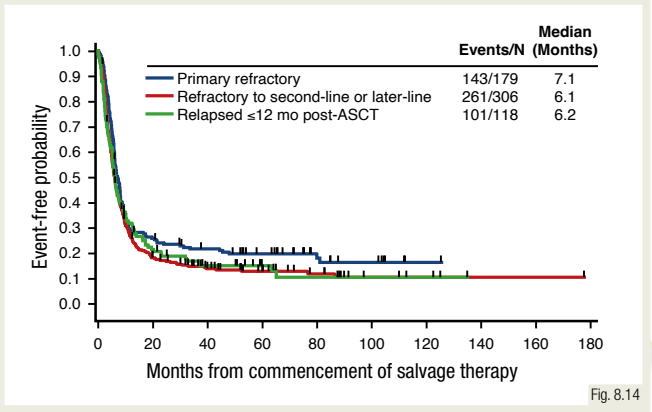


Fig. 8.14

ASCT, autologous stem-cell transplantation.

R/R transplant-ineligible patients should be treated with standard chemoimmunotherapy or with novel approved combinations such as rituximab-bendamustine-Pola, or tafasitamab-lenalidomide.

The outcome of elderly R/R DLBCL patients is poor, and treatment with novel agents such as BsAbs or others within clinical trials is recommended.

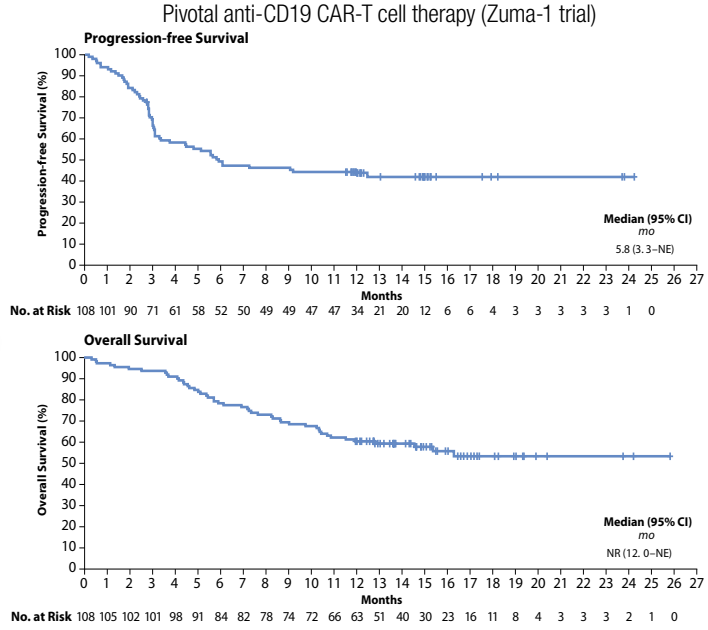
The SCHOLAR-1 analysis identified patients with dismal prognosis: those with primary refractory disease to first-line therapy or refractory to salvage treatment.

Second-generation anti-CD19 chimeric antigen receptor (CAR)-T cells are available in clinical practice.

CAR-T cells are approved in R/R patients after two lines of therapy, or as a first salvage treatment in primary refractory or early relapse.

The most common toxicities related to CAR-T cells are cytokine release syndrome, immune-mediated neurotoxicity and long-term cytopenias.

Pivotal anti-CD19 CAR-T cell therapy (Zuma-1 trial)



CAR, chimeric antigen receptor; CI, confidence interval; NE, not estimable; NR, not reached. Fig. 8.15

REVISION QUESTIONS

1. What is the standard treatment in young patients with R/R DLBCL?
2. Name some schemes of chemoimmunotherapy used in patients with R/R DLBCL.
3. Briefly describe the role of CAR-T cells.

Summary: Diffuse large B-cell lymphoma

- DLBCL is the most frequent histotype of non-Hodgkin lymphomas, with a median age at diagnosis of 60-69 years
- Histology, IHC and FISH are essential at diagnosis
- The IPI is an instrument that helps to predict prognosis
- The risk of recurrence in the CNS should be considered
- The standard treatment in DLBCL at first line is R-CHOP
- R-CHOP is inadequate for the treatment of aggressive lymphoma with rearrangement of *MYC* and *BCL2*
- The standard treatment in young patients with relapsed DLBCL is chemoimmunotherapy (cisplatin- and cytarabine-based) followed by high-dose ChT and stem-cell transplantation
- Anti-CD19 CAR-T cells are registered in patients who have failed at least two prior lines of ChT

Further Reading

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Image sources: **Fig 8.1.** Surveillance, Epidemiology, and End Results Program; **8.2.** Cheson BD, et al. J Clin Oncol 2014;32:3059-3067; **8.3.** author-generated; **8.4.** adapted from Swerdlow SH, et al. Blood 2016;127:2375-2390; **8.5.** Chapuy B, et al. Nat Med 2018;24:679-690; **8.6.** Ziepert M et al, J Clin Oncol 2010; 28:2373-2380; **8.7.** Sehn LH. Hematology Am Soc Hematol Educ Program 2012;2012:402-409; **8.8.** Bartlett NL, et al. J Clin Oncol 2019;37:1790-1799; **8.9.** Peyrade F, et al. Lancet Oncol 2011;12:460-468; **8.10.** Vitolo U, et al. J Clin Oncol 2017;35:3529-3537; **8.11.** Nowakowski GS, et al. J Clin Oncol 2021;39:1317-1328; **8.12.** Tilly H, et al. N Engl J Med 2022;386:351-363; **8.13.** Gisselbrecht C, et al. J Clin Oncol 2010; 28:4184-4190; **8.14.** Crump M, et al. Blood 2017;130:1800-1808; **8.15.** Neelapu SS, et al. N Engl J Med 2017;377:2531-2544.

9 Follicular lymphoma

Pathology and biology

Follicular lymphoma (FL) is composed of germinal centre (GC) B cells and shows a follicular (nodular) growth pattern recalling the normal follicles.

Sometimes, large parts of the involved lymph nodes (LNs) are invaded by cells with a diffuse pattern: in this case the designation is FL follicular and diffuse.

On immunohistochemistry, cells typically express B-cell surface antigens such as CD20, follicle centre B-cell markers CD10, B-cell lymphoma 6 (BCL6) and cytoplasmic BCL2 protein (in contrast to normal GC cells).

Morphological features of follicular lymphoma

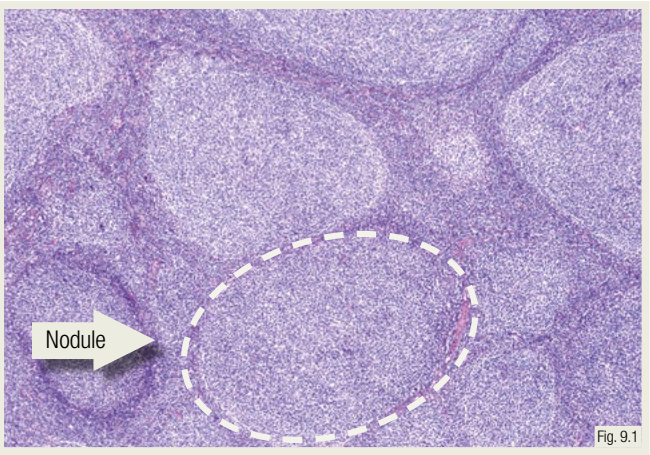


Fig. 9.1

Small cleaved cells (centrocytes) and large, non-cleaved cells (centroblasts)

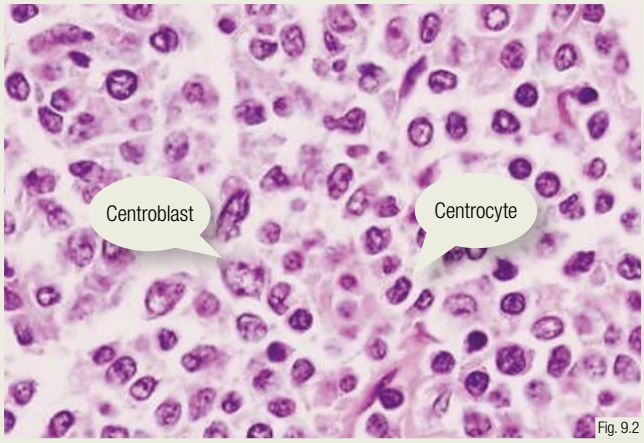


Fig. 9.2

FL is composed of variable proportions of small- to medium-sized cells with a cleaved nucleus (centrocytes) and large cells with a round to oval nucleus and several nuclear membrane-bound nucleoli (centroblasts).

In the fifth edition of the World Health Organization (WHO) classification, FL grading is no longer mandatory.

For FL exhibiting a focal or extensive diffuse growth pattern, the recommended diagnosis is 'diffuse large B-cell lymphoma (DLBCL) with FL', even though sheets of large cells are not present.

FL is caused by the translocation t(14;18), bringing the *BCL2* gene on chromosome (Chr) 18 near to immunoglobulin heavy chain (*IGH*) gene on Chr14, which acts as promoter: BCL2 protein overexpression.

As the BCL2 protein has antiapoptotic functions, these cells lose their programmed cell-death capacities and become long-lived, accumulating in the organism.

The accumulation of lymphocytes enlarges the LN, invades the bone marrow (BM) and other organs, while the t(14;18) translocation predisposes to further oncogenic mutations.

t(14;18) translocation

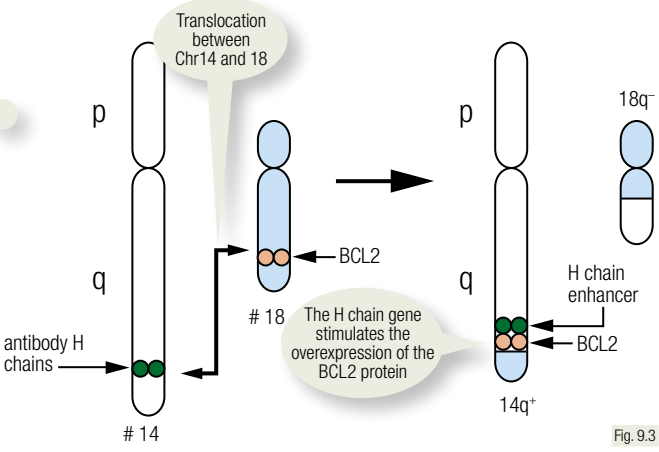


Fig. 9.3

BCL2, B-cell lymphoma 2; Chr, chromosome; H, heavy.

REVISION QUESTIONS

1. Why are FLs so-called?
2. FL is composed of which two types of lymphoid cells?
3. Why have FL cells lost their apoptotic capacity?

Clinical presentation and prognosis

The majority of cases have widespread disease (stage III-IV), with involved LNs above and below the diaphragm, and more than 50% have BM involvement.

Usually FL evolves slowly; patients can notice their LNs growing and spontaneously regressing; they seldom have symptoms or cytopenia.

Standard staging examinations include positron emission tomography–computed tomography (PET–CT) and BM examination. If PET–CT is not available, staging can be sufficiently reliable with CT scan instead.

Overall survival of FL patients, according to the decade of diagnosis

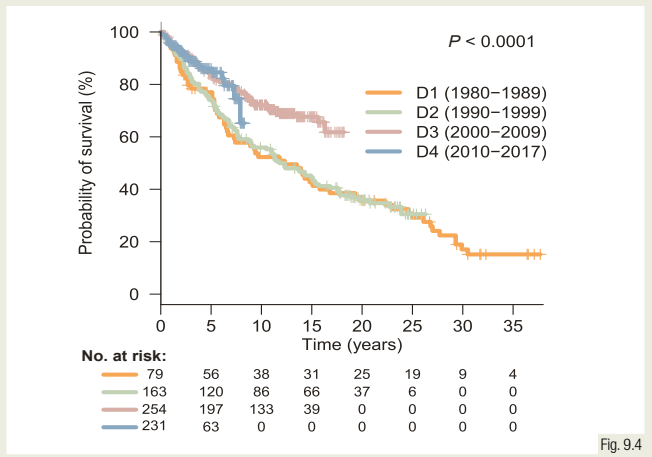


Fig. 9.4

D, decade; FL, follicular lymphoma.

Cumulative incidence of histological transformation at first recurrence

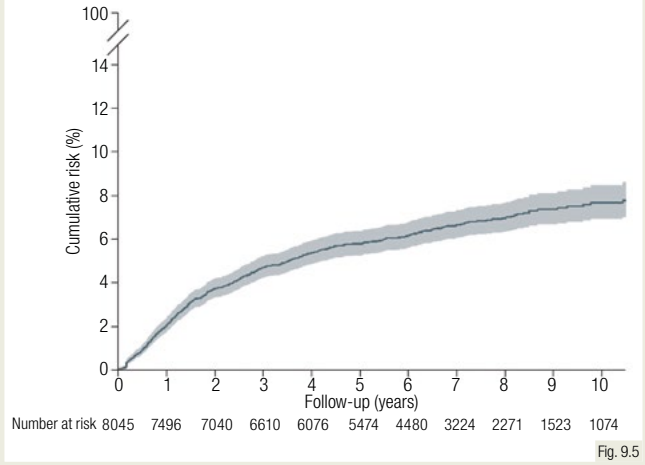


Fig. 9.5

The shaded area shows the 95% CI (confidence interval).

The median survival for FL patients was ~10 years in the last decades but recently, thanks to better supportive care and new treatments, it has increased to 12–18 years.

Most patients with FL will eventually die of their disease; thus, the cause-specific survival curve never reaches a plateau. FL is therefore considered incurable with conventional treatment.

A frequent cause of death is transformation into a more aggressive lymphoma, mostly DLBCL; this occurs in 1% to 3% of patients per year across different series and treatment approaches.

The prognosis of FL patients can be estimated with the help of a clinical prognostic score, called FLIPI (Follicular Lymphoma International Prognostic Index), based on the following clinical factors: age, haemoglobin (Hb), lactate dehydrogenase (LDH), stage and number of nodal sites.

Several other prognostic indices including clinical variables (e.g. FLIPI 2, PRIMA-PI, Follicular Lymphoma Evaluation Index [FLEX]) have been developed for FL over the last 2 decades. More recently, molecular (mutations or gene expression) or PET parameters have been incorporated (e.g. m7-FLIPI, 23-GEP).

Early relapse of FL within 24 months of chemoimmunotherapy (progression of disease within 2 years [POD24]) is now established as a robust marker of poor survival.

Overall survival according to the FLIPI risk groups

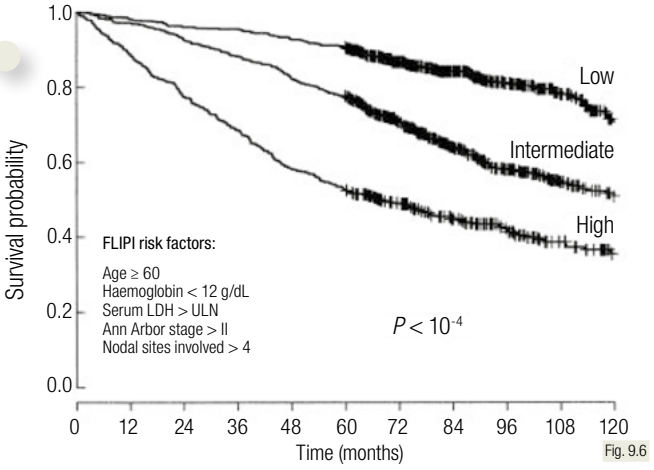


Fig. 9.6

FLIPI, Follicular Lymphoma International Prognostic Index; LDH, lactate dehydrogenase; ULN, upper limit of normal.

REVISION QUESTIONS

1. Is FL a curable disease?
2. How often does FL transform into a high-grade disease?
3. How is it possible to predict the outcome of an FL patient?

First-line treatment – single agents

In the small proportion of patients with localised disease (stage I-II) at diagnosis, involved-site radiotherapy (ISRT) (24-36 Gy) is one of the standard treatment options.

In advanced disease, randomised trials demonstrated that a 'watch-and-wait' strategy (W+W) allows chemotherapy (ChT) to be delayed for years without any survival disadvantage.

In asymptomatic patients for whom W+W is not acceptable, monotherapy with rituximab results in a high response rate (RR) with durable responses and good quality of life.

OS of patients randomised to receive immediate systemic therapy with oral chlorambucil or observation

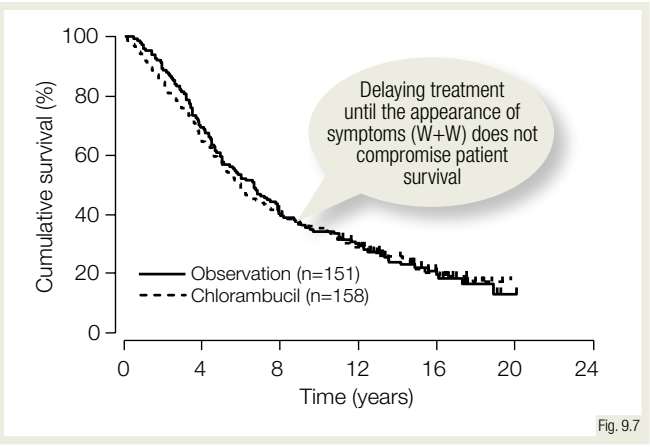


Fig. 9.7

OS, overall survival; W+W, watch-and-wait.

Overall survival of patients randomised to receive CHOP-B or oral cyclophosphamide

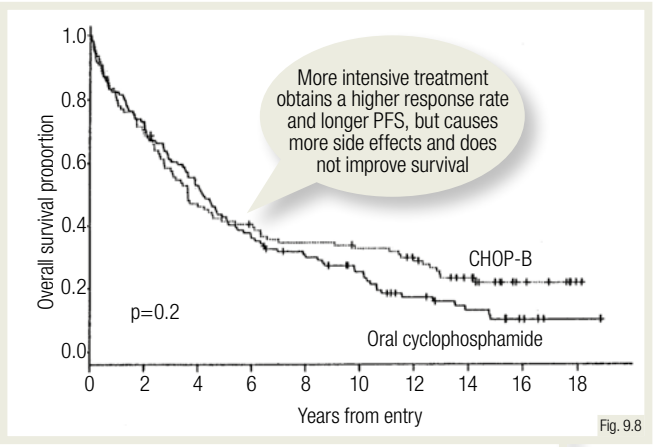


Fig. 9.8

CHOP-B, cyclophosphamide, doxorubicin, vincristine, prednisone and bendamustine; PFS, progression-free survival.

Single agents are less active than combinations but cause fewer side effects. Survival is not affected by the lower activity, as second-line therapy is very effective.

The RRs to single agents are in the range of 60%-80%, with 20%-40% complete response (CR) and a response duration of 1.5-2.5 years, depending mainly on baseline prognostic factors.

Bendamustine is increasingly being used due to its favourable therapeutic index (high RR with little toxicity).

When patients have a high disease burden or become symptomatic, the choice of treatment varies from single agent (i.e. rituximab) to intensive combination chemoimmunotherapy.

Low-dose radiotherapy (RT) or radioimmunotherapy (RIT) are also active against FL.

Although the activity of these agents is similar, their toxicity profiles can be quite different. Fludarabine is more myelotoxic, while rituximab is better tolerated.

Event-free survival in randomised follicular lymphoma patients

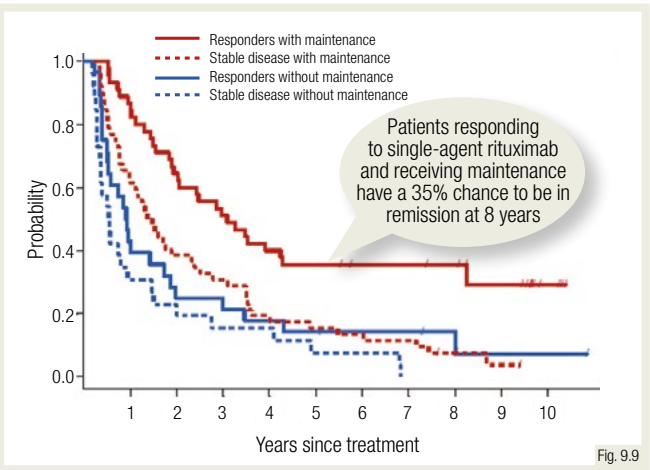


Fig. 9.9

REVISION QUESTIONS

1. What are the advantages of a W+W strategy?
2. Is single-agent or combination ChT better?
3. Which is the single-agent treatment with the best therapeutic index?

First-line treatment – combination therapy

The addition of rituximab (R) to several ChT regimens ('R-ChT') was shown to improve progression-free survival (PFS) and, in a meta-analysis, also overall survival (OS), and has therefore become the standard.

R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone) is a very active regimen in FL, resulting in a long PFS but, because it is relatively toxic and does not improve OS, is not universally used.

In patients responding to R-CHOP, the continuation of treatment with rituximab given every 2 months (maintenance) further prolongs PFS, but not OS.

Forest plot of overall survival comparison, ChT vs R+ChT

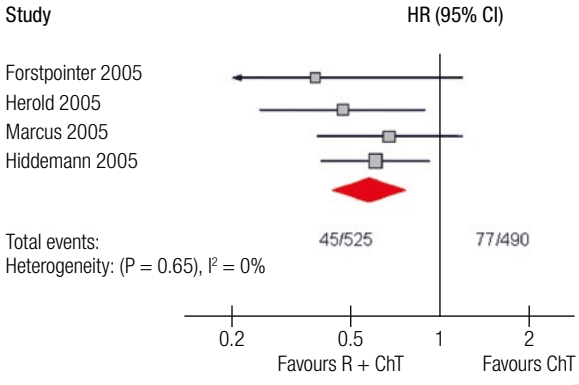


Fig. 9.10

ChT, chemotherapy; CI, confidence interval; HR, hazard ratio; R, rituximab.

PFS of patients randomised to receive rituximab maintenance or observation (no additional treatment)

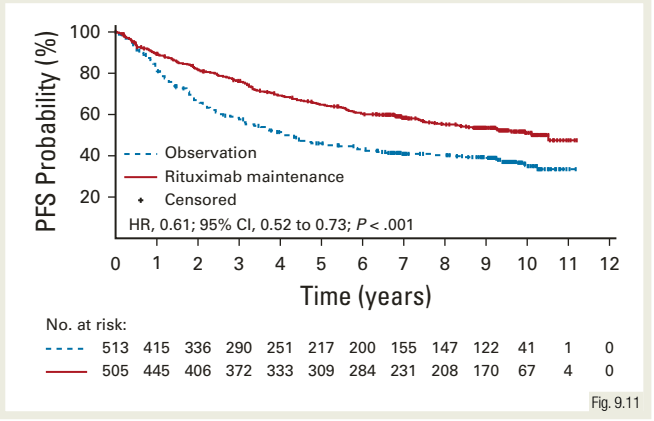


Fig. 9.11

CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.

Other combinations such as R-CVP (rituximab, cyclophosphamide, vincristine and prednisone) or R-FM (rituximab, fludarabine and mitoxantrone) are not superior to R-CHOP in randomised comparisons.

Two randomised studies showed that the bendamustine-R (B-R) regimen is as active as R-CHOP, but induces significantly fewer side effects.

R-CHOP may be preferred in fit patients with clinically aggressive disease.

The combination of rituximab with lenalidomide (R^2 regimen) has been shown to have similar efficacy to R-ChT (with all regimens followed by rituximab maintenance therapy).

The role of RT in stage III to IV FL is limited to local palliative treatment of symptomatic disease.

Autologous stem-cell transplantation (ASCT) has been used to consolidate first remission in randomised trials but, due to its toxicity without OS advantage, it should not be used outside trials.

PFS of patients randomised to receive rituximab+chemotherapy or rituximab+lenalidomide (R^2)

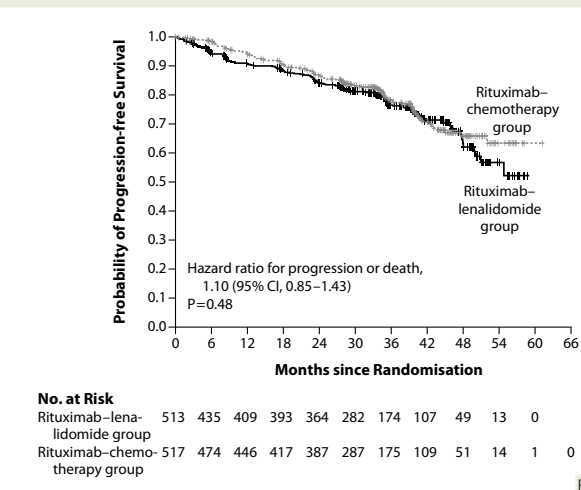


Fig. 9.12

CI, confidence interval; PFS, progression-free survival.

REVISION QUESTIONS

1. Which treatment has improved the survival of FL patients in the last decade?
2. Is R-CHOP the standard first-line ChT for all patients with FL?
3. How can a remission obtained with ChT be prolonged?

Options at relapse/progression

A biopsy should be performed at each relapse to exclude transformation, particularly if there are indirect signs such as elevated LDH or rapidly growing tumours.

As with many other indolent cancers, FL can relapse slowly after longer intervals and can respond to a rechallenge with the previous regimen.

Low-dose ISRT (2 × 2 Gy) can provide adequate palliation in patients with an indolent relapse and not many sites of disease.

PFS of patients with FL according to first, second or third rituximab treatment.

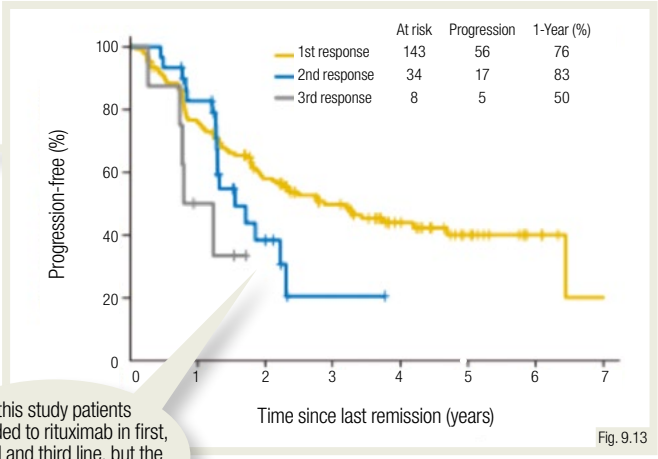


Fig. 9.13

FL, follicular lymphoma; PFS, progression-free survival.

Response rates according to selected regimens

Treatment regimen	First line		Relapse	
	ORR	CRR	ORR	CRR
R-CHOP	96%	73%	72%	16%
R-Bendamustine	99%	30%	92%	60%
R-F(C)M	91%	72%	95%	41%
Radioimmunotherapy	95%	75%	74%	15%
Rituximab	77%	36%	28%	2%
Chlorambucil/PDN	74%	13%	47%	5%
Fludarabine	65%	37%	48%	22%
R²	61%	48%	78%	34%
Tazemetostat	-	-	69%	13%
Copanlisib	-	-	61%	17%
Mosunetuzumab	-	-	80%	60%

Fig. 9.14

CRR, complete response rate; ORR, overall response rate; PDN, prednisone; R, rituximab; R², rituximab and lenalidomide; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; R-F(C)M, rituximab, fludarabine, mitoxantrone ± cyclophosphamide.

Alternatively, a single agent (ChT, rituximab) can be effective, the choice depending on prior treatments and response duration.

For early and/or aggressive relapses, combination ChT is preferred, with the addition of rituximab (if not given in the previous 6 months) or obinutuzumab.

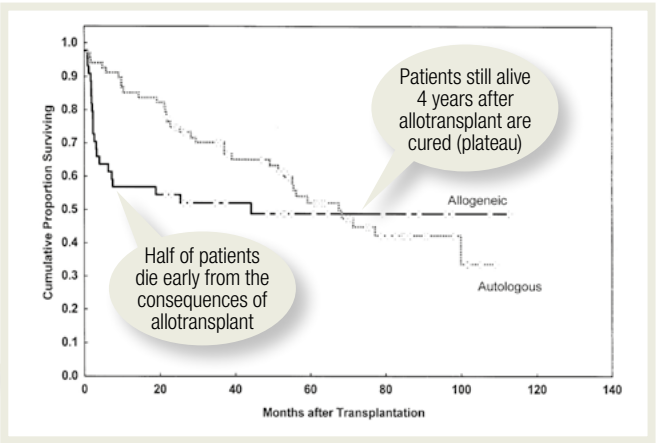
Consolidation of second or subsequent remissions with ASCT can further prolong remission and possibly survival, particularly in patients who experienced early treatment failure.

Tazemetostat is an oral inhibitor of EZH2 (enhancer of zeste homologue 2) that has shown activity, particularly in patients with *EZH2* mutations, but also in a small proportion of patients with EZH2 wild-type FL.

Options at relapse/progression include several novel agents (e.g. lenalidomide, tazemetostat, copanlisib) with a plan for ASCT in CR or chimeric antigen receptor (CAR)-T-cell therapy.

Allogeneic stem-cell transplantation (alloSCT) can be curative but should only be proposed to relapsed fit and motivated patients, due to the high incidence of severe side effects and mortality.

OS after high-dose therapy followed by autologous or allogeneic stem-cell transplantation



OS, overall survival.

Fig. 9.15

REVISION QUESTIONS

1. Is there a standard second-line treatment for FL?
2. Are all patients with relapsed FL candidates for ASCT or alloSCT?
3. Should rituximab be added to each line of ChT?

Summary: Follicular lymphoma

- Histology: nodules resembling follicles, contain both centrocytes and centroblasts
- Biology: translocation t(14;18) causes BCL2 overexpression, inhibiting apoptosis
- The risk of transformation to aggressive lymphoma is around 30% at 10 years
- Usually indolent behaviour, but incurable except for the (rare) stage I-II
- Prognostic factors (FLIPI): age, Hb, LDH, stage, number of nodal sites
- If asymptomatic, observe without treatment; alternative is single-agent rituximab
- If symptomatic, choose between single agent or more aggressive treatment (such as R-CHOP)
- Remission can be maintained with rituximab or obinutuzumab
- For indolent relapse, try previous regimen, low-dose RT, rituximab/obinutuzumab or lenalidomide
- For aggressive relapse, consider ASCT or CAR-T-cell therapy

Further Reading

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Image sources: **Fig 9.1.** Ramnani D. https://www.webpathology.com/image.asp?n=4&Case=819; **9.2.** courtesy of A Carvajal-Cuenca and E Campo; **9.3.** adapted from Kimball's Biology Pages ©John W. Kimball; **9.4.** Mozas P, et al. Blood Cancer J 2020;10:31; **9.5.** Federico M, et al. Lancet Haematol 2018;5:e359-e367; **9.6.** Solal-Celigny P, et al. Blood 2004;104:1258-1265; **9.7.** Ardeshna KM, et al. Lancet 2003;362:516-522; **9.8.** Peterson BA, et al. J Clin Oncol 2003;21:5-15; **9.9.** Martinelli G, et al. J Clin Oncol 2010;28:4480-4484; **9.10.** adapted from Schulz H, et al. J Natl Cancer Inst 2007;99:706-714; **9.11.** Bachy E, et al. J Clin Oncol 2019;37:2815-2824; **9.12.** Morschhauser F, et al. N Engl J Med 2018;379:934-947; **9.13.** Kahl B, et al. J Clin Oncol 2014;32:3096-3102; **9.14.** courtesy of the authors; **9.15.** Hosing C, et al. Ann Oncol 2003;14:737-744.

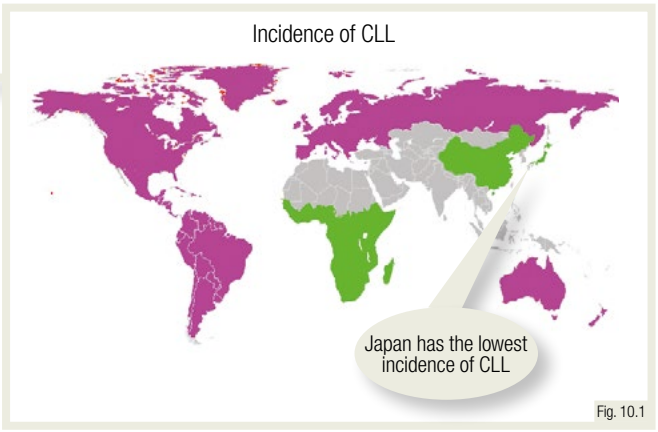
10 Chronic lymphocytic leukaemia/small lymphocytic lymphoma

Epidemiology and classification

Chronic lymphocytic leukaemia (CLL) is the most common leukaemia in the world, but uncommon in East Asia and Sub-Saharan Africa.

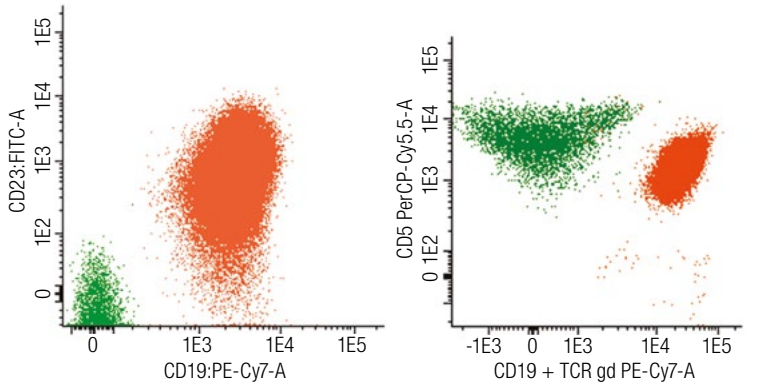
Incidence in the Western world is 4.9/100 000 persons/year. The median age at diagnosis is 70 years.

CLL is nearly twice as common in men as it is in women.



CLL, chronic lymphocytic leukaemia.

Flow cytometry findings showing a CD19-, CD23- and CD5-positive population



CLL cells resemble normal, small, mature-appearing B lymphocytes morphologically, but have a weak surface immunoglobulin expression.

CLL diagnosis requires >5 × 10^9/L clonal B lymphocytes in blood with a typical immunophenotype: CD5+, CD19+, CD23+, CD20dim, CD43+ and kappa (κ) or lambda (λ) light chains.

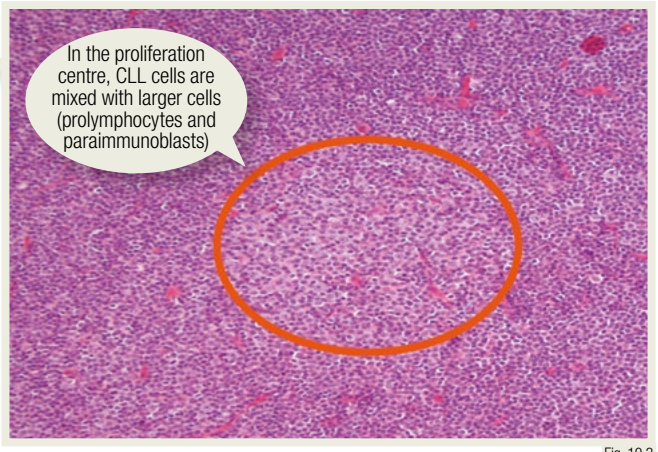
CD200 is positive in CLL and can be used to differentiate it from leukaemic mantle cell lymphoma.

Most CLL cells are quiescent, but proliferation centres (pseudofollicles) can be seen in the bone marrow (BM), lymph nodes (LNs) and spleen.

A low number of clonal cells (<5 × 10^9/L) in the blood, but no lymphadenopathy, splenomegaly or symptoms, is classified as monoclonal B-cell lymphocytosis (MBL), sometimes a precursor of CLL.

No clonal lymphocytes in the blood, but infiltration of cells with a CLL phenotype in LNs, spleen and/or BM is defined as small lymphocytic lymphoma (SLL).

CLL in a lymph node with a proliferation centre



CLL, chronic lymphocytic leukaemia.

REVISION QUESTIONS

1. Is there a gender difference in CLL incidence?
2. What distinguishes CLL cells from normal B cells?
3. What is MBL?

Staging and prognostic markers

CLL is often an incidental finding. The majority of patients (80%) are asymptomatic at diagnosis and one third of patients will never need any therapy.

Clinical staging (Rai and Binet) is based on findings of lymphadenopathy, splenomegaly, anaemia and thrombocytopenia.

The CLL-IPI (International Prognostic Index) includes clinical staging, age and biological markers (e.g. β2 microglobulin and mutational status of the immunoglobulin heavy variable [*IGHV*] and *TP53* genes).

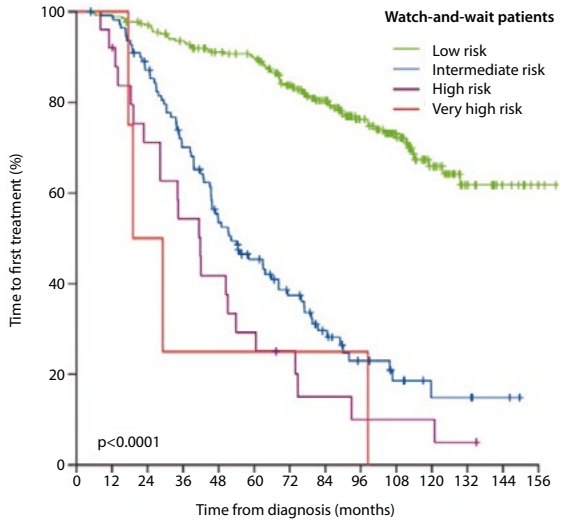
Rai and Binet are the main clinical staging systems in CLL

Rai:	Binet:
0: Lymphocytosis only 1: Lymphadenopathy 2: Splenomegaly 3: Anaemia (<11 g/L) 4: Thrombocytopenia (<100x10^9/L)	A: Palpable disease in ≤2 locations (neck, axillar and inguinal lymph nodes, spleen and liver) B: ≥3 involved areas C: Anaemia (<10 g/L) and/or thrombocytopenia (<100x10^9/L)

Fig. 10.4

CLL, chronic lymphocytic leukaemia.

Time to first treatment in CLL patients according to CLL-IPI risk groups



CLL, chronic lymphocytic leukaemia; IPI, international prognostic index.

Fig. 10.5

Genomic aberrations in CLL/SLL have a strong impact on prognosis and therapeutic choice. Analysis is recommended before initiation of therapy.

Del(17p), del(13q), del(11q) and trisomy 12 are detected by fluorescent *in situ* hybridisation (FISH) and *TP53* mutations by sequencing (Sanger sequencing or next-generation sequencing [NGS]).

Del(17p) and *TP53* mutations are strong negative prognostic factors, while del(13q) is related to an excellent prognosis, if the only abnormality.

The mutational status of the *IGHV* gene is a strong independent prognostic marker with unfavourable prognosis, if unmutated.

Complex karyotype and mutations in the *NOTCH, SF3B1, BIRC3* and *RPS15* genes may affect survival, but are not yet used in clinical practice.

Subsets of the immunoglobulin B-cell receptor have different prognoses, but their role in the clinical setting is still uncertain.

Overall survival in CLL patients according to CK, P53 aberrations (del[17p] and/or *TP53* mutation), trisomy 12, trisomy 19 and *IGHV* mutational status

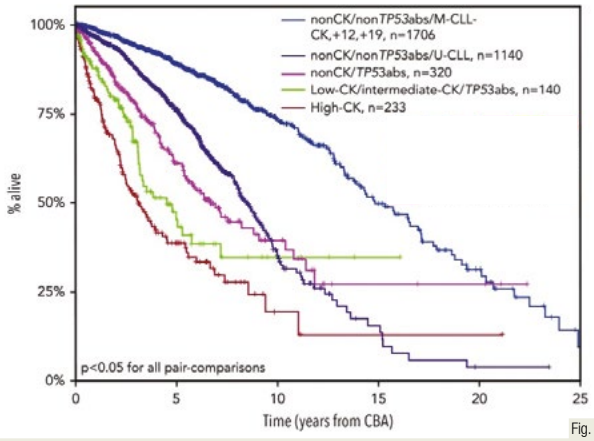


Fig. 10.6

CBA, chromosome banding analyses; CK, complex karyotype; CLL, chronic lymphocytic leukaemia; IGHV, immunoglobulin heavy variable; M-CLL, mutated CLL; U-CLL, unmutated CLL.

REVISION QUESTIONS

1. What proportion of CLL patients are asymptomatic at diagnosis?
2. How does the unmutated *IGHV* gene affect the prognosis?
3. Which chromosomal abnormality is associated with the worst prognosis?

First-line treatment

A watch-and-wait strategy is generally applied for asymptomatic patients, since no overall survival (OS) advantage has been demonstrated with early therapy.

Treatment decision is based on tumour burden, symptoms, age, comorbidities, patient preferences, *TP53* aberrations, del(11q) and *IGHV* mutation, as well as on drug availability.

Treatment options are chemoimmunotherapy (CIT) or targeted drugs, such as Bruton tyrosine kinase inhibitors (BTKis): ibrutinib, acalabrutinib or zanubrutinib, and B-cell lymphoma 2 inhibitor (BCL2i): venetoclax.

Treatment indications according to the iwCLL
Disease-related symptoms: - weight loss - fatigue - fever - night sweats
Cytopenia, as anaemia and thrombocytopenia, due to progressive marrow failure
Progressive or symptomatic splenomegaly and/or lymphadenopathy
Progressive lymphocytosis according to iwCLL criteria
Symptomatic or functional extranodal involvement
Autoimmune complications poorly responding to corticosteroids

iwCLL, International Workshop on Chronic Lymphocytic Leukemia.

Fig. 10.7

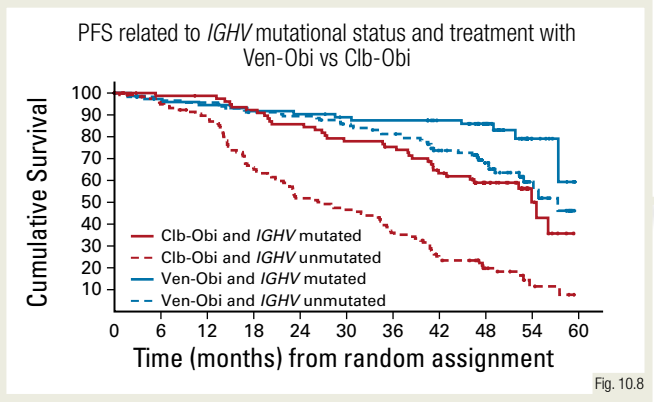


Fig. 10.8

Clb-Obi, chlorambucil-obinutuzumab; IGHV, immunoglobulin heavy chain variable; OS, overall survival; PFS, progression-free survival; Ven-Obi, venetoclax-obinutuzumab.

Chemotherapeutic options are chlorambucil, bendamustine and fludarabine with cyclophosphamide, together with an anti-CD20 antibody, rituximab or obinutuzumab.

CIT may be used in patients with mutated *IGHV*, if no *TP53* aberrations (fludarabine and cyclophosphamide with rituximab in young and fit patients, otherwise bendamustine with rituximab or chlorambucil with obinutuzumab).

Continuous BTK inhibition, and time-limited BCL2 inhibition with obinutuzumab, have shown longer progression-free survival (PFS) than CIT. Adding CD20-targeting antibodies to a BTKi does not seem to be of any benefit.

TP53 mutation/del(17p) is a predictor of poor response to CIT, both as first-line therapy and in relapse. Continuous BTK inhibition is currently the best treatment option.

Allogeneic stem-cell transplantation should be discussed for eligible CLL patients with *TP53* mutation/del(17p), and be performed, in most cases, after response to second-line treatment.

Combination therapies of new drugs seem effective, but data on long term efficacy, toxicity, PFS and OS are awaited.

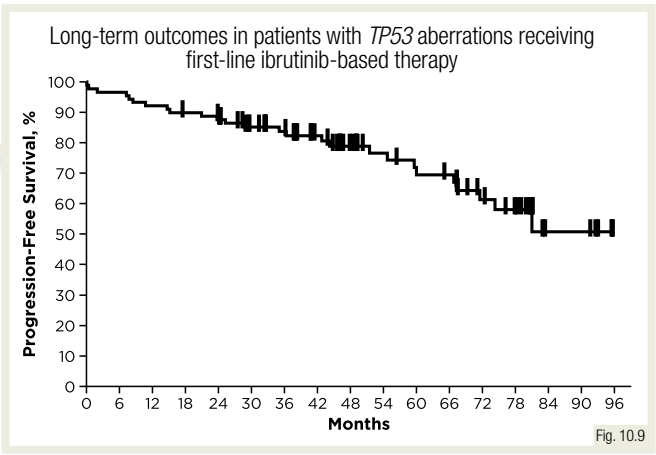


Fig. 10.9

REVISION QUESTIONS

1. Should asymptomatic CLL/SLL patients be treated?
2. In which group of patients is treatment with CIT appropriate?
3. Which are the treatment options for patients with del(17p) or *TP53* mutation?

Therapeutic options at relapse and side effects

As with first-line therapy, treatment is mostly initiated only if the disease is active and symptomatic.

Due to clonal evolution, *TP53* mutation/del(17p) is more common in relapsed/refractory disease; therefore, analysis for this aberration should be repeated before therapeutic decisions.

IGHV mutational status does not change during the course of the disease and does not need to be repeated.

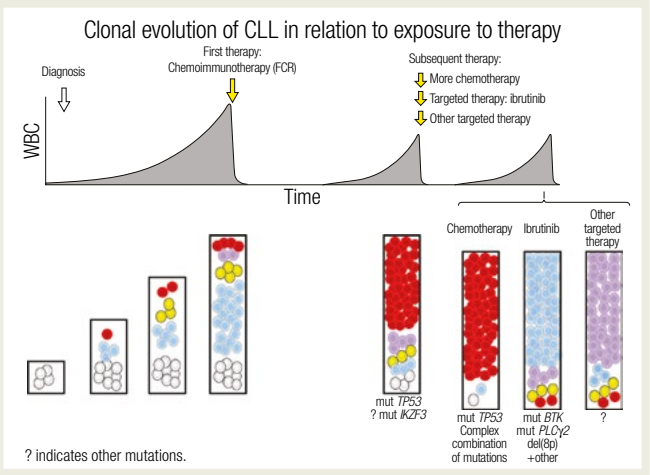


Fig. 10.10

BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukaemia; FCR, fludarabine, cyclophosphamide and rituximab; WBC, white blood cell.

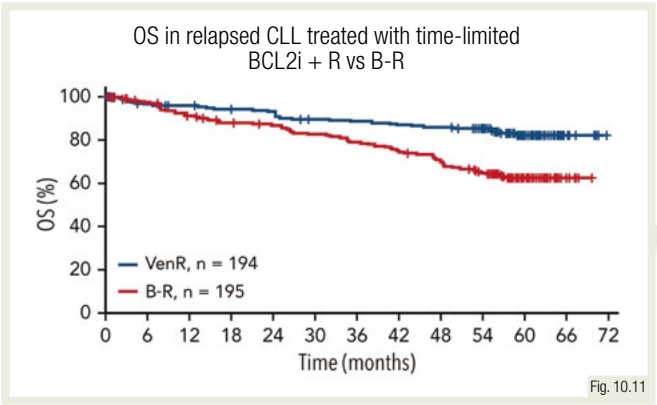


Fig. 10.11

BCL2i, B-cell lymphoma 2 inhibitor; B-R, bendamustine plus rituximab; CLL, chronic lymphocytic leukaemia; OS, overall survival; R, rituximab; VenR, venetoclax plus rituximab.

The choice of therapy depends on response, length of remission and side effects of prior therapy, comorbidities and risk of complications as well as available treatment options.

CIT is seldom repeated, even when duration of remission is long. BTKis or BCL2is (as continuous monotherapy or time-limited with anti-CD20 antibodies) are better alternatives.

In cases of unacceptable toxicity or resistance to BTKis and/or BCL2is, a phosphoinositide 3-kinase (PI3K) inhibitor is an option, mostly in combination with an anti-CD20 antibody.

Side effects of BTKis include bleeding, atrial fibrillation and hypertension, but new-generation BTKis are better tolerated. BCL2is increase the risk of tumour lysis syndrome (TLS).

Mutations in the *BTK*, *PLCG2* and *BCL2* genes lead to treatment resistance; non-covalent (reversible) BTKis may offer a therapeutic option.

Upcoming therapies with bispecific antibodies and chimeric antigen receptor (CAR)-T cells have shown promising results in refractory patients.

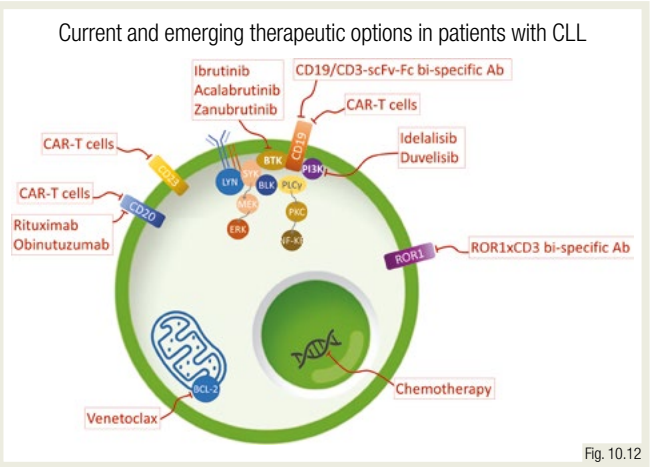


Fig. 10.12

Ab, antibody; BCL-2, B-cell lymphoma 2; BTK, Bruton tyrosine kinase; CAR, chimeric antigen receptor; CLL, chronic lymphocytic leukaemia; Fc, fragment crystallisable region; PI3K, phosphoinositide 3-kinase; ROR1, receptor tyrosine kinase-like orphan receptor 1; scFv, single-chain variable fragment.

REVISION QUESTIONS

1. Is analysis of *IGHV* mutational status necessary before relapse therapy is started?
2. Which factors need to be considered before initiating relapse treatment?
3. Which are the most common side effects of BTKis?

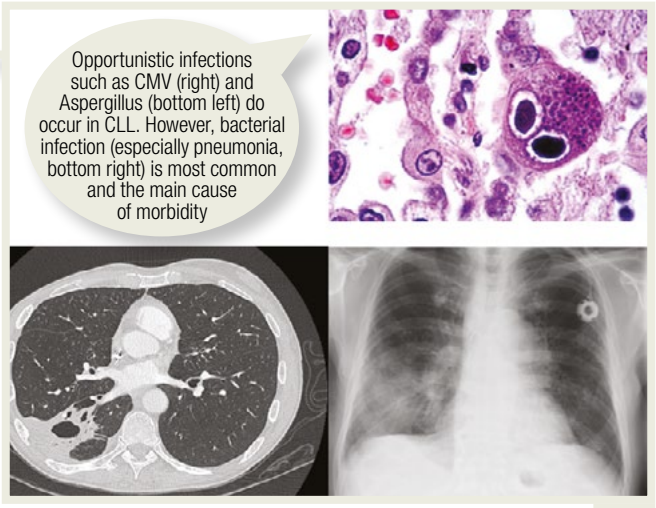
Complications and preventive measures

The immune system is impaired, due to the disease or specific treatments, leading to an increased risk of infectious and autoimmune complications.

Hypogammaglobulinaemia is common and increases with disease duration and certain therapies. Immunoglobulin substitution is recommended if severe and/or repeated infections occur.

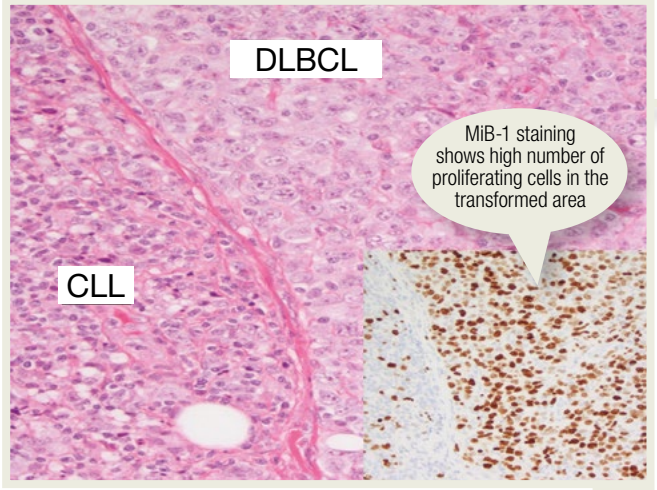
Vaccination decreases the risk of infections, especially early in disease and before therapy. Conjugated pneumococcal vaccines and repeated Covid-19 messenger RNA (mRNA) vaccines improve immune response.

CLL patients have an increased risk of bacterial infections



CLL, chronic lymphocytic leukaemia; CMV, cytomegalovirus. Fig. 10.13

Bone marrow sample of a CLL patient with Richter's transformation



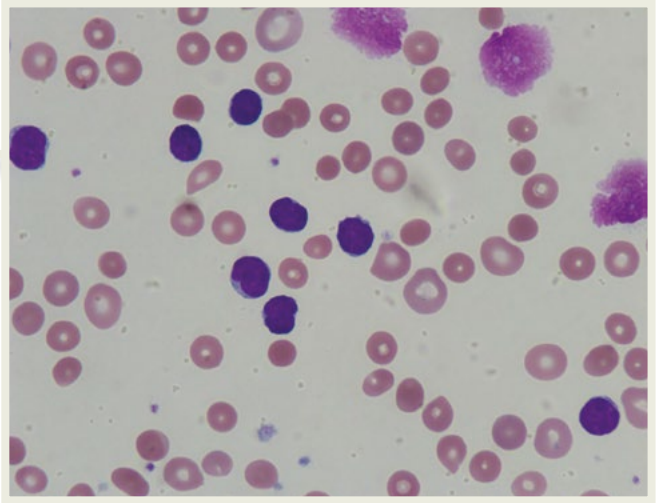
CLL, chronic lymphocytic leukaemia; DLBCL, diffuse large B-cell lymphoma. Fig. 10.14

CLL/SLL may transform into an aggressive lymphoma, mainly diffuse large B-cell lymphoma (DLBCL), known as Richter syndrome (RS).

RS occurs in 2%-15% of CLL cases. Rapid discordant growth of LNs, fast emergence of B symptoms or an unexpected rise in lactate dehydrogenase (LDH) are suggestive of RS.

The outcome for RS is worse than for primary DLBCL. Autologous or allogeneic stem-cell transplantation could be considered in this particular situation.

Peripheral blood smear in patient with CLL presenting AIHA, showing lymphoid cells, spherocytes and smudge cells



AIHA, autoimmune haemolytic anaemia; CLL, chronic lymphocytic leukaemia. Fig. 10.15

Autoimmune haemolytic anaemia (AIHA) occurs in 5%-10% of CLL cases. It can be present at diagnosis but is more common in advanced stages.

Therapy-related AIHA can occur during and after all types of therapy, but tends to be more severe after fludarabine treatment.

First-line therapy for AIHA is high-dose steroids and/or rituximab. Cyclophosphamide or other CLL-specific therapy can be used, and splenectomy performed in refractory cases.

REVISION QUESTIONS

1. Why are CLL patients prone to infections?
2. What is RS?
3. How common is AIHA in CLL patients?

Summary: Chronic lymphocytic leukaemia/small lymphocytic lymphoma

- The CLL/SLL cell is a small B lymphocyte with a unique phenotype (CD5+, CD19+, CD23+) with clonality
- Lymphocytosis is required for CLL diagnosis; otherwise, the disease is classified as SLL
- Rai/Binet clinical staging and cytogenetic aberrations are the most used prognostic tools and are assessed before therapy decisions
- Asymptomatic cases should not be treated
- Continuous BTK inhibition or time-limited BCL2 inhibition in combination with an anti-CD20 antibody are recommended in most patients
- CIT can lead to long-duration remission in patients with mutated *IGHV* and without *TP53* aberrations
- Allogeneic stem-cell transplantation should be considered in fit patients with del(17p) and/or *TP53* mutation and in multi-refractory disease
- AIHA and transformation to high-grade lymphoma are both serious complications
- Infections are common and vaccination is recommended early in the disease

Further Reading

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Image sources: **Fig 10.5.** International CLL-IPI Working Group. Lancet Oncol 2016;17:779-790; **10.6.** Baliakas P, et al. Blood 2019;133:1205-1216; **10.8.** Al-Sawaf O, et al. J Clin Oncol 2021;39:4049-4060; **10.9.** Allan JN, et al. Br J Haematol 2022;196:947-953; **10.10.** Lazarian G, et al. J Clin Oncol 2017;35:984-993; **10.11.** Seymour JF, et al. Blood 2022;140:839-850; **10.12.** Moreno C, et al. J Exp Clin Cancer Res 2021;40:321; **10.15.** Al Hadidi S & Udden M. Clin Case Rep 2020;8:1112-1113. All other figures courtesy of the authors.

11 Mantle cell lymphoma

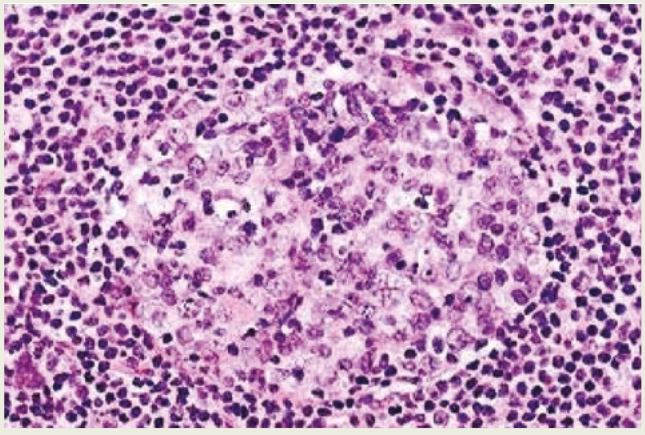
Pathology and biology

The disease is named after its histological appearance. Cells resemble those of the mantle zone surrounding normal germinal centre (GC) follicles.

Mantle cell lymphoma (MCL) cells can proliferate in a nodular or diffuse pattern accumulating in the lymphoid tissue. Cytologically, two cell types are distinguished: typical and blastoid.

Typical MCL cells have intermediate size and irregular nuclei, while in the more aggressive blastoid variant, cells are large, with finely dispersed chromatin.

Histological appearance of MCL: cells are distributed around the atrophic naked germinal centre, revealing a mantle zone pattern



MCL, mantle cell lymphoma. Fig. 11.1

Immunohistochemical staining of cyclin D1: the positive nuclear reaction indicates cyclin D1 overexpression

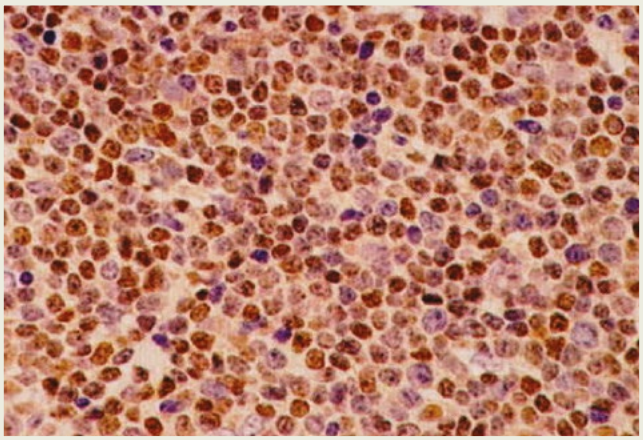


Fig. 11.2

The typical immunophenotype expression resembles that of mature B lymphocytes (CD19+, CD20+, CD79a+) but with coexpression of the T-cell antigen CD5.

In contrast to other CD5+ lymphoma (chronic lymphocytic leukaemia), MCL is CD23-negative and lacks expression of the GC-associated antigens B-cell lymphoma 6 (BCL6) and CD10.

The genetic hallmark of MCL is the translocation t(11;14)(q13;q32), found in >95% of cases, which brings the immunoglobulin heavy chain (IGH) promoter near to the *cyclin D1* gene.

This genetic alteration triggers the overexpression of cyclin D1, a protein that promotes cell proliferation and inhibits apoptosis.

MCL is the lymphoma with the highest rate of secondary cytogenetic alterations, such as *ATM* or *p53* inactivation by mutation and deletion, both associated with shorter overall survival (OS).

On the other hand, a minority of MCLs have an indolent clinical course. These cases carry only the t(11;14) translocation and few other genomic alterations.

Possible evolution of MCL over time

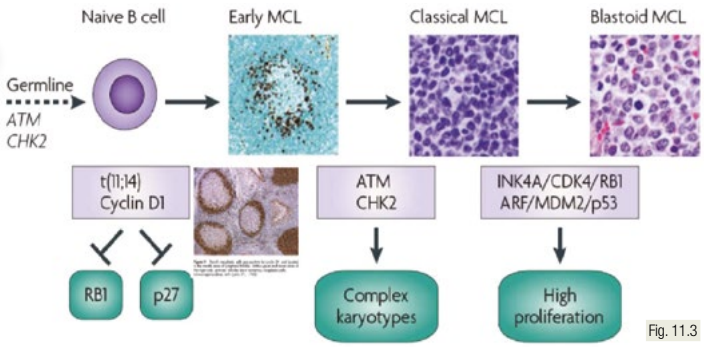


Fig. 11.3

ATM, ataxia telangiectasia mutated; CDK4, cyclin-dependent kinase 4; MCL, mantle cell lymphoma; RB1, retinoblastoma 1.

REVISION QUESTIONS

1. What is the explanation for the term 'mantle cell' lymphoma?
2. What is the typical immunophenotype in MCL?
3. What is the genetic key event in MCL, and what are the secondary genetic alterations?

Clinical presentation, prognosis

The incidence of MCL is 2-3/100 000 persons/year, comprising ~5%-10% of all non-Hodgkin lymphomas (NHLs).

Median age at diagnosis is 63-70 years; males develop this disease more frequently than females (male:female ratio = 3-4:1).

The median survival is only 4-5 years, showing no survival plateau. MCL has one of the worst prognoses of all NHLs and is mostly considered incurable.

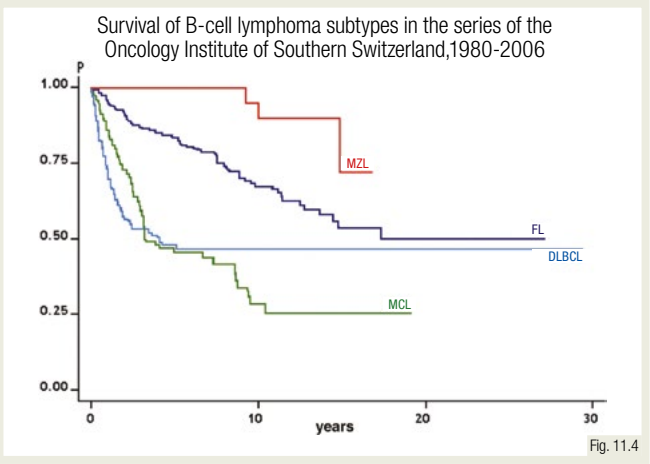


Fig. 11.4

DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma.

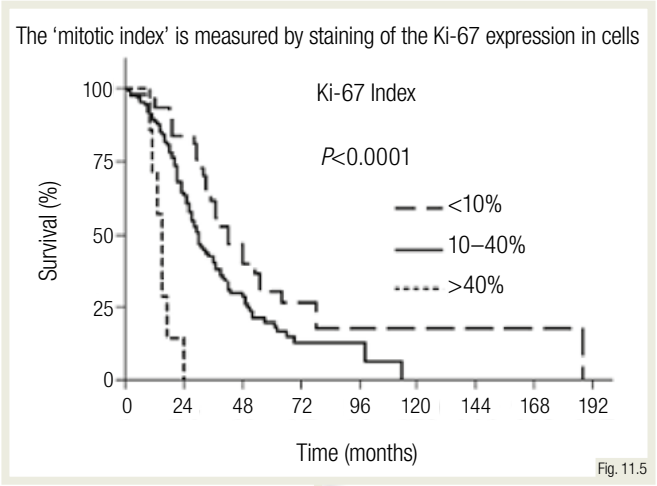


Fig. 11.5

The mitotic index, an immunohistochemical stain that measures Ki-67 expression in cells, is an important predictor of the clinical course of the disease.

The prognosis of MCL patients can be estimated with the help of a clinical prognostic score, called MIPI (Mantle Cell Lymphoma International Prognostic Index), or with the combined MIPI (MIPI-c) which includes the Ki-67 mitotic index.

The MIPI score is calculated by using age, lactate dehydrogenase (LDH) level, performance status (PS) and absolute leukocyte count. It has an impact on the choice of therapy and prognosis.

Staging examinations include positron emission tomography (PET) or computed tomography (CT) and bone marrow (BM) examination. Endoscopy should be performed in patients with localised stages or gastrointestinal (GI) symptoms.

Most patients present with stage IV disease. Extranodal involvement is common (>90%), especially in the BM (90% of cases) and the GI tract (up to 60%).

In contrast to indolent lymphomas, patients should receive treatment at diagnosis, except for the few cases (10%-15%) with clinically slow progression.

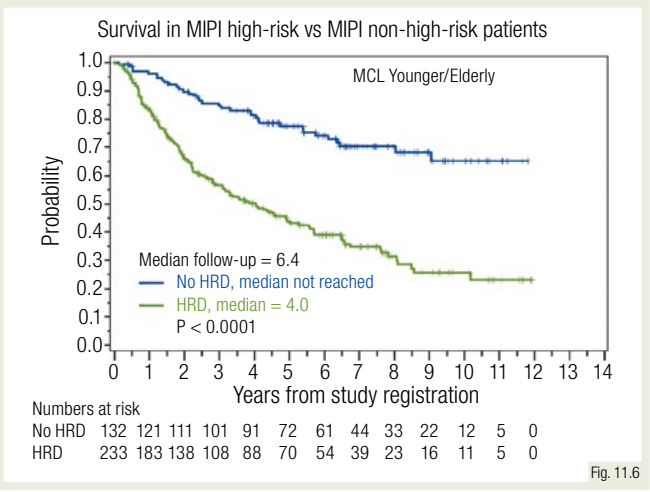


Fig. 11.6

HRD, high-risk disease; MCL, mantle cell lymphoma; MIPI, Mantle Cell Lymphoma International Prognostic Index.

REVISION QUESTIONS

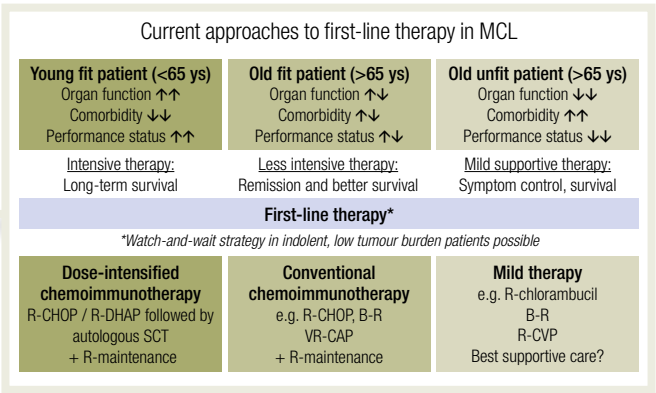
1. How does the overall prognosis of MCL compare with other lymphomas?
2. How do patient characteristics and Ki-67 expression affect OS?
3. At which stage do most patients present with MCL?

Treatment

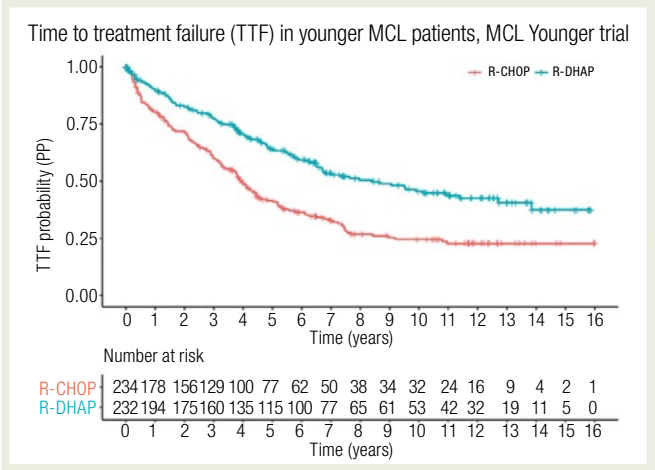
At time of diagnosis, most patients require treatment, dependent on their overall PS. Chemoimmunotherapy remains the main treatment modality.

For young and fit patients, dose-intensified chemoimmunotherapy, followed by autologous stem-cell transplantation (ASCT), is the standard. A watch-and-wait strategy in indolent, low tumour burden patients is possible.

The addition of rituximab to the induction therapy increases the quality and duration of responses; it is now part of all current induction regimens.



B-R, bendamustine plus rituximab; MCL, mantle cell lymphoma; R, rituximab; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; R-CVP, rituximab, cyclophosphamide and prednisone; R-DHAP, rituximab, dexamethasone, high-dose cytarabine and cisplatin; SCT, stem-cell transplantation; VR-CAP, bortezomib, rituximab, cyclophosphamide, doxorubicin and prednisone. Fig. 11.7



MCL, mantle cell lymphoma; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; R-DHAP, rituximab, dexamethasone, high-dose cytarabine and cisplatin. Fig. 11.8

Central nervous system (CNS) prophylaxis may be discussed for patients at high risk of CNS involvement, identified by elevated LDH, poor PS, blastoid variant, high MIPI score and B symptoms.

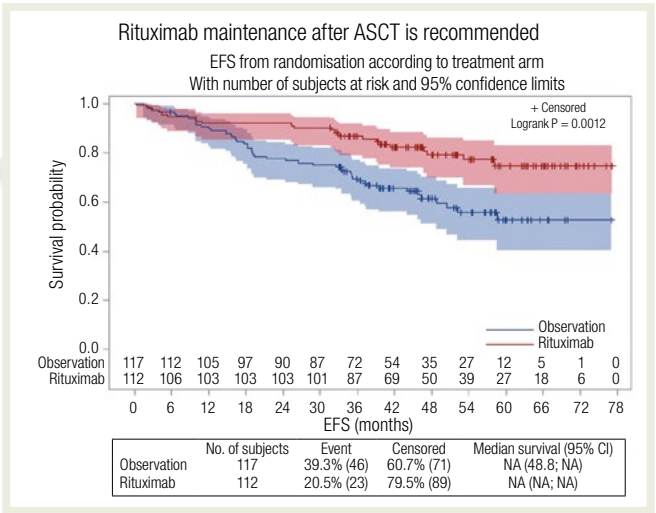
Regimens combining rituximab and high-dose cytarabine (AraC) chemotherapy (ChT) are a validated and very effective therapeutic approach in younger patients.

High-dose methotrexate-containing regimens combined with AraC, followed by consolidation with ASCT, is an alternative dose-intensified approach, but less commonly used in Europe.

Rituximab maintenance after ASCT every 2 months for 3 years is associated with higher rates of both progression-free survival (PFS) and OS and is standard of care.

Molecular remission after induction is a strong prognostic factor for long-term remission. The incorporation of new drugs such as bortezomib, lenalidomide or ibrutinib in first-line protocols is the next step towards improving patients' OS.

The goal of these intensive therapies is a deeper remission and long-term lymphoma-free survival, justifying more toxicities.



ASCT, autologous stem-cell transplantation; CI, confidence interval; EFS, event-free survival; NA, not applicable. Fig. 11.9

REVISION QUESTIONS

1. What is the main treatment modality for MCL?
2. In which way is the choice of treatment intensity dependent on patient characteristics?
3. Which regimens are mostly favoured by clinicians?

Treatment (continued)

In older patients, conventional chemoimmunotherapy is the treatment choice, with an overall response rate (ORR) of ~90%. It is appropriate for patients who are not candidates for ASCT. Although not curative, most patients will achieve complete remission.

Bendamustine in combination with rituximab (B-R) and R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone) are commonly used regimens in elderly patients. ORRs and OS rates are comparable; however, B-R is associated with fewer side effects.

Bortezomib in combination with R-CAP (rituximab, cyclophosphamide, doxorubicin and prednisone; VR-CAP) shows better PFS and OS compared with R-CHOP, with more toxicity, and may be a good option for aggressive MCL in elderly patients not eligible for ASCT.

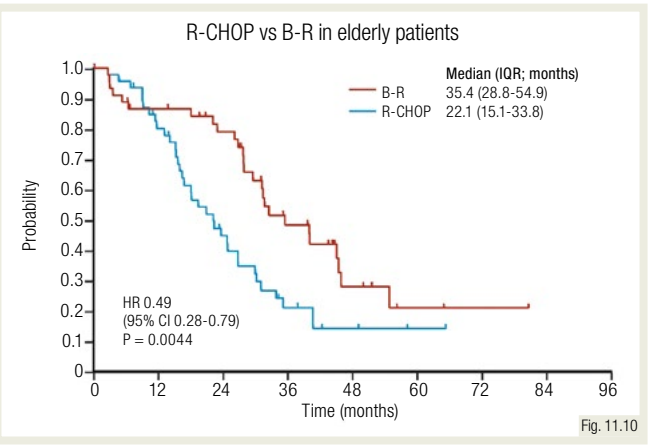


Fig. 11.10

B-R, bendamustine plus rituximab; CI, confidence interval; HR, hazard ratio; IQR, interquartile range; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone.

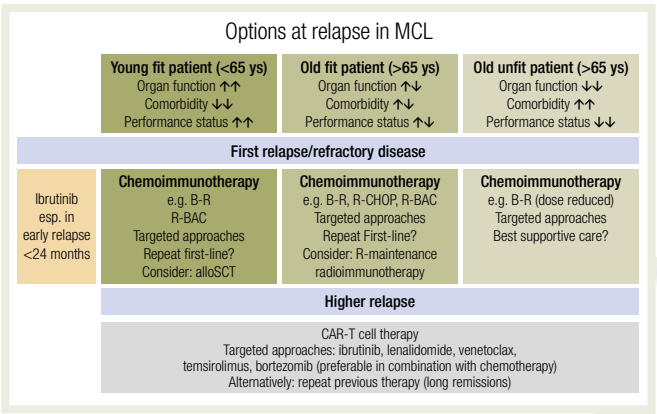


Fig. 11.11

alloSCT, allogeneic stem-cell transplantation; B-R, bendamustine and rituximab; CAR, chimeric antigen receptor; MCL, mantle cell lymphoma; R-BAC, rituximab, bendamustine and cytarabine; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone.

Rituximab as maintenance therapy every 2 months following R-CHOP ChT significantly improves PFS, even though its activity is lower than in indolent B-cell NHL.

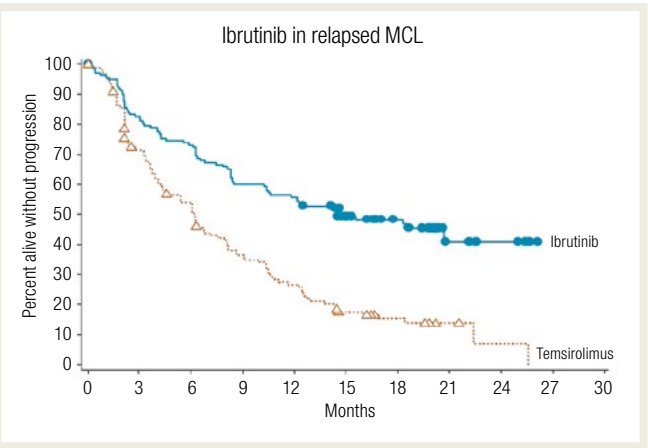
For patients with relapsed MCL, the choice of therapy depends upon multiple factors, including prior therapy, duration of response and patient characteristics, which impact the ability to tolerate ASCT.

In first relapse, AraC-containing therapy or B-R are options depending on prior therapy and response duration. For patients who have not yet received ASCT, this option can be used to consolidate second remission.

Ibrutinib is an oral, irreversible inhibitor of Bruton tyrosine kinase (BTK) and has shown significant activity in the relapsed setting. BTK inhibition in early relapse seems to be favourable compared with salvage chemoimmunotherapy.

Patients with relapsed or refractory MCL ineligible for intensive ChT or stem-cell transplantation have longer PFS with lenalidomide compared with other monotherapies.

Trials combining lenalidomide with rituximab are promising in MCL as maintenance therapy, upfront therapy for frail patients and in relapsed disease. Future trials are warranted for this well-tolerated regimen.



MCL, mantle cell lymphoma.

Fig. 11.12

REVISION QUESTIONS

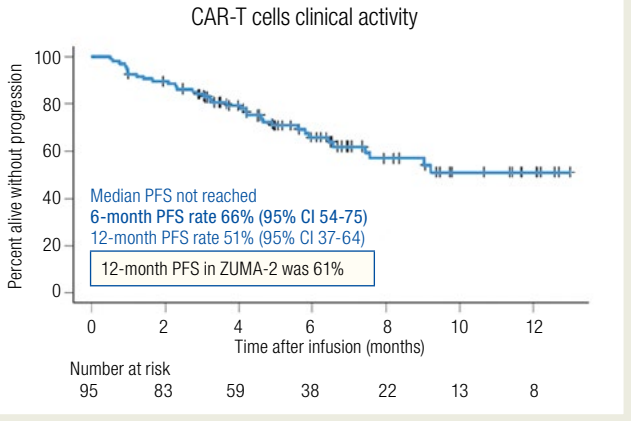
1. Which chemotherapeutic approach is mostly chosen in elderly patients?
2. Which targeted therapy is very effective in second-line and refractory patients?
3. What are the options at first relapse?

Novel and future therapies

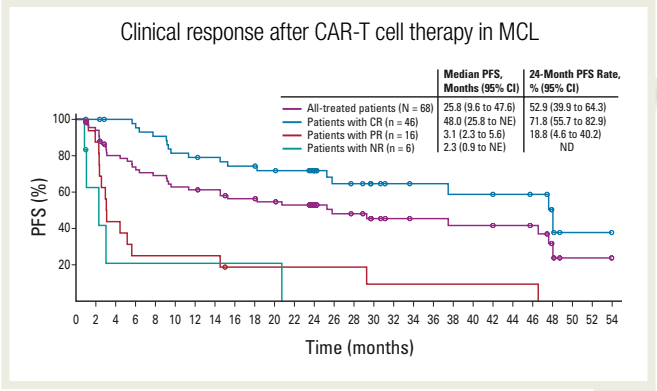
Anti-CD19 chimeric antigen receptor (CAR)-T cell therapy achieves durable remissions in the majority of patients with higher relapse, but is associated with serious and potentially life-threatening toxicity.

Brexucabtagene autoleucel is a CAR-T cell therapy, effective in relapsed or refractory MCL, with an ORR of 93% and complete response (CR) rate of 67%. At 12 months, PFS and OS are 61% and 83%, respectively.

Patients who experience a CR soon after CAR-T cell therapy have a much longer time till progression than patients not achieving CR.



CAR, chimeric antigen receptor; CI, confidence interval; PFS, progression-free survival. Fig. 11.13



CAR, chimeric antigen receptor; CI, confidence interval; CR, complete response; MCL, mantle cell lymphoma; ND, no data; NE, not estimable; NR, no response; PFS, progression-free survival; PR, partial response. Fig. 11.14

Durable response rates with CAR-T cell therapy are seen in high-risk populations with *TP53* mutation, blastoid variant, high Ki-67, high MIPI and older patients, and seem equally effective compared with non-high-risk patients.

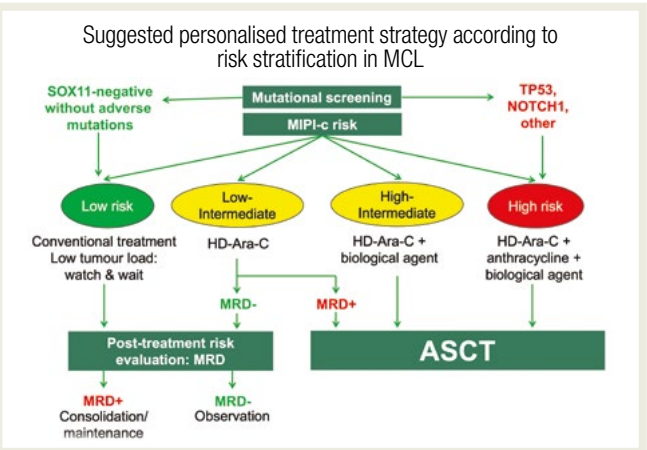
It is preferable that this complex therapy is administered in an experienced centre, due to elaborate logistic needs and potential severe side effects such as cytokine release syndrome (CRS), neurological toxicities and opportunistic infections.

Due to the treatment-related mortality, allogeneic stem-cell transplantation (alloSCT) is generally only proposed to fit patients who have relapsed after ASCT. Initial results of non-myeloablative alloSCT are promising, but longer follow-up is necessary.

Next-generation BTK inhibitors (such as zanubrutinib, acalabrutinib and pirtobrutinib), BCL2 inhibitors, immunomodulatory agents or bispecific antibodies as novel agents further widen the therapeutic landscape.

Trials incorporating novel agents in the frontline or relapsed settings in combination with conventional or high-dose chemoimmunotherapy show promising results in achieving longer PFS and OS in this challenging disease.

Future risk-adapted approaches, involving molecular, clinical and patient characteristics, will further help tailor the amount or type of therapy to achieve the most optimal long-term response with the least toxicity for MCL patients.



ASCT, autologous stem cell transplantation; HD-Ara-C, high-dose cytarabine-based regimen; MCL, mantle cell lymphoma; MIPI-c, combined MCL (mantle cell lymphoma) International Prognostic Index; MRD, minimal residual disease. Fig. 11.15

REVISION QUESTIONS

1. What variables determine the choice of secondary treatment in MCL?
2. In which patients should CAR-T cell therapy be considered?
3. Which molecular targeted substances are efficient in relapsed MCL?

Summary: Mantle cell lymphoma

- Histology: mantle zone cells surrounding normal GC follicles
- Biology: the translocation t(11;14)(q13;q32) leading to cyclin D1 overexpression is typical
- MCL prognosis can be estimated based on the MIPI and c-MIPI
- Usually aggressive in behaviour, therefore most patients are treated at diagnosis
- Initial treatment is always a ChT approach, depending on patient characteristics
- Young patients should be treated with aggressive regimens followed by ASCT as first line
- Elderly patients should initially be treated with conventional ChT combinations
- Rituximab maintenance therapy should be discussed after response
- At relapse, young patients should be evaluated for alloSCT and CAR-T cell therapy
- Molecular targeted substances have widened the options for treatment in disease relapses and in first-line in combination with chemoimmunotherapy

Further Reading

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Image sources: **Fig. 11.1, 11.2.** Yatabe Y, et al. Am J Surg Pathol 1996;20:1110-1122; **11.3.** Jares P, et al. Nat Rev Cancer 2007;7:750-762; **11.4.** Ghielmini M, Zucca E. Blood 2009;114:1469-1476; **11.5.** Hoster E, et al. Blood 2008;111:558-565; **11.6.** Dreyling M, ASH 2019. Courtesy of Martin Dreyling; **11.8.** Hermine O, et al. Lancet 2016;388:565-575; **11.9.** adapted from Le Gouill S, et al. N Engl J Med 2017;377:1250-1260; **11.10.** Rummel MJ, et al. Lancet 2013;381:1203-1210; **11.12.** Dreyling M, et al. Lancet 2015;387:770-778; **11.13.** adapted from Wang M, et al. N Engl J Med 2020;382:1331-1342; **11.14.** Wang M, et al. J Clin Oncol 2023;41:555-567. All other figures courtesy of the authors.

12 Extranodal marginal zone lymphoma of MALT type

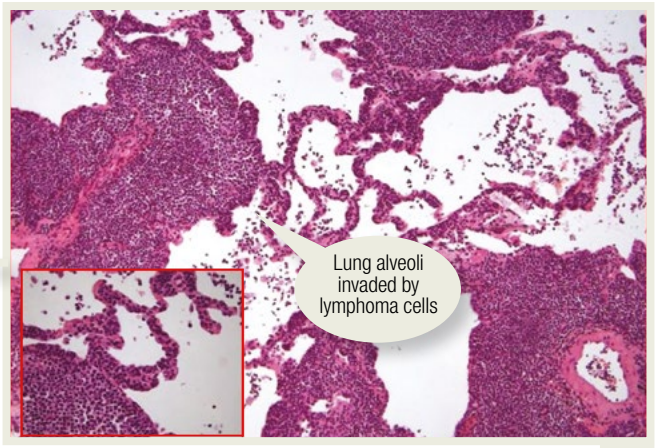
Pathology

MALT lymphoma is a subtype of marginal zone lymphoma (MZL), deriving from the marginal zone of lymphoid follicles.

It develops in extranodal sites (i.e. outside the lymph nodes [LNs]). The MALT acronym stands for 'mucosa-associated lymphoid tissue'.

It is composed of morphologically heterogeneous small B cells, and scattered, large cells (blasts) as in the marginal zone of reactive follicles.

Pulmonary MZL



MZL, marginal zone lymphoma.

Fig. 12.1

Lymphoepithelial lesions

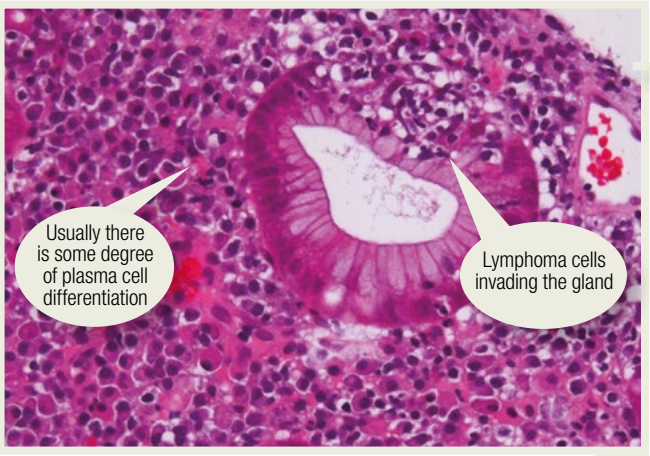


Fig. 12.2

Lymphoma cells can infiltrate and disrupt the mucosal crypts and glands, forming lymphoepithelial lesions, typical but not pathognomonic of MALT lymphoma.

There are no specific immunohistochemical markers for MALT lymphoma. Cells express CD20, surface immunoglobulin (Ig, usually IgM) and lack CD5 and CD10.

The presence of Ig light chain restriction can often be difficult to demonstrate in small biopsy specimens.

Monoclonality can be detected by polymerase chain reaction (PCR) in most cases, but, by itself, cannot be diagnostic of MALT lymphoma.

If large cells form solid or sheet-like proliferations, this must be reported as an associated diffuse large B-cell lymphoma (DLBCL), indicating histological transformation.

The disease can occur in any anatomical site: stomach (most common site), thyroid, salivary glands, lung, orbits/conjunctiva, breast, skin and others.

Large cell component

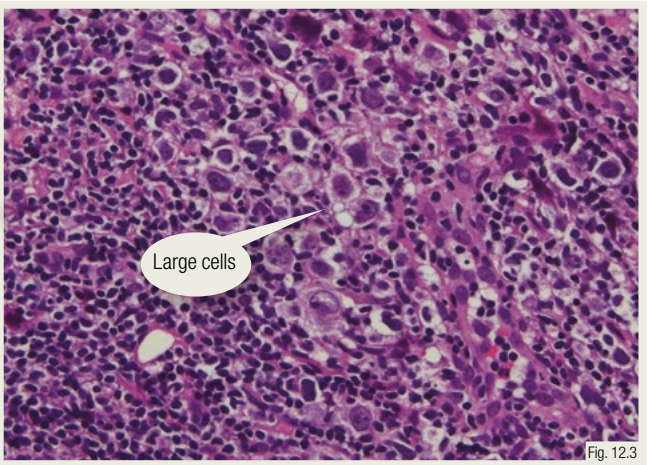


Fig. 12.3

REVISION QUESTIONS

1. What does 'MALT' mean?
2. What is a lymphoepithelial lesion?
3. In which anatomical sites can extranodal MZLs occur?

Epidemiology and biology

Many MALT lymphomas originate from lymphoid tissue acquired in the background of a chronic inflammation, caused by an autoimmune disorder or by infections.

Somatic hypermutation and intraclonal variation of the Ig heavy chain variable (*IGHV*) genes are consistently found, suggesting a continuous antigen-driven process.

Hashimoto's thyroiditis or Sjögren's syndrome have been linked to MALT lymphomas of the thyroid and of the lachrymal and salivary glands, respectively.

THE MALT CONCEPT

Mucosa-Associated Lymphoid Tissue

- Native MALT
  normally present in certain extranodal sites
  (e.g. Peyer's patches)
- Acquired MALT
  where lymphoid tissue is not a natural component
  (e.g. Sjögren, Hashimoto, *H. pylori*-gastritis)

H. pylori, *Helicobacter pylori*; MALT, mucosa-associated lymphoid tissue. Fig. 12.4

Immunohistochemical staining of *Helicobacter pylori* in a gastric biopsy

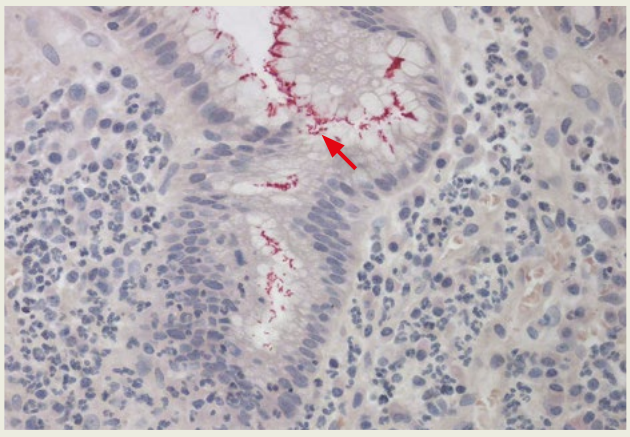


Fig. 12.5

In gastric MALT lymphoma there is evidence that a chronic infection with *Helicobacter pylori (H. pylori)* has a pathogenetic role.

A history of chronic *H. pylori* infection is present in most patients with gastric MALT lymphoma and the bacterium can usually be detected in the stomach.

Eradication of *H. pylori* infection with antibiotics and proton pump inhibitors (PPIs) results in histological regression in ~75% of gastric MALT lymphomas.

Other infectious agents are linked to non-gastric MALT lymphomas. *Chlamydophila psittaci* has been associated with ocular adnexal lymphoma.

Other examples are *Borrelia burgdorferi* in cutaneous lymphomas and *Campylobacter jejuni* in immunoproliferative small intestinal disease (IPSID).

Eradication of these agents is also reported to induce MALT lymphoma regression in some cases, but the evidence is less solid than for *H. pylori*.

Immunohistochemical staining of *Chlamydophila psittaci* in an orbital biopsy

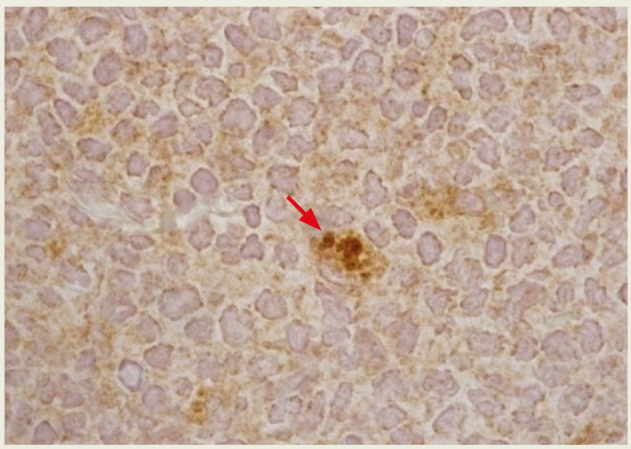


Fig. 12.6

REVISION QUESTIONS

1. Which conditions are associated with the development of MALT?
2. Which are the lines of evidence implicating *H. pylori* infection in the pathogenesis of gastric MALT lymphoma?
3. In which other anatomical sites of MALT lymphoma have bacterial infections been involved?

Molecular biology

Unbalanced genomic aberrations (trisomy 3, trisomy 18, 6q23 deletion) and chromosomal translocations are recurrently observed in MALT lymphomas.

The most common translocation is the t(11;18)(q21;q21), fusing *BIRC3* on 11q21 with *MALT1* on 18q21.

The t(14;18)(q32;q21) chromosomal translocation brings *MALT1* under the control of the promoter region of the *IGHV* genes with *MALT1* deregulation.

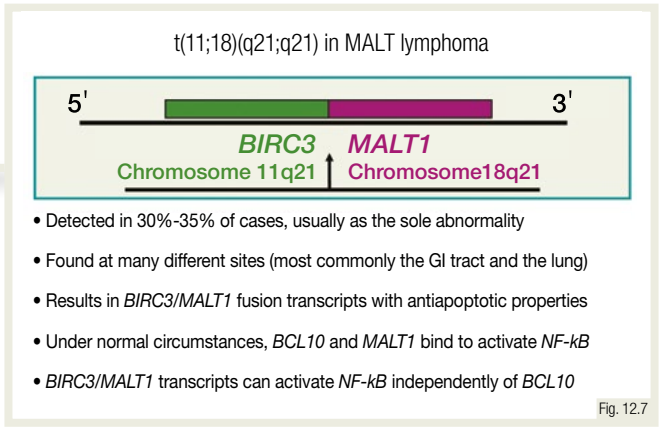


Fig. 12.7

BCL10, B-cell lymphoma 10; GI, gastrointestinal; MALT1, mucosa-associated lymphoid tissue 1; NF-kB, nuclear factor-kappa B.

H. pylori and lymphoma pathogenesis

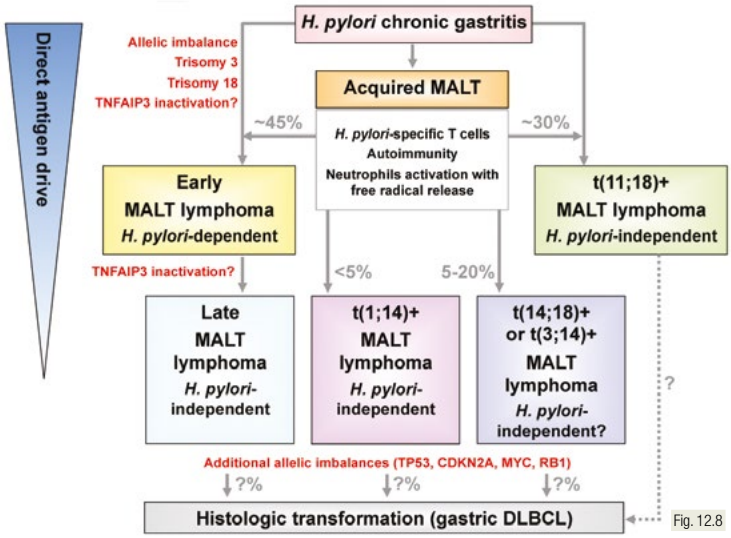


Fig. 12.8

DLBCL, diffuse large B-cell lymphoma; *H. pylori*, *Helicobacter pylori*; MALT, mucosa-associated lymphoid tissue; RB1, retinoblastoma 1; TNFAIP3, tumour necrosis factor alpha-induced protein 3.

Less common is the t(1;14)(p22;q32) translocation, which results in a high level of B-cell lymphoma 10 (BCL10) expression due to its juxtaposition to the IGHV promoter region.

A pathogenetic model has been proposed for gastric MALT lymphoma incorporating the chronic antigenic stimulation and the genetic lesions.

At least four genetic lesions determine the activation of the nuclear factor-kappa B (NF-κB) signalling pathway, making this an interesting therapeutic target.

The NF-κB pathway has a central physiological role in regulating immunity, inflammation, cell survival and apoptosis.

The chromosomal translocations are mutually exclusive and show different frequencies at different anatomical sites.

Gastric MALT lymphomas with t(11;18) are often *H. pylori*-negative and do not respond to antibiotics, but may have a lower risk of histological transformation.

Most common lesions in extranodal MZLs

Chromosomal aberrations	Involved genes	NF-κB pathway activation	Frequency	Preferential anatomical site
t(11;18)(q21;q21)	*BIRC3-MALT1*	Yes	15%-40%	Stomach, lung
t(14;18)(q32;q21)	*IGHV-MALT1*	Yes	20%	Lung, salivary gland, skin, ocular adnexa
t(1;14)(p22;q32)	*IGHV-BCL10*	Yes	<5%	Stomach, lung
t(3;14)(p13;q32)	*IGHV-FOXP1*	No	<5%	Unclear
6q23 loss	*TNFAIP3*	Yes	15%-30%	Equal distribution
Trisomy 3/3q gain	Unclear	Unclear	20%-40%	Equal distribution
Trisomy 18/18q gain	Unclear	Unclear	20%-40%	Equal distribution

Fig. 12.9

BCL10, B-cell lymphoma 10; IGHV, immunoglobulin heavy chain variable; MALT1, mucosa-associated lymphoid tissue 1; MZL, marginal zone lymphoma; NF-kB, nuclear factor-kappa B; TNFAIP3, tumour necrosis factor alpha-induced protein 3.

REVISION QUESTIONS

1. Which is the most common chromosomal translocation in MALT lymphomas?
2. Which important signalling pathway is affected in the majority of cases?
3. Does the presence of t(11;18) have any clinical relevance?

Clinical presentation, work-up and treatment

Presenting symptoms are related to the primary site. High lactate dehydrogenase (LDH) or beta-2 microglobulin levels as well as B symptoms are extremely rare.

MALT lymphoma is usually localised. The clinical course is indolent with long-term overall survival (OS) rates >80% at 5 years. *H. pylori*-associated gastric MALT lymphomas and cutaneous MZLs may have a particular indolent course.

Dissemination to regional LNs or to multiple mucosal sites can occur in up to 25% of cases. Bone marrow (BM) is involved in <20% of cases.

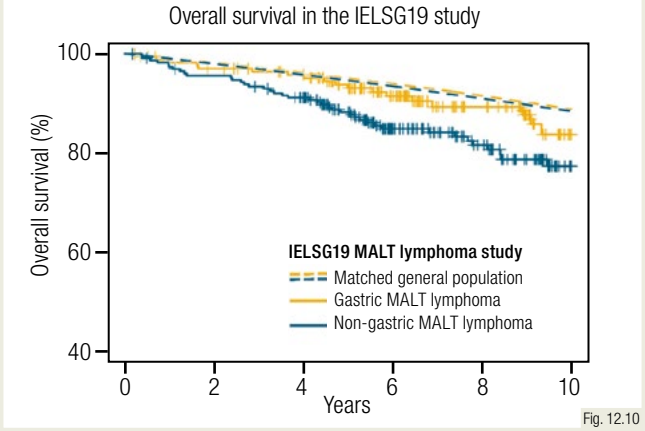


Fig. 12.10

IELSG, International Extranodal Lymphoma Study Group; MALT, mucosa-associated lymphoid tissue.

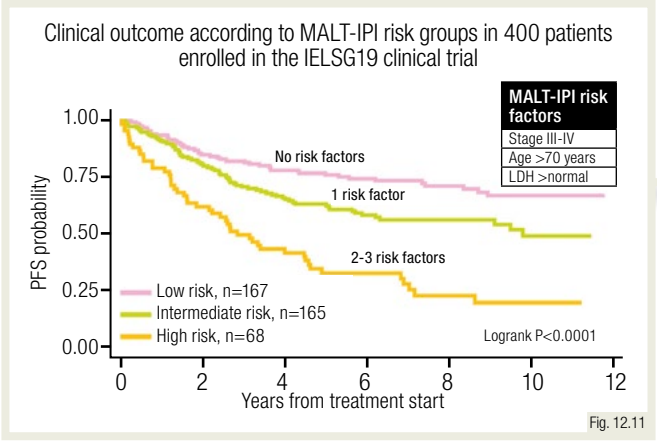


Fig. 12.11

IELSG, International Extranodal Lymphoma Study Group; IPI, International Prognostic Index; LDH, lactate dehydrogenase; MALT, mucosa-associated lymphoid tissue; PFS, progression-free survival.

Work-up should include blood counts, biochemistry, whole-body computed tomography (CT) and BM biopsy.

The MALT lymphoma International Prognostic Index (MALT-IPI) predicts outcome.

H. pylori status should be determined either by immunohistochemistry (IHC), breath test or serology in patients with gastric MALT. Gastroduodenal endoscopy with multiple biopsies is recommended in all MALT lymphomas. In gastric MALT, endoscopic ultrasound provides prognostic information.

^{18}F fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET)–CT can be useful when radiotherapy (RT) is planned.

H. pylori eradication is the initial choice for localised gastric MALT lymphoma. After 4-6 weeks a breath test should be performed to confirm *H. pylori* eradication.

Triple/quadruple therapy (e.g. PPI, clarithromycin, amoxicillin or metronidazole) is most commonly used to eradicate *H. pylori*. Despite different criteria for histological response, overall, 75% of patients achieve durable remissions.

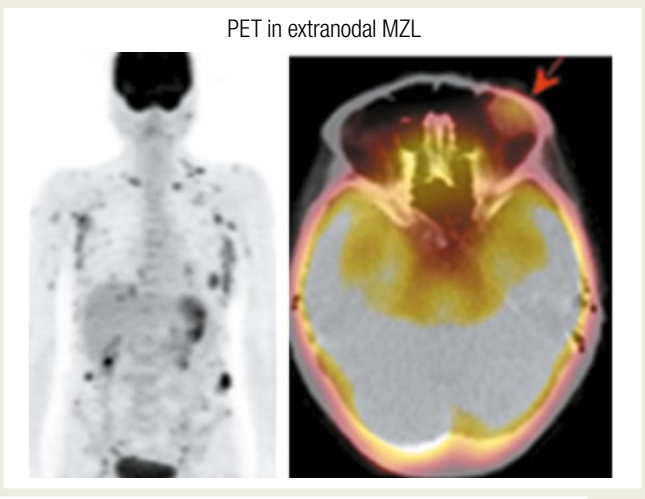


Fig. 12.12

MZL, marginal zone lymphoma; PET, positron emission tomography.

REVISION QUESTIONS

1. How often do patients with MALT lymphoma present with advanced disease?
2. What is the front-line treatment for localised *H. pylori*-positive gastric MALT lymphoma?
3. What proportion of patients with MALT lymphoma are expected to be long-term survivors?

Treatment (continued) and follow-up

Gastric MALT lymphoma usually regresses within 6 months after *H. pylori* eradication but delayed (>12 months) responses have been reported.

Endoscopic follow-up is recommended with multiple biopsies at 3-6 months after antibiotics, then twice a year for 2 years.

Minimal residual disease is sometimes seen, but can be safely followed with watchful waiting in patients without symptoms or clinical/endoscopic progression.

Endoscopy

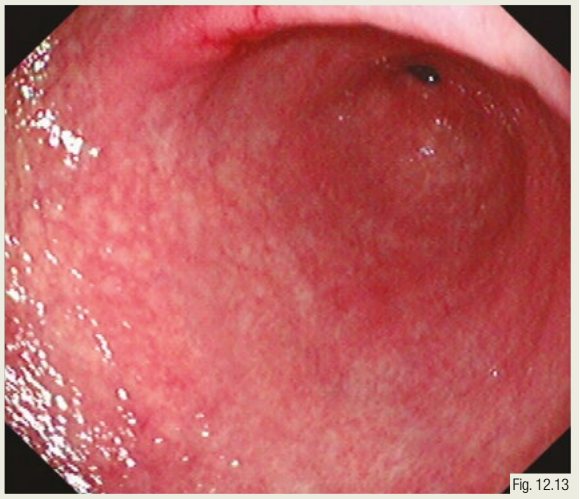


Fig. 12.13

Annual endoscopy, blood counts and clinical, radiological or ultrasound examinations are recommended, as these patients are at higher risk for gastric carcinoma.

For *H. pylori*-negative or antibiotic-resistant gastric MALT lymphomas, or for non-gastric localisations, no specific treatment can be considered as standard.

RT (24 Gy) is often recommended for localised non-gastric or antibiotic-resistant gastric cases, resulting in an excellent long-term local control.

Radiotherapy results in MALT lymphoma

Series	n.	Site	RT dose (Gy)	Freedom from treatment failure
Goda, 2010	192	Gastric and non-gastric	17.5-35	95% at 10 years for thyroid 92% for stomach 68% for salivary glands 67% for orbit
Wirth, 2013	102	Gastric	26-46	88% at 10 years
Ohga, 2013	53	Orbit	24-30	91% at 5 years
Kim, 2013	64	Gastric	30-44	89% at 5 years
Nam, 2014	48	Gastric	30-45	84% at 5 years
Harada, 2014	86	Orbit	30-46	88% at 10 years
Teckie, 2017	294	Gastric and non-gastric	≤30 Gy (80%) >30 Gy (15%)	95% at 10 years
Niwa, 2020	81	Orbit	30-36	94% at 5 years
Fang, 2021	75	Gastric and non-gastric	24-40	71% at 10 years
Yahalom, 2021	178	Gastric	22-43	60% at 10 years
Nam, 2021	145	Gastric	24-40	94% at 5 years
MacManus, 2021	60	Non-gastric	24-31	79% at 5 years
Hoskin, 2021	41	Gastric and non-gastric	24	100% at 5 years
Hoskin, 2021	43	Gastric and non-gastric	4	88% at 5 years

Toxicity can be reduced using modern techniques and minimising the RT dose to non-target organs

MALT, mucosa-associated lymphoid tissue; RT, radiotherapy.

Fig. 12.14

In patients with disseminated disease, a watch-and-wait policy in asymptomatic patients is acceptable, as in most indolent lymphomas.

When front-line systemic therapy is required, chemoimmunotherapy (with a non-intensive regimen) is an appropriate treatment option.

Histological presence of sheets of large cells should be treated according to the recommendations for DLBCL treatment.

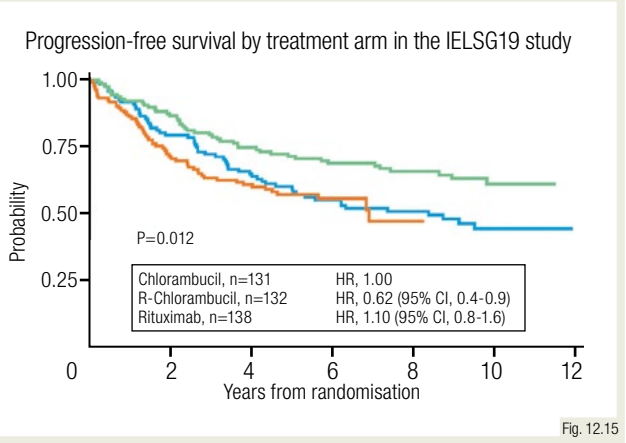


Fig. 12.15

CI, confidence interval; HR, hazard ratio; IELSG, International Extranodal Lymphoma Study Group; R, rituximab.

REVISION QUESTIONS

1. Is systemic treatment always needed for patients with disseminated MALT lymphoma?
2. What is the standard therapy for disseminated MALT lymphoma?
3. Are aggressive chemotherapy (ChT) regimens the first-line therapeutic approach for patients with non-gastric MALT lymphoma?

Summary: Extranodal marginal zone lymphoma of MALT type

- Histology: heterogeneous small cells, scattered large cells and plasma cell differentiation
- Epidemiology: association with chronic inflammation and pathogenetic role of *H. pylori* infection in gastric lymphoma
- Biology: translocation t(11;18) and other genetic alterations causing NF-κB dysregulation
- Usually indolent behaviour, with prolonged survival irrespective of treatment
- *H. pylori* eradication may result in lymphoma regression in most *H. pylori*-positive gastric MALT lymphoma
- Endoscopic evaluations should be performed regularly during the follow-up of patients with gastric MALT lymphoma due to the increased risk of gastric carcinoma
- The MALT-IPI represents a tool to identify patients with different clinical outcomes
- RT can be used in *H. pylori*-negative and localised non-gastric cases
- Rituximab plus ChT is effective in disseminated disease; aggressive regimens are not usually needed

Further Reading

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Image sources: **Fig. 12.1, 12.2, 12.3, 12.5.** Courtesy Luca Mazzucchelli, Locarno, Switzerland; **12.6.** courtesy Maurilio Ponzoni, Milan, Italy; **12.11.** based on information from Thieblemont C, et al. Blood 2017;130:1409-1417; **12.12.** courtesy Luca Ceriani, Bellinzona, Switzerland; **12.13.** courtesy Michele De Boni, Feltre, Italy; **12.15.** based on information from Zucca E, et al. J Clin Oncol 2017;35:1905-1912. All other figures courtesy of the authors.

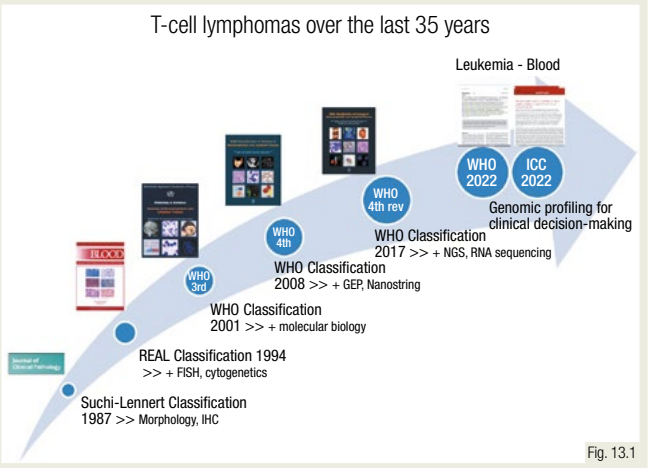
13 Nodal peripheral T-cell lymphomas

Epidemiology and classification

Over the last 35 years, technological advances have improved our knowledge about the biology of NK (natural killer)/T-cell derived malignancies.

The result is a better understanding of the cell of origin, the molecular/genetic features and the pathogenetic mechanisms of NK/T-cell lymphomas.

The improvement in this knowledge is reflected and summarised in successive international classifications of lymphoid neoplasms.



FISH, fluorescent *in situ* hybridisation; GEP, gene expression profiling; ICC, International Consensus Classification; IHC, immunohistochemistry; NGS, next-generation sequencing; REAL, Revised European-American Lymphoma Classification; WHO, World Health Organization.

Most frequent nodal and extranodal PTCL entities*, §	
Nodal T-follicular helper (TFH) cell lymphoma - Nodal TFH cell lymphoma, angioimmunoblastic type (AITL) - Nodal TFH cell lymphoma, follicular type - Nodal TFH cell lymphoma, not otherwise specified (NOS)	Nodal (80%)
Anaplastic large cell lymphoma, ALK+ (ALK+ ALCL)	
Anaplastic large cell lymphoma, ALK- (ALK- ALCL)	
Peripheral T-cell lymphoma, NOS (PTCL-NOS)	
Intestinal T-cell and NK-cell lymphoid proliferations and lymphomas - Monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL) - Enteropathy-associated T-cell lymphoma (EATL) - Intestinal T-cell lymphoma, NOS - Indolent T-cell lymphoproliferative disorder of the GI tract - Indolent NK-cell lymphoproliferative disorder of the GI tract	Extranodal (20%)
Breast implant-associated anaplastic large cell lymphoma (BIA-ALCL)	
Extranodal NK/T-cell lymphoma (NKTCL)	
Hepatosplenic T-cell lymphoma (HSTCL)	

Fig. 13.2

*According to the International Consensus Classification (2022) and 5th WHO Classification (2022).
§Primary cutaneous, leukaemic and virus-associated subtypes are omitted.
ALK, anaplastic lymphoma kinase; GI, gastrointestinal; NK, natural killer; PTCL, peripheral T-cell lymphoma; WHO, World Health Organization.

Peripheral (post-thymic) T-cell lymphomas (PTCLs) represent 10% of all lymphomas and are subdivided into nodal or extranodal, according to their main clinical presentation.

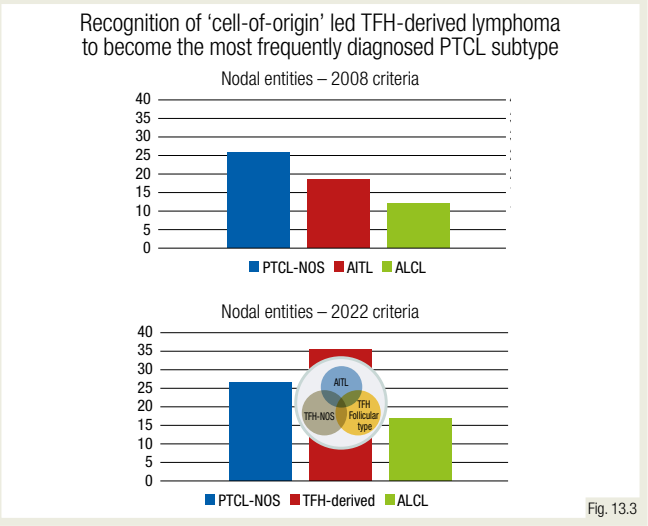
The nodal PTCL entities are: (i) T-follicular helper (TFH); (ii) anaplastic large cell lymphoma (ALCL), anaplastic lymphoma kinase-positive (ALK+) or negative (ALK-); (iii) PTCL not otherwise specified (PTCL-NOS).

Nodal PTCL presents in elderly patients (median age at diagnosis ~65 years), except for ALK+ ALCL, which is more common in children and young adults.

The recent recognition of TFH as the cell of origin in many nodal PTCLs resulted in TFH lymphoma becoming the most frequent nodal PTCL entity.

TFH lymphoma consists of three types: angioimmunoblastic T-cell lymphoma (AITL), which is the most frequent, follicular and NOS.

A new extranodal entity of ALCL occurring in association with breast implants has been described. The frequency of nodal systemic ALCL (sALCL) is unchanged.



AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large cell lymphoma; TFH, T-follicular helper; PTCL, peripheral T-cell lymphoma; PTCL-NOS, peripheral T-cell lymphoma, not otherwise specified.

REVISION QUESTIONS

1. Improved knowledge of which biological features has significantly advanced our understanding of NK/T-cell lymphomas?
2. Which type of nodal PTCL occurs predominantly in children and young adults?
3. Which entity is currently the most frequently diagnosed nodal PTCL?

Pathology and biology

The International Consensus Classification (ICC) provides diagnostic algorithms for nodal PTCL. ALCL tumour cells are large, CD30+, epithelial membrane antigen+, infiltrate nodal sinuses, show cohesive growth and often have horseshoe-shaped nuclei.

If carrying a t(2;5) translocation, ALCL expresses the ALK fusion protein (ALK+ ALCL), which is associated with younger age and better prognosis.

ALK- ALCL can harbour rearrangements of the *DUSP22* or *TP63* genes in 20%-30% and 5%-10% of cases, respectively. These rearrangements have a prognostic implication.

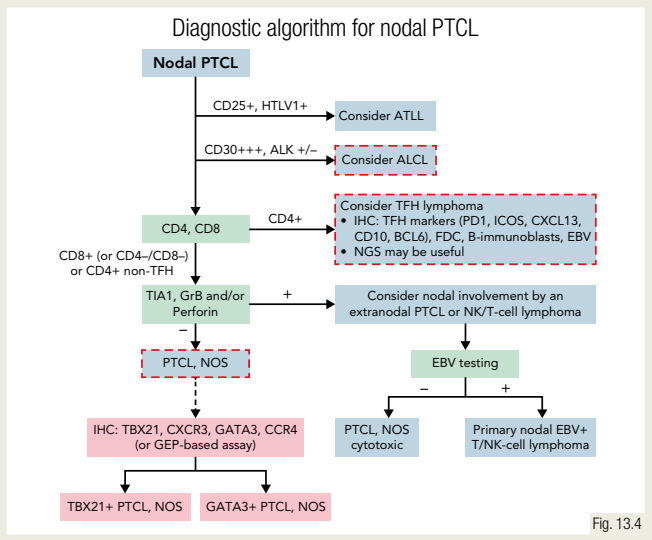
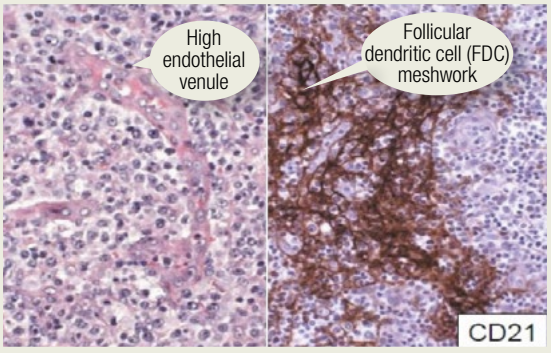


Fig. 13.4

ALCL, anaplastic large cell lymphoma; ALK, anaplastic lymphoma kinase; ATLL, adult T-cell leukaemia/lymphoma; BCL6, B-cell lymphoma 6; EBV, Epstein–Barr virus; FDC, follicular dendritic cell; GEP, gene expression profiling; HTLV1, human T-lymphotropic virus 1; ICOS, inducible T-cell costimulator; IHC, immunohistochemistry; NGS, next-generation sequencing; NK, natural killer; NOS, not otherwise specified; PD1, programmed cell death protein 1; PTCL, peripheral T-cell lymphoma; TFH, T-follicular helper.

Nodal PTCL – entity-specific features: I. TFH-lymphoma, AITL type



Mutations (%)	AITL
RHOA	45/72 (63%)
TET2	31/64 (48%)
IDH2	22/66 (33%)
DNMT3A	19/64 (30%)

Fig. 13.5

AITL, angioimmunoblastic T-cell lymphoma; FDC, follicular dendritic cell; PTCL, peripheral T-cell lymphoma; TFH, T-follicular helper.

In TFH lymphoma of AITL type, tumour cells are CD4+ and express TFH markers such as CXCL13, programmed cell death protein 1 (PD-1), inducible T-cell costimulator (ICOS), CD10 and B-cell lymphoma 6 (BCL6).

Mutations in epigenetic modifier genes such as *TET2*, *DNMT3A*, isocitrate dehydrogenase 2 (*IDH2*), and other gene mutations such as *RHOA* G17V are common.

AITL lesions show a vivid CD21+ follicular dendritic cell (FDC) meshwork. Presence of Epstein–Barr virus (EBV)+ large B-blasts is common. Secondary EBV+ DLBCL (diffuse large B-cell lymphoma) can arise from coexisting B-cell clones.

PTCL-NOS is a heterogeneous category and is still a diagnosis by exclusion. The malignant clone can exhibit a cytotoxic (possibly worse prognosis) or a helper phenotype.

Gene-expression profiling suggests two main subgroups with a TBX21 or a GATA3 signature. The GATA3 subgroup has been associated with a worse outcome.

Recent findings indicate that *DNMT3A* mutations define a specific cytotoxic (CD8+) subset among PTCL-NOS with TBX21 signature, characterised by adverse prognosis.

Nodal PTCL – entity-specific features: II. PTCL-NOS (left); III. ALK+ and ALK- ALCL (right)

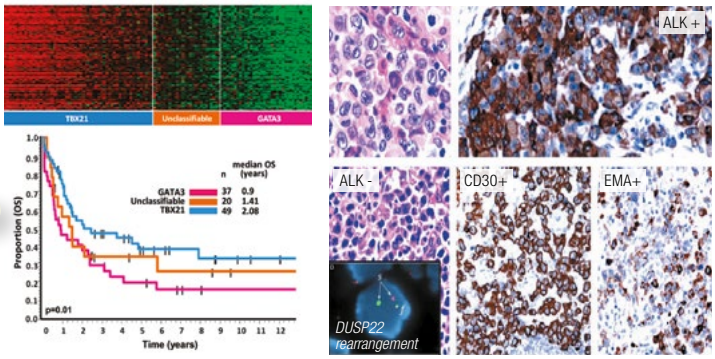


Fig. 13.6

ALCL, anaplastic large cell lymphoma; ALK, anaplastic lymphoma kinase; GATA3, GATA binding protein 3; GEP, gene expression profiling; OS, overall survival; PTCL, peripheral T-cell lymphoma; PTCL-NOS, peripheral T-cell lymphoma, not otherwise specified.

REVISION QUESTIONS

1. Which gene rearrangements with prognostic implications are found in a subset of ALK- ALCL?
2. Which secondary malignancy can arise from the tumour microenvironment in AITL?
3. Which are the two main gene expression signatures identified in PTCL-NOS and associated with different outcomes?

Clinical presentation and prognosis

Nodal PTCL often presents with B symptoms, disseminated disease, elevated lactate dehydrogenase (LDH) and some degree of bone marrow infiltration, which may be morphologically difficult to assess.

In TFH-AITL type, autoimmune features and polyclonal hypergammaglobulinaemia are common. Immune dysfunction leads to frequent infectious complications (e.g. EBV viraemia).

In nodal ALCL, concomitant extranodal involvement of bone and soft tissue and/or skin is not uncommon.

Common clinical presentation in nodal PTCL

- 45 y/o with fever, fatigue, night sweats, PS 3
- Elevated LDH (770 U/l)
- Multiple lymphadenopathies and bone marrow infiltration
- Lymph node biopsy: CD3+, CD4+, CD10+, CXCL-13+, PD-1+, BCL6+, ICOS+, CD21+ in FDC meshwork, EBER+ in large B-immunoblasts
- Mutations in tumour biopsy: *DNMT3A, IDH2*
- *Diagnosis: TFH-lymphoma – angioimmunoblastic type (AITL)*

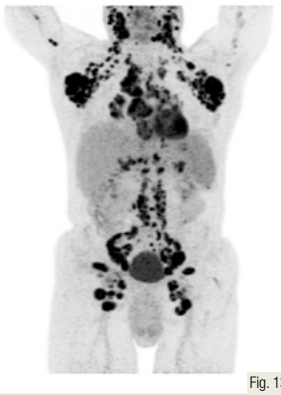
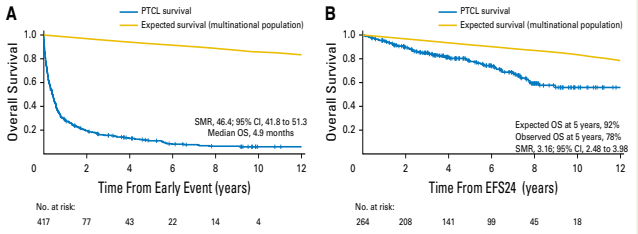


Fig. 13.7

BCL6, B-cell lymphoma 6; EBER, Epstein–Barr early RNA; FDC, follicular dendritic cell; ICOS, inducible T-cell costimulator; IDH2, isocitrate dehydrogenase 2; LDH, lactate dehydrogenase; PD-1, programmed cell death protein 1; PS, performance status; PTCL, peripheral T-cell lymphoma; TFH, T-follicular helper.

Event-free survival at 24 months (EFS24) is a useful endpoint to stratify subsequent outcome in nodal PTCL



(A) OS of patients who did not achieve EFS24; (B) OS of patients who achieved EFS24.

Fig. 13.8

CI, confidence interval; OS, overall survival; PTCL, peripheral T-cell lymphoma; SMR, standardised mortality ratio.

The International Prognostic Index (IPI) has been shown to be a useful prognostic tool also in nodal PTCL.

Comparisons of IPI with the National Comprehensive Cancer Network (NCCN)-IPI and the prognostic index for T-cell lymphoma (PIT), did not show superiority of these indices over IPI.

Event-free survival at 24 months (EFS24) has been shown to be an effective endpoint to stratify subsequent outcome in nodal PTCL.

The favourable prognostic impact of *ALK+* gene rearrangement and unfavourable prognosis for *TP63* gene rearrangement are well-established.

Presence of a *DUSP22* gene rearrangement in ALK- ALCL has been associated with a favourable prognosis, comparable to that of ALK+ ALCL in five out of seven reports on this topic.

Some studies have reported an adverse prognosis associated with the presence of pre-therapeutic circulating EBV-DNA in AITL and PTCL-NOS. However, these findings are still controversial.

5-year OS of adult ALCL according to rearrangement status in seven independent cohorts

		ALCL subset			
		DUSP22r	ALKr	TP63r	Triple-neg
Mayo (Blood 2014)	USA	90% (n=22)	85%	18%	37%
DK archival (Blood 2017)	Denmark	80% (n=5)	85%	0%	30%
Nordic+Mayo (ASH 2017)	Nordic + USA	90% (n=8)	NR	NR	45%
Piris M, et al (Haematologica 2019)	Spain	100% (n=6)	80%	NR	38%
BCCA (BJH 2019)	Canada	40% (n=12)	70%	NR	25%
Sibon D (Lugano 2021)	France	57% (n=45)	NR	NR	NR
NLG-T-01 (ASH 2022)	Nordic	83% (n=6)	Not included	NR	44%

Fig. 13.9

ALCL, anaplastic large cell lymphoma; ALKr, anaplastic lymphoma kinase rearranged; DUSP22r, DUSP22 rearranged; OS, overall survival; NR, not reported; TP63r, TP63 rearranged; Triple-neg, not rearranged for ALK, DUSP22 or TP63.

REVISION QUESTIONS

1. Which of the nodal PTCL entities is more likely to present with autoimmune features and EBV viraemia?
2. Which endpoint would you select in your study design to effectively risk-stratify for outcome?
3. What is the prognostic implication of a rearranged *TP63* gene in ALK- ALCL?

Treatment

CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone), ± etoposide (CHOEP), has been used as first-line therapy and included in the 2015 European Society for Medical Oncology (ESMO) guidelines. Platinum-based non-anthracycline regimens are not superior.

The five largest upfront PTCL trials have tested: CHOEP + autologous stem-cell transplantation (ASCT; phase II trials); randomised additions to CH(O)P of alemtuzumab, brentuximab vedotin (BV) and romidepsin, and ASCT vs allogeneic SCT (alloSCT) as upfront consolidation (phase III trials).

Of the four randomised trials, only the addition of BV showed superiority of the experimental over the comparator arm.

The NLG-T-01 and the ECHELON-2 trials

NLG-T-01: CHOEP14-14x6 + ASCT (BEAM)
No ALK+ ALCL included

ECHELON-2: BV-CHP21 vs CHOP21
72% ALCL (50% ALK- and 22% ALK+)

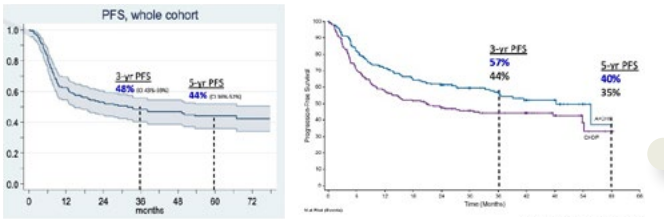


Fig. 13.11

ALCL, anaplastic large cell lymphoma; ALK, anaplastic lymphoma kinase; ASCT, autologous stem-cell transplantation; BV-CHP, brentuximab vedotin + cyclophosphamide, doxorubicin and prednisone; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone; CHOEP, cyclophosphamide, doxorubicin, etoposide, vincristine and prednisone; CI, confidence interval; NLG, Nordic Lymphoma Group; OS, overall survival; PFS, progression-free survival.

The 'big five' upfront trials in PTCL: questions and answers

Study	N pts	ALK+ ALCL	Question	Outcome
NLG-T-01, Ph II	160	Excl	PFS and OS of bi-weekly CHOEP+ASCT?	5yr OS: 51% 5yr PFS: 44% Best subtype outcome: ALK- ALCL
ACT-1 (young): CHOP+ASCT ± ALZ (low dose), Ph III ACT-2 (elderly): CHOP ± ALZ (higher dose), Ph III	131 116	Excl	ALZ + CHOP > CHOP?	ACT-1: No difference (BUT better outcome in ALZ-treated pts with ERBB4 pathway upregulation, mainly females) ACT-2: No difference Higher ALZ dose, > toxicity than ACT1
AlloSCT vs ASCT, Ph III	104	Excl	AlloSCT > ASCT?	No difference AlloTx < relapses, but > TRM
ECHELON-2 (CHP-BV vs CHOP), Ph III	452	Incl	CHP-BV > CHOP?	CHP-BV > CHOP in ALCL Trial not powered to analyse other PTCL subtypes
RO-CHOP (CHOP+RO vs CHOP), Ph III	421	Excl	RO-CHOP > CHOP?	No difference In some TFH lymphomas, long CRs

Fig. 13.10

ALCL, anaplastic large cell lymphoma; ALK, anaplastic lymphoma kinase; alloSCT, allogeneic stem-cell transplantation; alloTx, allogeneic treatment; ALZ, alemtuzumab; ASCT, autologous stem-cell transplantation; BV, brentuximab vedotin; CHOEP, cyclophosphamide, doxorubicin, etoposide, vincristine and prednisone; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone; CHP, cyclophosphamide, doxorubicin and prednisone; CR, complete response; Excl, excluded; Incl, included; NLG, Nordic Lymphoma Group; OS, overall survival; PFS, progression-free survival; Ph, phase; PTCL, peripheral T-cell lymphoma; RO, romidepsin; TFH, T-follicular helper; TRM, treatment-related mortality.

Large registry studies support upfront consolidation with ASCT (except for ALK+ ALCL and stage I disease). The addition of etoposide improves the outcome in ALCL, particularly in ALK+ ALCL.

A large phase II upfront trial (NLG-T-01, ALK+ ALCL excluded) on dose-dense CHOEP + upfront ASCT showed 5-year overall survival (OS) and progression-free survival (PFS) of 51% and 44%, respectively.

A phase III trial showed superior 3-year PFS and OS for patients treated with BV-CHP vs CHOP in ALCL (72% of all included patients, 20% ALK+ and 52% ALK-). The trial was not powered for other PTCL subtypes.

The large first-line PTCL trials run so far show that most treatment failures occur during induction therapy, due to refractory disease. New drugs improving induction treatments are needed.

A graft-versus-lymphoma effect after alloSCT is well-documented in PTCL. However, due to toxicity and treatment-related mortality, alloSCT is usually not recommended upfront in nodal PTCL.

About 25% of chemosensitive patients relapse early (<2 years) after end of treatment, suggesting a possible role for minimal residual disease monitoring.

What have we learned from the large upfront PTCL trials?

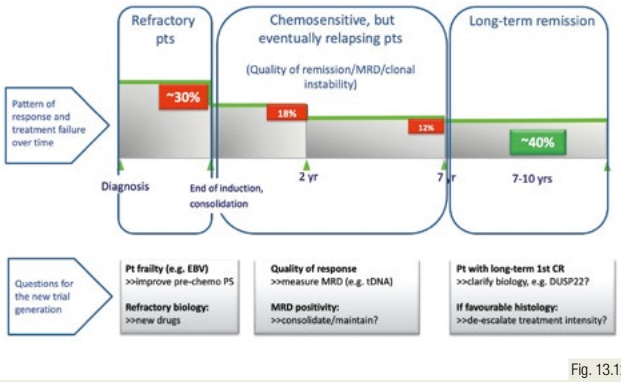


Fig. 13.12

CR, complete response; EBV, Epstein–Barr virus; MRD, minimal residual disease; PS, performance status; PTCL, peripheral T-cell lymphoma.

REVISION QUESTIONS

1. Should doxorubicin be substituted by platinum-based drugs in the induction therapy of nodal PTCL?
2. Which PTCL subtype was excluded in the NLG-T-01 trial and included in the ECHELON-2 trial?
3. According to the relapse pattern observed in the large upfront PTCL trials, when, during the course of treatment, do most failures occur?

Relapsed/refractory disease and new treatments

No standard treatment exists for relapsed/refractory (R/R) nodal PTCL. In chemosensitive, transplant-eligible R/R PTCL patients, consolidative alloSCT should be preferred over ASCT.

Many drugs have been tested, alone or in combination with chemotherapy (ChT), according to patients' fitness/frailty and transplant eligibility.

Novel agents under evaluation include monoclonal antibodies (mAbs), hypomethylating agents, ALK inhibitors, phosphoinositide 3-kinase (PI3K) inhibitors and Janus kinase (JAK) inhibitors.

Relapsed/refractory nodal PTCL – examples of treatment regimens according to transplant eligibility and subtype specificity

FIT (transplant*-eligible)	
Second-line therapy or beyond	**Nodal PTCL entity**
If possible, PTCL clinical trial	
Combination regimens	
ICE (ifosfamide, carboplatin, etoposide)	All entities
DHAP/DHAX (dexa, cytarabine, cisplatin/oxaliplatin)	All entities
GDP (gemcitabine, dexa, oxaliplatin)	All entities
IVAC-MTX (ifosfamide, etoposide, cytarabine, methotrexate)	All entities
Chemotherapy + radiotherapy	All entities
Single agents	
Anti-CD30 conjugates (e.g. BV)	ALCLs, some PTCL-NOS
ALK inhibitors (e.g. crizotinib)	ALCL, ALK-positive
IMiDs (e.g. lenalidomide)	TFHL, some PTCL-NOS
Hypomethylating agents (e.g. 5-azacytidine)	TFHL
HDAC inhibitors (e.g. belinostat)	TFHL

FRAIL (transplant-ineligible)	
Second-line therapy or beyond	**Nodal PTCL entity**
If possible, PTCL clinical trial	
Single agents	
BV	ALCLs, CD30-positive TFHL and PTCL-NOS
5-azacytidine	TFHL
Bendamustine	All entities
Lenalidomide	TFHL, some PTCL-NOS
Anti-CD52 Ab (alemtuzumab)	Leukaemic CD52-positive TFHL
Gemcitabine	All entities
ALK inhibitors (e.g. crizotinib [1st gen]; alectinib, ceritinib [2nd gen])	ALCL, ALK-positive
JAK inhibitors (e.g. ruxolitinib)	ALCLs
PI3K inhibitors (e.g. duvelisib)	Some TFHL and PTCL-NOS
Cyclosporin A	TFHL
Radiotherapy	All entities

Fig. 13.13

Ab, antibody; ALCL, anaplastic large cell lymphoma; ALK, anaplastic lymphoma kinase; alloSCT, allogeneic stem cell transplantation; BV, brentuximab vedotin; dexa, dexamethasone; HDAC, histone deacetylase; IMiD, immunomodulatory imide drug; JAK, Janus kinase; PI3K, phosphoinositide 3-kinase; PTCL, peripheral T-cell lymphoma; PTCL-NOS, PTCL not otherwise specified; TFHL, T-follicular helper cell-derived lymphoma; 1st gen, 2nd gen, first generation, second generation.

*Recommended transplant modality: non-myeloablative alloSCT.

Clinical activity of novel agents approved or under investigation for the treatment of R/R PTCL

	ORR	CR rate	ORR PTCL-NOS	ORR AITL	ORR ALCL
FDA-approved					
Romidepsin	25%	15%	29%	30%	24%
Belinostat	26%	11%	23%	54%	15%
Pralatrexate	29%	15%	32%	8%	29%
Brentuximab vedotin	69%	44%	33%	54%	86%
Novel agents					
Crizotinib					88%
Duvelisib*	50%	22%			
Ruxolitinib	27%	8%			
Cerdulatinib	35%	31%			
5-Azacitadine	53%	32%			

*Only drug, from the FDA-approved list, approved by the European Medicines Agency, but only for the ALCL subtype.

Fig. 13.14

AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large cell lymphoma; CR, complete response; FDA, Food and Drug Administration; NOS, not otherwise specified; ORR, overall response rate; PTCL, peripheral T-cell lymphoma; R/R, relapsed/refractory.

The anti-CD52 mAb alemtuzumab is effective as monotherapy or combined with ChT in CD52+ nodal PTCL. Therapy-induced CD52 loss is common.

The highest single-agent activity in R/R PTCL has been seen for BV, limited to R/R ALCL with an 86% overall response rate (ORR), and for crizotinib (ALK inhibitor), in ALK+ ALCL (ORR 88%).

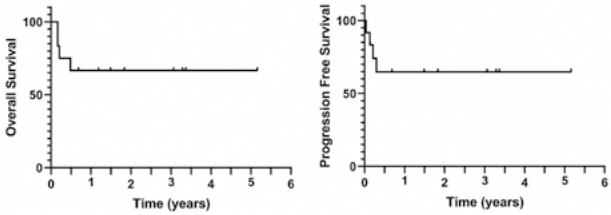
The hypomethylating agent 5-azacytidine has recently been tested vs physician's choice in a phase II randomised trial in R/R TFH lymphoma. The final analysis of the trial is pending at the time of publication.

Recently, the Food and Drug Administration (FDA) approved crizotinib in children and young adults, based on phase II data showing ORR and complete response (CR) rates of 88% and 81%, respectively, with 39% and 22% sustained CRs at 6 and 12 months, respectively.

Another recently reported phase II study in ALK+ ALCL showed an ORR of 83% and a CR of 58% with 2-year PFS and OS of 65% and 66%, respectively.

Bispecific antibodies (e.g. CD30, CD16) and chimeric antigen receptor (CAR)-T-cell-based therapy are also currently under clinical evaluation in R/R PTCLs.

Crizotinib (ALK inhibitor) in R/R ALK+ ALCL



Parameter	
Number of patients	11
Type	R/R ALCL ALK+
Median prior lines of therapy	3
ORR/CR	83%/58%
2 yr PFS and OS	65% and 66%

Fig. 13.15

ALCL, anaplastic large cell lymphoma; ALK, anaplastic lymphoma kinase; CR, complete response; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; R/R, relapsed/refractory.

REVISION QUESTIONS

1. Which transplant modality would you choose in a chemosensitive R/R PTCL patient?
2. Which drug has been tested in a randomised phase II trial versus physician's choice?
3. What is the ORR and the CR rate for crizotinib in R/R ALK+ ALCL?

Summary: Nodal peripheral T-cell lymphomas

- Nodal PTCLs represent ~80% of all PTCLs and consist of TFH-derived lymphoma (the most frequent), sALCL and PTCL-NOS
- TFH lymphoma consists of three types, of which AITL is the most frequent. It has distinctive morphological, immunohistochemical and genetic features, with frequent mutations in epigenetic modifier genes
- sALCL can be ALK+ or ALK-. ALK+ ALCL occurs mostly in children and young adults. A subset of ALK- ALCL carries prognostic gene rearrangements (*DUSP22*: favourable; *TP63*: unfavourable)
- PTCL-NOS is still a diagnosis of exclusion, but includes two subsets with prognostic gene expression signatures (TBX21: better prognosis; GATA3: worse prognosis)
- In general, nodal PTCL presents with B symptoms, disseminated disease, elevated LDH and some degree of bone marrow infiltration
- TFH lymphoma, AITL type, can present with autoimmune features, polyclonal hyperglobulinaemia and EBV viraemia. It is debated whether circulating EBV-DNA has prognostic significance
- ALCL can, besides the nodal involvement, also present with bone, soft tissue and skin involvement
- The IPI is useful to prognosticate nodal PTCL, and EFS24 can be applied for risk stratification, trial design and patient counselling
- According to the 2015 ESMO guidelines, in chemosensitive patients, CHOP with the addition of etoposide consolidated with ASCT is the preferred strategy. The use of BV-CHP in line with the results of the ECHELON-2 trial has been approved only for the ALCL type
- BV in R/R ALCL and crizotinib in R/R ALK+ ALCL have the best ORR and CR rates. Other novel agents such as mAbs, hypomethylating agents, PI3K inhibitors and JAK inhibitors are still under clinical evaluation

Further Reading

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Image sources: **Fig. 13.4.** Campo E, et al. Blood 2022;140:1229-1253; **13.6 (left).** adapted from Iqbal J, et al. Blood 2014;123:2915-2923; **13.6 (right).** adapted from De Leval L, Gaulard P. Histopathology 2011;58:49-68; **13.8.** Maurer M, et al. J Clin Oncol 2017;35:4019-4026; **13.11 (left).** d'Amore F, et al. J Clin Oncol 2012;30:3093-3099; **13.11 (right).** Horwitz S, et al. Lancet 2019;393:229-240; **13.13.** adapted from d'Amore F, et al. Peripheral T-cell lymphomas: ESMO-EHA Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2024 (in development). https://www.esmo.org/guidelines/guidelines-by-topic/esmo-clinical-practice-guidelines-haematological-malignancies/peripheral-t-cell-lymphomas; **13.14.** Mehta-Shah N. Hematology Am Soc Hematol Educ Program 2019;2019:41-46; **13.15 (left).** adapted from Gambacorti-Passerini C, et al. JNCI 2014;106:djt378; **13.15 (right).** Bossi E, et al. Am J Hematol 2020;95:E319-E320. All other figures courtesy of the authors.

14 Hodgkin lymphoma

Epidemiology, histology, pathology

Hodgkin lymphoma (HL) is a B cell-derived malignancy with an incidence of 3-4/100 000 persons/year. Young adults are most often affected.

Classical HL (cHL) accounts for ~95% of HL cases; 5% of patients present with nodular lymphocyte-predominant HL (NLPHL; also classified as lymphocyte-predominant B-cell lymphoma by the International Consensus Classification [ICC]).

In cHL, four histological subtypes can be distinguished: nodular sclerosis, mixed cellularity, lymphocyte-rich and lymphocyte-depleted; NLPHL represents a distinct entity.

Age distribution in Hodgkin lymphoma

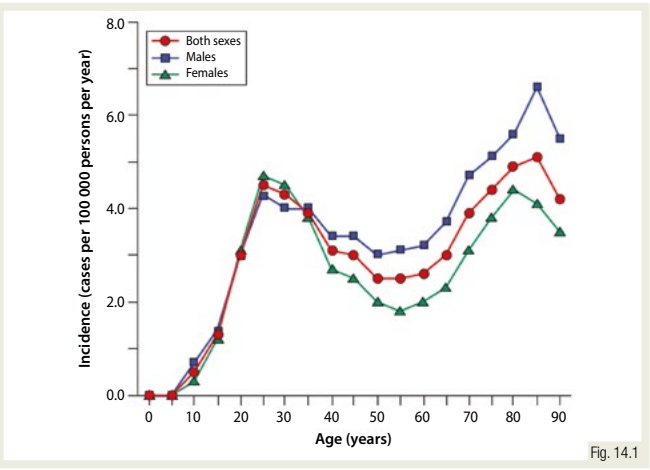

Fig. 14.1

Tumour tissue in classical Hodgkin lymphoma (CD30 staining)

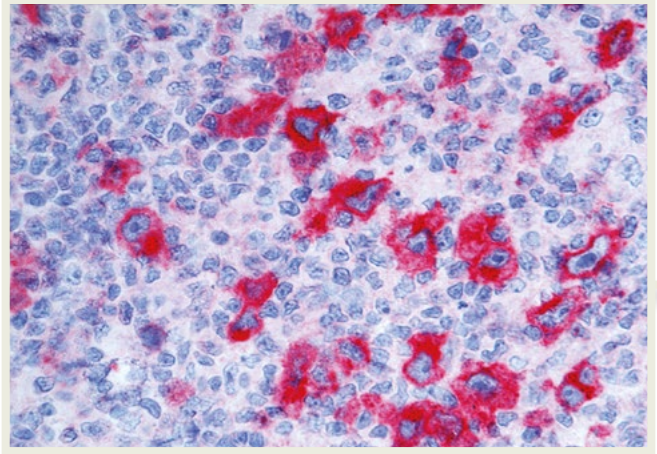

Fig. 14.2

The detection of Hodgkin and Reed–Sternberg (H-RS) cells is mandatory for the diagnosis of cHL; lymphocyte-predominant (LP) cells are disease-defining in NLPHL.

In HL, <1% of the cells in the affected tissue are malignant. They are embedded in an inflammatory background composed of reactive cells.

The H-RS cells in cHL are consistently positive for CD15 and CD30. In contrast, LP cells typically express CD20 and CD45 but lack CD30.

NF-κB pathway in classical Hodgkin lymphoma

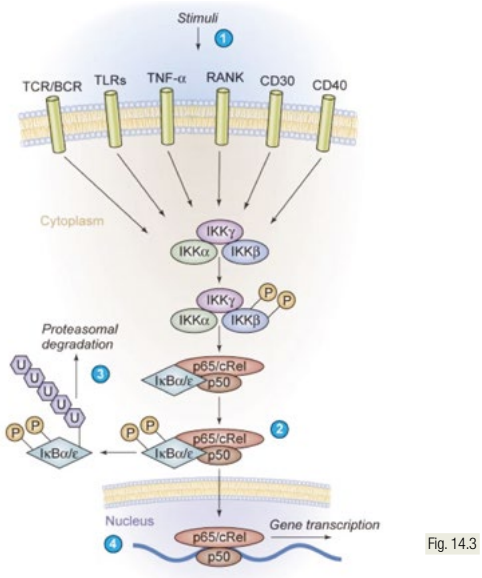

Fig. 14.3

BCR, B-cell receptor; IKK, inhibitor of NF-κB kinase; NF-κB, nuclear factor-kappa B; TCR, T-cell receptor; TLR, toll-like receptor; TNF-α, tumour necrosis factor-alpha.

Different signalling pathways play important roles in cHL.

These include the nuclear factor kappa B (NF-κB), the Janus kinase (JAK) and the signal transducer and activator of transcription (STAT) pathways.

In addition, genomic alterations of the 9p24.1 locus are often found in cHL. They are associated with an increased susceptibility to immune checkpoint inhibition.

REVISION QUESTIONS

1. What are the subtypes of HL?
2. Which cells are disease-defining in cHL?
3. What are the typical surface antigens that differ between cHL and NLPHL?

Clinical presentation and prognosis

HL usually presents with indolent lymphadenopathy. Involvement of the liver, spleen or bone marrow is less common.

Approximately 40% of cHL patients present with B symptoms. Severe pruritus or painful lymph nodes (LNs) after alcohol ingestion are reported by some patients.

Symptom burden and extent of disease in patients with NLPHL is generally lower than in individuals with cHL.

Diagnostic work-up in Hodgkin lymphoma

Diagnosis
- Lymph node biopsy (or a biopsy from another organ with suspected affection)

Staging and risk stratification
- Medical history and physical examination
- X-ray of the chest
- Contrast-enhanced CT scan of the neck, chest and abdomen
- PET
- Full blood cell count and blood chemistry, ESR
- HBV, HCV and HIV screening

Pretreatment examinations
- ECG
- Echocardiography
- Pulmonary function test
- Reproductive counselling (in patients of reproductive age)
- Serum pregnancy test (in female patients of reproductive age)

Fig. 14.4

CT, computed tomography; ECG, electrocardiogram; ESR, erythrocyte sedimentation rate; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; PET, positron emission tomography.

HL risk group allocation according to EORTC/LYSA and GHSG

	EORTC/LYSA	GHSG
Treatment group		
Limited stages	CS I–II without risk factors (supradiaphragmatic)	CS I–II without risk factors
Intermediate stages	CS I–II with ≥1 risk factor (supradiaphragmatic)	CS I, CS IIA with ≥1 risk factor CS IIB with risk factor(s) C and/or D, but not A/B
Advanced stages	CS III–IV	CS IIB with risk factor(s) A and/or B CS III/IV
Risk factors	A: Large mediastinal mass B: Age ≥50 years C: Elevated ESR D: ≥4 nodal areas	A: Large mediastinal mass B: Extranodal disease C: Elevated ESR D: ≥3 nodal areas

Fig. 14.5

CS, clinical stage; EORTC, European Organisation for Research and Treatment of Cancer; ESR, erythrocyte sedimentation rate; GHSG, German Hodgkin Study Group; HL, Hodgkin lymphoma; LYSA, Lymphoma Study Association.

The number of involved LN areas is one of the factors that determine the risk group.

Depending on the Ann Arbor stage and the presence or absence of risk factors, patients are allocated to different treatment groups.

In Europe, patients are usually divided into three risk groups (early favourable, early unfavourable and advanced).

More than 80% of HL patients achieve long-term remission and can be considered cured after stage-adapted first-line treatment.

In the case of relapse, a second durable remission is achieved in >50% of patients if adequate salvage therapy is administered.

In patients with a second relapse, cure is uncommon. However, the prognosis has improved substantially in recent years.

Prognosis of HL patients has improved over the last decades

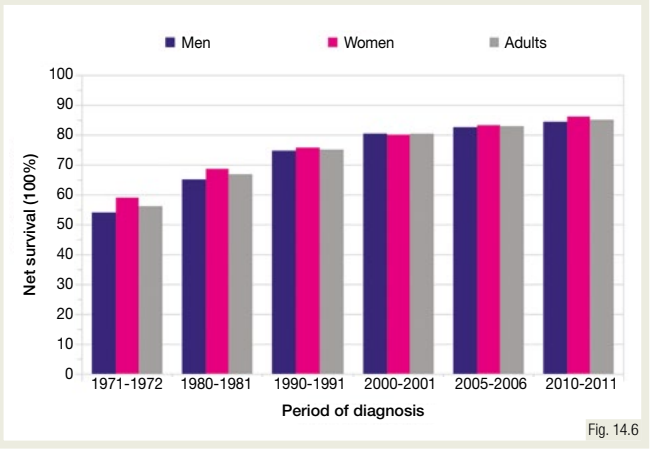

Fig. 14.6

HL, Hodgkin lymphoma.

REVISION QUESTIONS

1. Are there relevant differences between cHL and NLPHL in terms of clinical presentation?
2. Which criteria influence the allocation of patients to certain risk groups?
3. What proportion of patients is cured with stage-adapted first-line treatment?

First-line treatment

Given the high cure rate in HL, treatment development aims to maintain efficacy while reducing toxicity.

In early-stage favourable HL, standard treatment consists of a brief chemotherapy (ChT; 2 cycles of ABVD [doxorubicin, bleomycin, vinblastine and dacarbazine]) followed by involved-site radiotherapy (ISRT) at 20 Gy.

Omission of consolidation RT based on the result of an interim positron emission tomography (PET) at the end of ChT results in a significant loss of tumour control.

PFS of PET-2-negative patients with early-stage HL after 2 cycles of ABVD alone or 2 cycles of ABVD plus consolidation RT

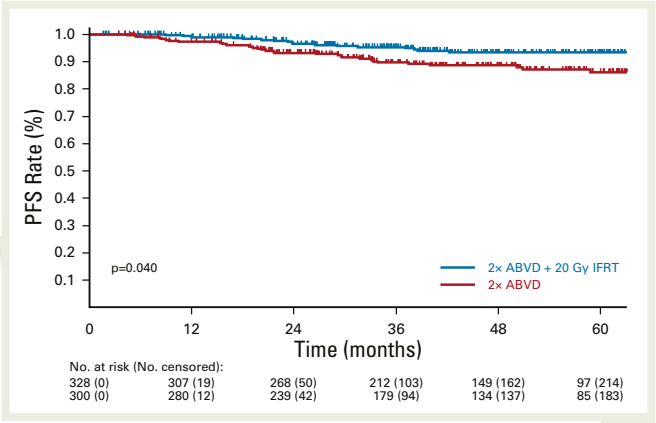

Fig. 14.7

ABVD, doxorubicin, bleomycin, vinblastine and dacarbazine; HL, Hodgkin lymphoma; IFRT, involved-field radiotherapy; PET, positron emission tomography; PFS, progression-free survival; RT, radiotherapy.

PFS of patients with intermediate-stage HL after '2+2' followed by PET-guided RT or '2+2' followed by RT irrespective of the interim PET result

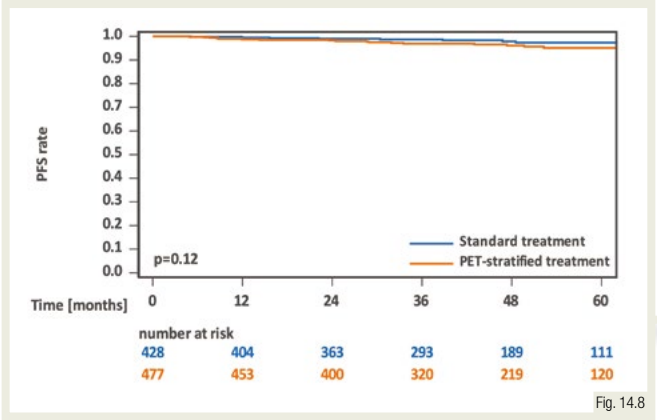

Fig. 14.8

HL, Hodgkin lymphoma; PET, positron emission tomography; PFS, progression-free survival; RT, radiotherapy.

In contrast to cHL, patients with stage IA NLPHL without clinical risk factors are treated sufficiently with RT alone.

Patients with intermediate-stage HL are usually treated with 4 cycles of ChT, optionally followed by RT.

After treatment with 2 cycles of escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone) and 2 cycles of ABVD ('2+2'), consolidation RT can be omitted in the case of a negative interim PET at the end of ChT.

In advanced HL, interim PET-guided escalated BEACOPP (4 cycles in patients with a negative PET after 2 cycles, 6 cycles in patients with positive PET after 2 cycles) followed by PET-guided RT should be considered for patients <60 years old.

Older patients and those who are not candidates for, or refuse, escalated BEACOPP should receive 6 cycles of ABVD-based ChT followed by PET-guided RT. Bleomycin should not be given beyond cycle 2 in older patients and omission should generally be considered in case of a negative interim PET after 2 cycles of ABVD.

In 2022, promising results were obtained for escalated BEACOPP and ABVD backbones in combination with the anti-CD30 antibody–drug conjugate brentuximab vedotin.

PFS of patients with advanced-stage HL treated with 4 or 6/8 cycles of escalated BEACOPP after a negative PET-2

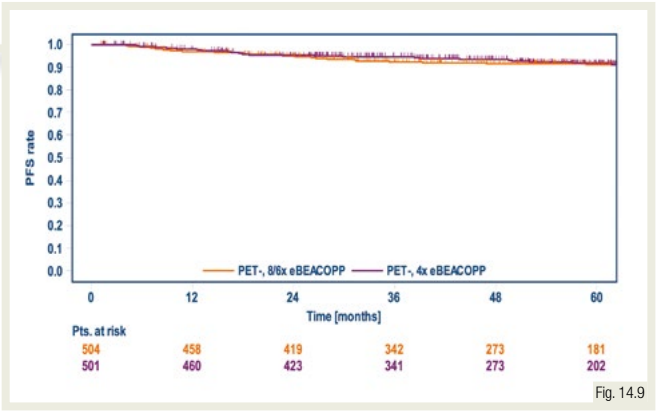

Fig. 14.9

BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone; eBEACOPP, escalated BEACOPP; HL, Hodgkin lymphoma; PET, positron emission tomography; PFS, progression-free survival; RT, radiotherapy.

REVISION QUESTIONS

1. How is early-stage HL usually treated?
2. Which ChT regimens can be used for the treatment of intermediate and advanced-stage HL?
3. Which drug is increasingly combined with conventional ChT in advanced cHL?

Treatment of relapsed disease

The standard second-line treatment for younger patients with relapsed HL consists of high-dose ChT and autologous stem-cell transplantation (ASCT), provided they respond to salvage treatment.

Prior to high-dose ChT, patients usually receive salvage treatment with protocols such as DHAP (dexamethasone, high-dose cytarabine and cisplatin), ICE (ifosfamide, carboplatin and etoposide) or GVD (gemcitabine, vinorelbine and liposomal doxorubicin) to reduce tumour burden and mobilise stem cells.

Poor-risk patients with cHL may benefit from tandem ASCT and maintenance treatment with brentuximab vedotin.

PFS of patients treated with high-dose ChT followed by ASCT ± BV maintenance

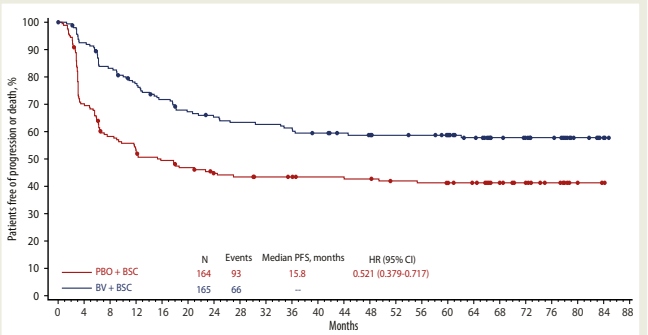

Fig. 14.10

ASCT, autologous stem-cell transplantation; BV, brentuximab vedotin; BSC, best supportive care; ChT, chemotherapy; CI, confidence interval; HR, hazard ratio; PBO, placebo; PFS, progression-free survival.

PFS of patients with relapsed NLPHL after different salvage approaches

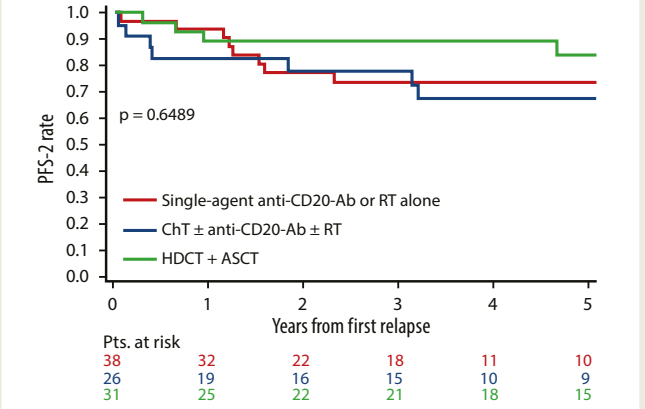

Fig. 14.11

Ab, antibody; ASCT, autologous stem-cell transplantation; ChT, chemotherapy; HDCT, high-dose chemotherapy; NLPHL, nodular lymphocyte-predominant Hodgkin lymphoma; PFS, progression-free survival; RT, radiotherapy.

In patients who received only limited amounts of ChT in the course of first-line treatment, salvage treatment with a different conventional ChT regimen and/or RT can be sufficient.

In relapsed NLPHL, single-agent anti-CD20 antibody treatment or other non-intensive approaches result in excellent response rates and long-term remission in a significant proportion of patients.

In patients with disease recurrence after high-dose ChT and ASCT, curative treatment options are very limited.

Some patients who failed high-dose ChT and ASCT achieve long-lasting remission if treated with an immune checkpoint inhibitor.

Allogeneic stem-cell transplantation (alloSCT) can be discussed in patients who are in complete remission after third-line treatment.

Patients with repeated relapses should be considered candidates for studies evaluating novel agents.

ORR and DOR with pembrolizumab in cHL patients who failed HDCT followed by ASCT and/or BV

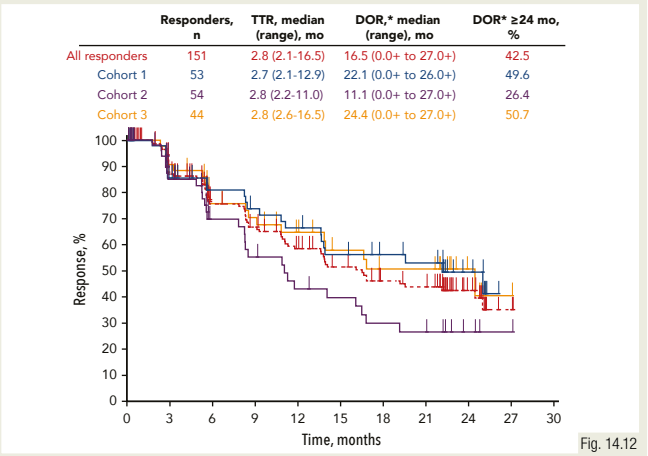

Fig. 14.12

ASCT, autologous stem-cell transplantation; BV, brentuximab vedotin; cHL, classical Hodgkin lymphoma; CI, confidence interval; CR, complete response; DOR, duration of response; HDCT, high-dose chemotherapy; HR, hazard ratio; ORR, overall response rate; PR, partial response; TTR, time to response.

REVISION QUESTIONS

1. What is the standard treatment for most patients with relapsed HL?
2. What treatment is mostly sufficient for patients with relapsed NLPHL?
3. What treatment results in high response rates in patients with cHL recurrence after high-dose ChT and ASCT?

Follow-up and long-term sequelae

Follow-up examinations should be conducted regularly to detect treatment-related late effects and disease recurrence as early as possible.

Follow-up visits should include physical examination and laboratory analyses (e.g. thyroid function tests in patients who have received mediastinal RT).

Surveillance imaging (e.g. computed tomography [CT] scan) is not indicated in the absence of signs or symptoms suggestive of progression.

Second primary malignancies after treatment for HL

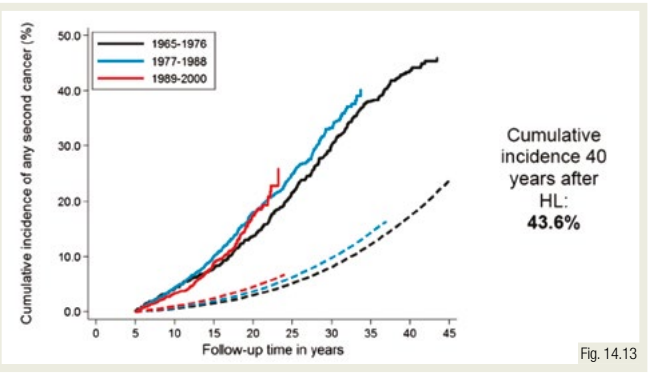

Fig. 14.13

HL, Hodgkin lymphoma.

Expected incidence: dashed line; observed incidence: solid line.

Radiation dose-dependent risk for the development of valvular heart disease among HL survivors

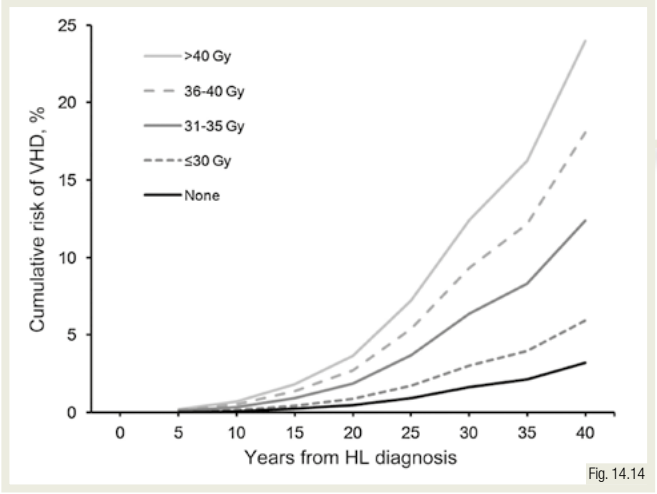

Fig. 14.14

Gy, Gray; HL, Hodgkin lymphoma; VHD, valvular heart disease.

Common long-term sequelae after HL treatment include second primary malignancies, infertility, heart and lung failure, hypothyroidism and fatigue.

Second haematological malignancies are distinguished from second solid tumours.

Among second haematological malignancies, acute myeloid leukaemia has a particularly poor prognosis.

Young women receiving mediastinal RT are especially at risk of developing breast cancer. Therefore, cancer screening is of major importance for this patient group.

Depending on the drugs given and the number of ChT cycles applied, a relevant proportion of patients may become permanently infertile.

Thus, reproductive counselling should be offered to younger patients before treatment.

Cumulative incidence of breast cancer for a 5-year survivor of HL treated at 20 years old, according to mean breast dose and duration of intact ovarian function.

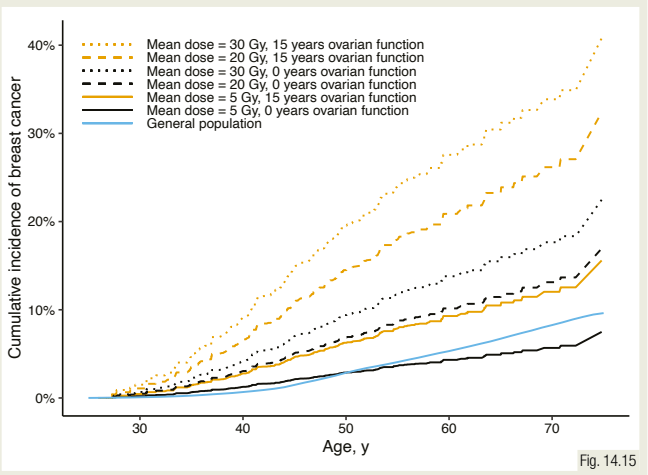

Fig. 14.15

Gy, Gray; HL, Hodgkin lymphoma.

REVISION QUESTIONS

1. What are common late sequelae after treatment for HL?
2. Which second haematological malignancy is associated with a particularly poor prognosis?
3. Which second solid tumour frequently occurs in women who received mediastinal RT at a young age?

Summary: Hodgkin lymphoma

- HL is a B-cell-derived malignancy mostly affecting young adults
- cHL accounts for the vast majority of cases whereas NLPHL represents a rare distinct entity
- Both cHL and NLPHL are characterised by a defined immunophenotype of the malignant cells
- HL patients usually present with indolent lymphadenopathy in part accompanied by B symptoms
- Treatment is chosen depending on the clinical stage and the presence or absence of risk factors
- Patients are categorised as having early favourable, intermediate- or advanced-stage disease
- Conventional ChT based on the ABVD and escalated BEACOPP protocols is administered in newly diagnosed HL
- High-dose ChT followed by ASCT represents the standard treatment for most patients with relapsed cHL
- Overall, 80%-90% of HL patients achieve long-term remission and can be considered cured
- Regular follow-up visits are necessary to detect relapses and long-term sequelae as early as possible

Further Reading

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Image sources: **Fig 14.1.** www.uptodate.com; **14.2.** courtesy S. Hartmann; **14.3.** Jost PJ & Ruland J. Blood 2007;109:2700-2707; **14.4, 14.5.** Eichenauer DA, et al. Ann Oncol 2018;29(Suppl 4):iv19-iv29; **14.6.** www.cancerresearchuk.org; **14.7.** Fuchs M, et al. J Clin Oncol 2019;37:2835-2845; **14.8.** Borchmann P, et al. Lancet Oncol 2021;22:223-234; **14.9.** Borchmann P, et al. Lancet Oncol 2017;18:454-463; **14.10.** Moskowitz CH, et al. Blood 2018;132:2639-2642; **14.11.** Eichenauer DA, et al. Blood 2018;132:1519-1525; **14.12.** Chen R, et al. Blood 2019;134:1144-1153; **14.13.** van Leeuwen FE & Ng AK. Hematology Am Soc Hematol Educ Program 2016;2016:323-330; **14.14.** Cutter DJ, et al. J Natl Cancer Inst 2015;107:djv008; **14.15.** Roberti S, et al. J Natl Cancer Inst 2022;114:1270-1278.

B

More advanced knowledge

15 Aetiology and epidemiology

Burden of lymphomas – incidence and mortality

Population registries collect data on incidence and mortality covering 15% of the world's population, with differences in data quality among high- and low-income countries.

The global incidence of lymphoma is 13.98/100 000 persons/year. It is the seventh most common cancer worldwide and its incidence is expected to increase by 42% over the next 20 years.

Among non-Hodgkin lymphomas (NHLs), the most common subtype is mature B-cell lymphoma (~85%), with diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma being the most frequent.

World population incidence rates of lymphomas (Globocan 2020)

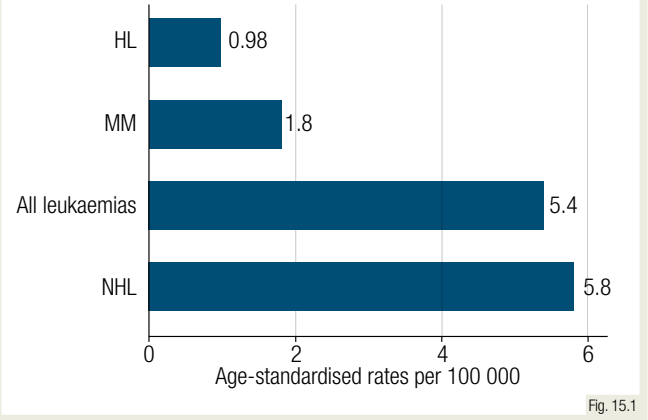
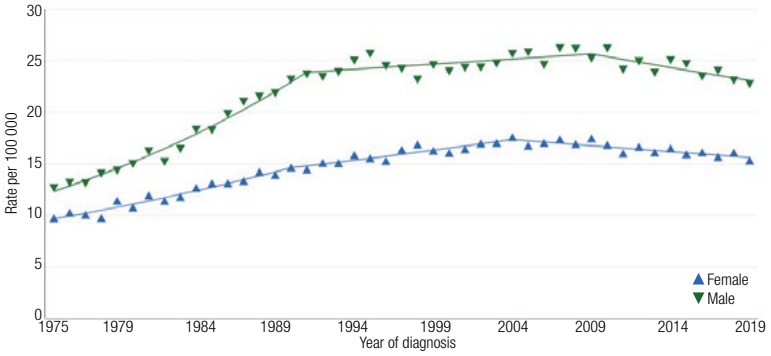


Fig. 15.1

HL, Hodgkin lymphoma; MM, multiple myeloma; NHL, non-Hodgkin lymphoma.

NHL age-adjusted SEER incidence rates, all ages, all races (1975-2019)



NHL, non-Hodgkin lymphoma; SEER, Surveillance, Epidemiology, and End Results.

Fig. 15.2

Western countries have higher incidence rates of lymphoma than Asian countries.

An increase in NHL incidence was observed during the 1980s and 1990s, for both males and females, reaching a plateau thereafter.

Better registration, Westernisation, human immunodeficiency virus (HIV) and earlier and better diagnosis, among others, could explain this increase.

Lymphoma is the seventh most common cause of cancer death worldwide. In 2020, ~311 594 people died of leukaemia, 259 793 of NHL, 117 077 of multiple myeloma (MM) and 23 376 of Hodgkin lymphoma (HL).

Half of deaths from lymphoma occur in people >65 years old. Mortality rates for NHL, HL, MM and leukaemias are higher for males, worldwide.

Lymphoma deaths are expected to increase from 712 000 cases in 2020 to 1 100 000 in 2040, mainly driven by natural demographic variations.

Lymphomas: age-standardised mortality rate per 100 000 (Globocan 2020)

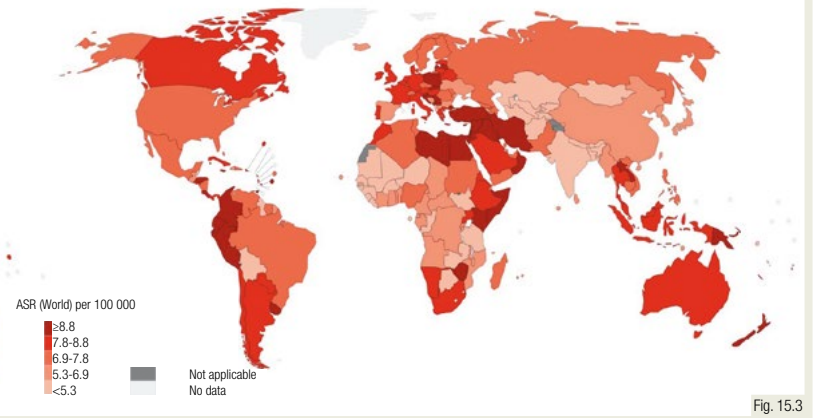


Fig. 15.3

ASR, age-standardised rate.

REVISION QUESTIONS

1. Is the incidence of lymphoma similar across subtypes?
2. Can you identify three potential factors that could explain the increase in lymphoma incidence at the end of the last century?
3. Do you think there are geographical differences in lymphoma mortality?

Well-established risk factors

For almost all subtypes, the likelihood of being diagnosed with a lymphoma is higher for males than females.

Increasing age is strongly associated with a higher risk of most lymphoid cancers. However, HL also affects young adults, and lymphoblastic lymphoma affects people <35 years old.

The incidence of some lymphomas is increased in specific ethnic groups, e.g. MM incidence is higher in African Americans and chronic lymphocytic leukaemia (CLL) is lower in Asians.

Incidence by age group of Hodgkin lymphoma and lymphoid cancers (excluding lymphoblastic lymphoma)

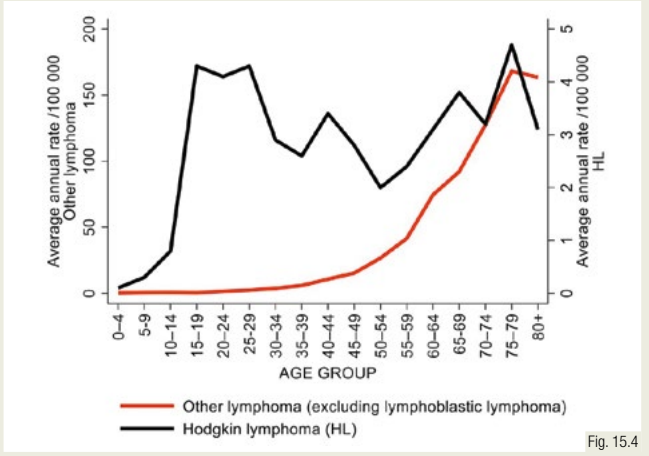
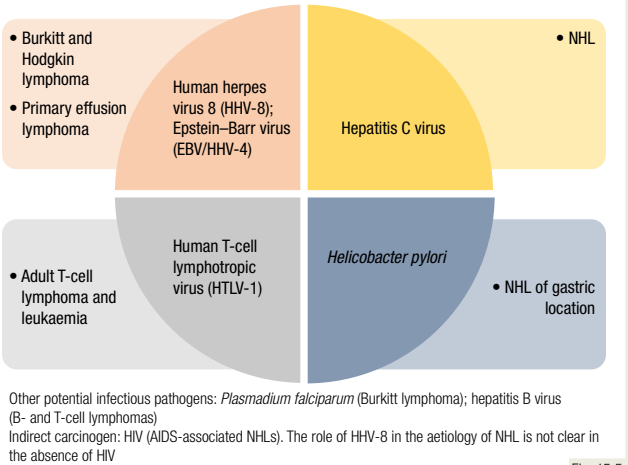


Fig. 15.4

Infections associated with lymphomas



Other potential infectious pathogens: *Plasmodium falciparum* (Burkitt lymphoma); hepatitis B virus (B- and T-cell lymphomas)
Indirect carcinogen: HIV (AIDS-associated NHLs). The role of HHV-8 in the aetiology of NHL is not clear in the absence of HIV

Fig. 15.5

AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus; NHL, non-Hodgkin lymphoma.

The causes of some lymphoma subtypes are:

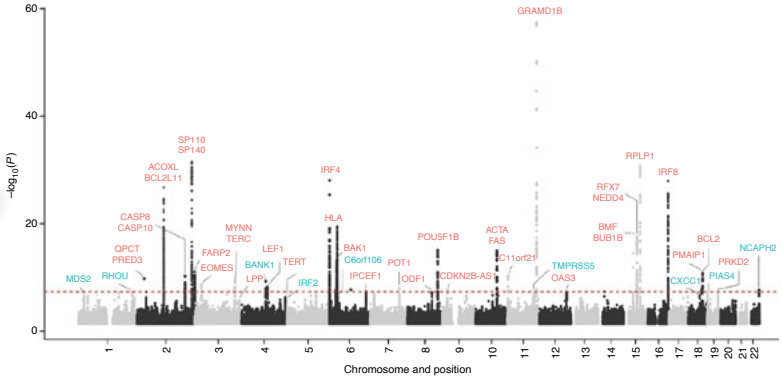
- Infectious pathogens (e.g. viruses: Epstein–Barr virus [EBV], human T-lymphotropic virus 1 [HTLV-1], hepatitis C virus; and bacteria: *Helicobacter pylori* [*H. pylori*]).
- A weakened immune system due to anticancer treatments, immunosuppressants or HIV (that acts as an indirect carcinogen).
- A weakened immune system due to autoimmune diseases (coeliac disease, Sjögren's syndrome, rheumatoid arthritis or systemic lupus erythematosus).

Having a first-degree relative with a lymphoma subtype is a risk factor for lymphoma, suggesting a genetic contribution to these cancers.

For instance, CLL has one of the highest familial risks for lymphoma and more than 40 single-nucleotide polymorphisms were identified in genome-wide association studies (GWAS).

However, to date, genetic susceptibility explains a very small proportion of lymphomas, suggesting environmental factors play an important role.

Previously identified (in red) and newly identified (in blue) CLL risk loci in the InterLymph consortium using GWAS for CLL



CLL, chronic lymphocytic leukaemia; GWAS, genome-wide association studies; InterLymph, International Lymphoma Epidemiology Consortium.

Fig. 15.6

REVISION QUESTIONS

1. Cite three non-modifiable risk factors associated with the aetiology of lymphoma.
2. What infectious agents are associated with lymphoma?
3. Which lymphoma subtype seems to have the strongest genetic component?

Anthropometric, lifestyle and environmental risk factors

Taller adult height has been associated with most lymphoma subtypes and evidence is accumulating on the relation between high body mass index and MM.

Some occupations such as farming or painting have been associated with several subtypes (e.g. farming for MM and CLL).

Occupational and environmental exposure to solvents and pesticides (in particular, herbicides and insecticides) has been linked to some lymphoma subtypes.

Association between height and risk of haematological malignancies from a meta-analysis of Psaltopoulou et al (2019)

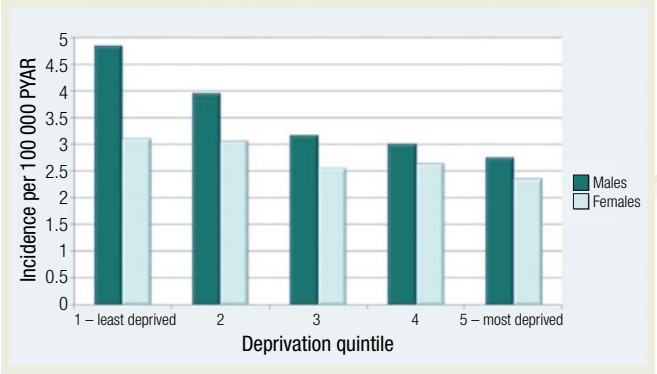
	Highest *vs.* lowest		
	n[1]	RR (95%CI)	Heterogeneity I^2, *p*
Men			
NHL	4	**1.16 (1.09–1.23)**	0.0%, 0.411
MM	3	1.08 (0.88–1.31)	50.4%, 0.133
Women			
NHL	9	**1.26 (1.15–1.37)**	44.5%, 0.072
DLBCL	6	**1.36 (1.20–1.53)**	0.0%, 0.996
FL	6	**1.22 (1.01–1.48)**	16.9%, 0.305
CLL/SLL	7	**1.28 (1.14–1.43)**	0.0%, 0.609
MM	4	**1.18 (1.03–1.36)**	51.1%, 0.105
Leukaemia	3	**1.31 (1.18–1.46)**	0.0%, 0.822
AML	3	**1.26 (1.11–1.44)**	0.0%, 0.995

Bold values indicate $p < 0.05$. [1]Number of study arms.

AML, acute myeloid leukaemia; CI, confidence interval; CLL, chronic lymphocytic leukaemia; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; RR, relative risk; SLL, small lymphocytic lymphoma.

Fig. 15.7

Age-standardised HL incidence in the study population (cohort of the UK population) by deprivation: in men and women



HL, Hodgkin lymphoma; PYAR, person-years at risk.

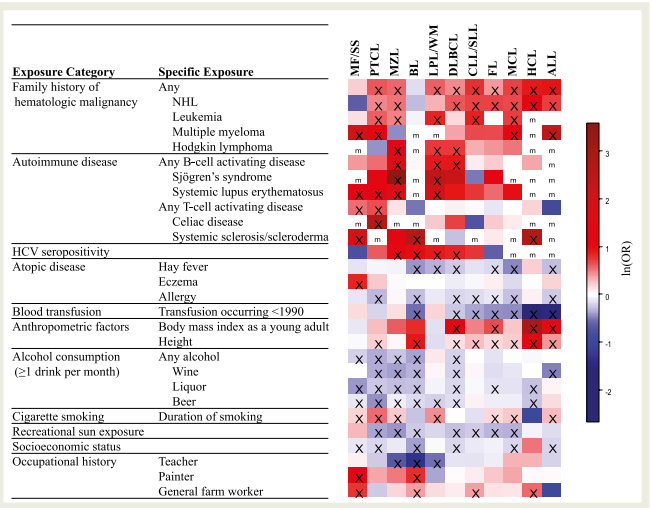
Fig. 15.8

Some women who have a breast implant may develop a rare type of lymphoma (anaplastic large cell lymphoma [ALCL]).

HL incidence increases with increased affluence. A delayed exposure to infectious agents in childhood is a proposed explanation.

Medical conditions such as diabetes may increase lymphoma risk while use of statins or metformin may decrease it.

Overall odds ratio (95% confidence interval) for all risk factors affecting one or more NHL subtypes



Red (blue) indicates the exposure increases (decreases) risk. x indicates analysis identified a statistically significant association, whereas m indicates missing due to lack of data.

ALL, acute lymphoblastic lymphoma; BL, Burkitt lymphoma; CLL/SLL, chronic lymphocytic leukaemia/small lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; HCL, hairy cell leukaemia; HCV, hepatitis C virus; LPL/WM, lymphoplasmacytic lymphoma/Waldenström macroglobulinaemia; MCL, mantle cell lymphoma; MF/SS, mycosis fungoides/Sézary syndrome; MZL, marginal zone lymphoma; NHL, non-Hodgkin lymphoma; PTCL, peripheral T-cell lymphoma.

Fig. 15.9

Sun exposure may decrease risk of several lymphoma subtypes, possibly through vitamin D production and its immunomodulatory effects.

The association between atopic diseases (e.g. allergy, eczema) and the risk for several types of lymphoma is unclear and is under investigation.

The effect that parity, alcohol consumption, tobacco and dietary factors have on NHL risk is uncertain and subject to continuous research.

REVISION QUESTIONS

1. Do you think that all NHL subtypes share the same risk factors?
2. Which anthropometric factor is associated with lymphoma?
3. Why are environmental factors considered in the aetiology of lymphoma?

Summary: Aetiology and epidemiology

- Lymphoid malignancies or 'lymphomas' are the seventh most common type of cancer
- The incidence and mortality of lymphoma varies widely across different regions of the world
- Globally, lymphomas represent a large burden in industrialised countries, but precise knowledge on the burden in developing countries is limited
- Incidence and mortality are higher in men than in women, for reasons not well understood
- The incidence of the most frequent lymphomas increases with age, but HL has a bimodal age distribution
- Some risk factors are common to several lymphoma subtypes, while others are subtype-specific
- Non-modifiable and well-established risk factors associated with most lymphomas are age, sex, ethnicity and family history of lymphoma
- Immune suppression is a major risk factor for lymphoma, including largely HIV and immunosuppressants
- Some specific lymphomas have been linked to specific infections, such HTLV-1 to adult T-cell leukaemia/lymphoma or *H. pylori* to NHL of gastric location
- Burkitt lymphoma has been linked to EBV and probably to concomitant environmental factors such as malaria
- There are other less well-known risk factors such as ultraviolet light exposure or atopic diseases

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16 Molecular biology of lymphomas

Genomic aberrations in lymphoma

Malignant B and T cells largely resemble differentiation stages of normal B and T lymphocytes. Hence, lymphomas can be classified based on the postulated cell of origin.

During the normal development of B and T lymphocytes, cells undergo immunoglobulin (*Ig*) gene remodelling to ensure mature cells express a diverse repertoire of antibodies.

Thus, lymphoma cells harbour monoclonal rearrangements of their B- or T-cell receptors, providing markers for minimal residual disease (MRD) for the differential diagnosis between benign and neoplastic disorders.

Immunoglobulin gene remodelling

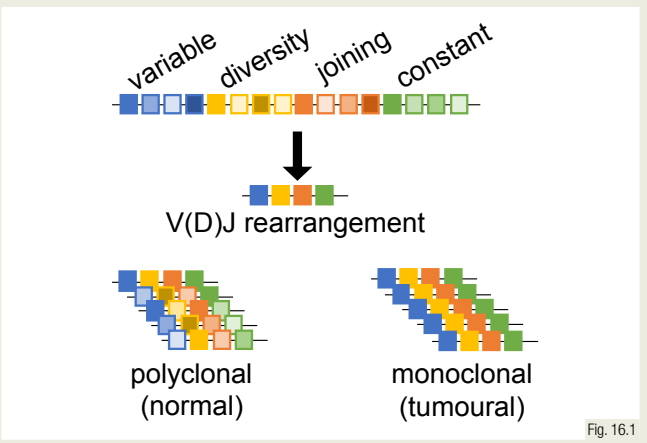


Fig. 16.1

V(D)J, variable-diversity-joining.

Lymphomas show recurrent genetic lesions

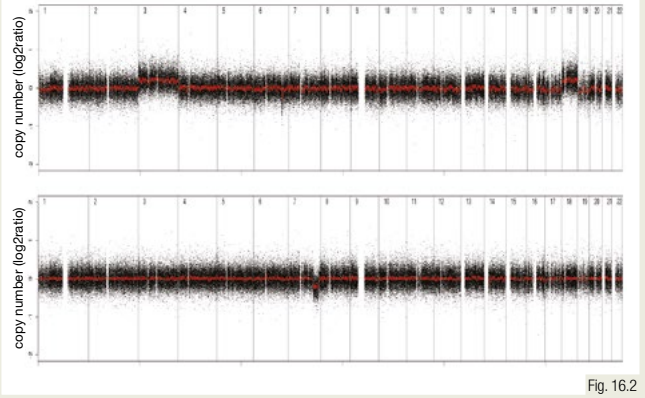


Fig. 16.2

The process of *Ig* gene remodelling requires the occurrence of double-strand DNA breaks, and increases the risk of acquiring genetic lesions at the *Ig* gene's loci and across the genome.

Besides chromosomal translocations involving *Ig* genes, mutations, copy number changes and other translocations are commonly observed in lymphoma cells.

However, a few lesions are specific for individual entities, such as translocations involving *CCND1* in mantle cell lymphoma or *ALK* (anaplastic lymphoma kinase) in ALK-positive anaplastic large cell lymphoma.

Classical techniques for the detection of chromosomal translocations include polymerase chain reaction (PCR), metaphase cytogenetics, fluorescent *in situ* hybridisation (FISH) and spectral karyotyping (SKY).

FISH is a robust technique that can also be performed on formalin-fixed paraffin-embedded sections.

Immunohistochemistry (IHC) can be used as an alternative to genetic assays to detect translocations that cause the ectopic expression of involved proteins (ALK or CCND1).

t(14;18) chromosomal translocation detected by PCR

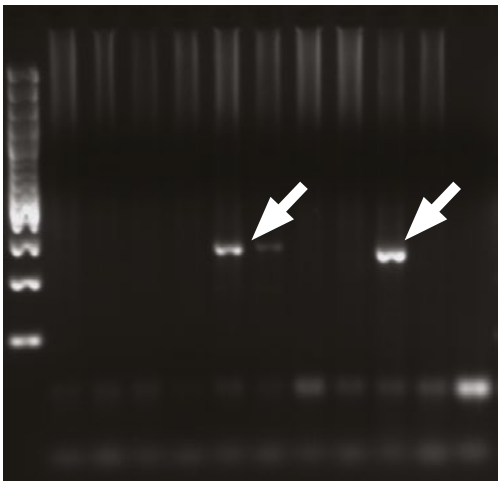


Fig. 16.3

PCR, polymerase chain reaction.

REVISION QUESTIONS

1. How can lymphoma clonality be determined?
2. What are the most common genetic aberrations in lymphomas?
3. Which techniques are available for the detection of chromosomal translocations?

New technologies in lymphoma biology

The knowledge on the pathogenesis of lymphoma was improved with the introduction of microarray technology in 1999-2000.

Since then, continuous improvements in technologies, mainly with the introduction of next-generation sequencing (NGS), have allowed further steps forward in the study of lymphoma genomics, transcriptomics, epigenomics and proteomics.

NGS consists of performing millions of sequencing reactions in parallel, allowing the repeated sequencing of large DNA stretches.

Next-generation sequencing

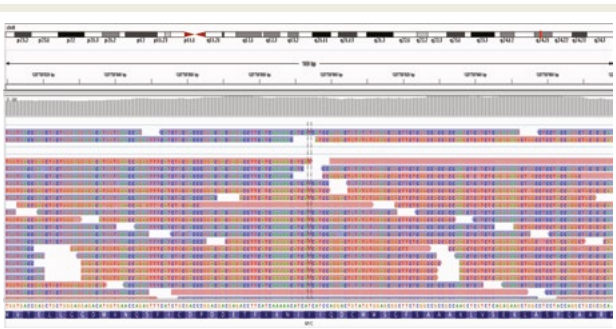
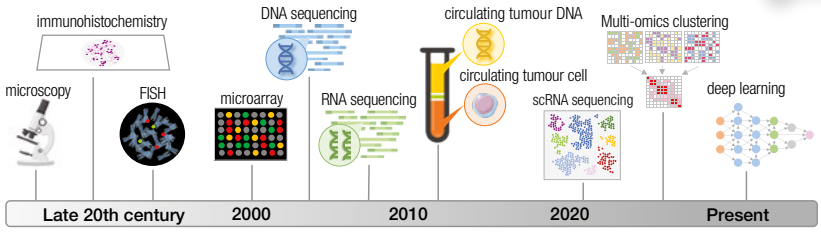


Fig. 16.4

Evolution of genomic techniques in the study of lymphoma biology



FISH, fluorescent *in situ* hybridisation; scRNA, single-cell RNA sequencing.

Fig. 16.5

Recently, novel techniques such as liquid biopsy, single-cell sequencing and advanced bioinformatic analyses have set new standards in the study of lymphoma biology.

Together with tumour cells, the non-neoplastic cells in the tumour microenvironment (TME) can affect patient outcomes and response to treatment.

The type and amount of non-neoplastic cells in the TME also heavily affect the results of studies performed on tumour biopsies. This has to be kept in mind.

NGS enabled the definition of the mutational landscape of lymphoid neoplasms, identifying many genes that are mutated with different frequencies in the various lymphomas.

Thanks to the NGS techniques, patient stratification has been improving. For example, diffuse large B-cell lymphoma (DLBCL), first divided into germinal centre B-cell-like (GCB) and activated B-cell-like (ABC), can be now classified into multiple genetically-defined subgroups.

Better genetic subclassifications will hopefully lead to improved prognosis stratification and, especially, to personalised therapeutic approaches, enhancing treatment efficacy and reducing toxicity.

Novel NGS-defined lymphoma subtypes

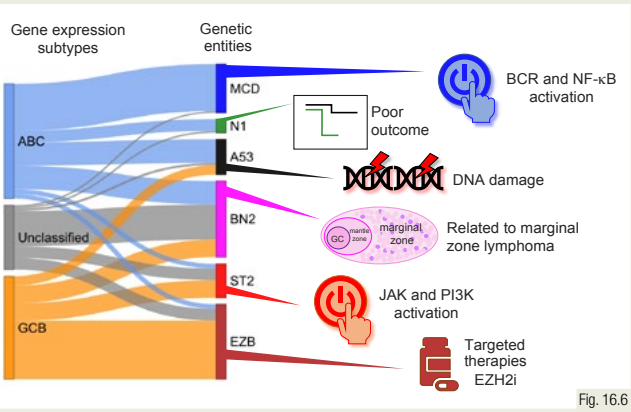


Fig. 16.6

ABC, activated B-cell-like diffuse large B-cell lymphoma; BCR, B-cell receptor; EZH2i, enhancer of zeste homologue 2 inhibitor; GCB, germinal centre B-cell-like diffuse large B-cell lymphoma; JAK, Janus kinase; NGS, next-generation sequencing; NF-κB, nuclear factor-kappa B; PI3K, phosphoinositide 3-kinase.

REVISION QUESTIONS

1. Which technique is the gold standard for biomarker testing in lymphoma diagnosis?
2. What are the most common applications of NGS?
3. What are the clinical implications of specific patient stratification?

Personalised medicine: a new era in lymphoma

Different lymphoma entities are now known to bear many recurrent somatic mutations at variable frequencies.

Individual tumours are heterogeneous populations of cells with molecular and biological variations; subclones can emerge with time and contribute to drug resistance and tumour relapse.

A few genes are highly mutated in a single lymphoma entity, such as *BRAF* in hairy cell leukaemia or *MYD88* in Waldenström macroglobulinaemia.

Examples of recurrent somatic mutations in lymphoma

Histotype	Main recurrent somatic mutations
Chronic lymphocytic leukaemia	*NOTCH1, TP52, SF3B1, ATM, MYD88*
Follicular lymphoma	*MLL2, EZH2, CREBBP, MEF2B, EP300, TNFSRF14, HIST1H1C, OCT2, ARID1A, STAT6, BCL2*
Mantle cell lymphoma	*NOTCH1, NOTCH2, UBR5, CCND1, TP53, ATM, MEF2B, MLL2, BIRC3, TRAF2, TRAF3*
Germinal centre B-cell-like diffuse large B-cell lymphoma	*EZH2, MLL2, CREBBP, EP300, BCL2, GNA13, SGK1, TP53, TNFRAS14, CD70, DTX1, TP53*
Activated B-cell-like diffuse large B-cell lymphoma	*MYD88, CD79a/b, CARD11, TNFAIP3, PRDM1, PIM1, MLL2, B2M, FOXO1, CREBBP, EP300, TP53*
Burkitt lymphoma	*MYC, TP53, TCF3, ID3, CCND3, GNA13*
Mucosa-associated lymphoid tissue (MALT) lymphoma	*TNFAIP3, CREBBP, KMT2C, TET2, SPEN, KMT2D, LRP1B, PRDM1, EP300, TNFRSF14, NOTCH1, NOTCH2, B2M*
Splenic marginal zone lymphoma	*NOTCH2, KLF2, MYD88, TP53, TNFAIP3, SPEN, NOTCH1, BIRC3, CARD11, MLL2, TBL1XR1, SIN3A, EP300, ARID1A*
Nodal marginal zone lymphoma	*MLL2, NOTCH2, PTPRD, KLF2, FAS, FAT4, GPR98, LRP1B, TBL1XR1, ABCA13, BCL10, SPEN, TAF1, TNFRSF14*

Fig. 16.7

Liquid biopsy: the new paradigm of personalised medicine

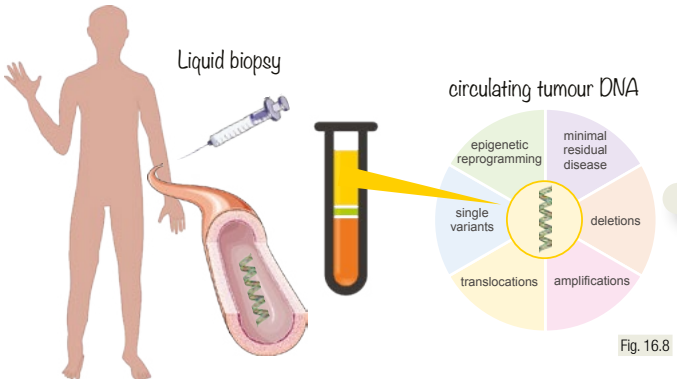


Fig. 16.8

Liquid biopsy has emerged as the new paradigm in personalised medicine, granting real-time monitoring of patients with the advantage of a non-invasive procedure.

Liquid biopsy is based on the presence of circulating tumour DNA (ctDNA) in blood samples, which can be analysed by applying appropriate sequencing and bioinformatic techniques.

Investigation of ctDNA enables the detection of MRD during treatment and follow-up, but also the possibility of obtaining the genetic characterisation of the lymphoma at diagnosis, and, in some cases, the diagnosis itself.

The most frequent mutations often affect common pathways and biological processes, such as chromatin remodelling, B-cell receptor signalling, the nuclear factor-kappa B (NF-κB) pathway, cell cycle and immune surveillance.

Novel therapeutic approaches target recurrent mutations. Patients with *EZH2* mutations benefit from EZH2 inhibitors, and tumours with mutated *MYD88* and *CD79a/b*, and wild-type *CARD1*, from Bruton tyrosine kinase (BTK) inhibitors.

Mutations can lead to drug resistance and relapse. Examples are *BTK/PLCG2* mutations compromising the response to BTK inhibitors in chronic lymphocytic leukaemia (CLL).

Model of clonal evolution at disease relapse

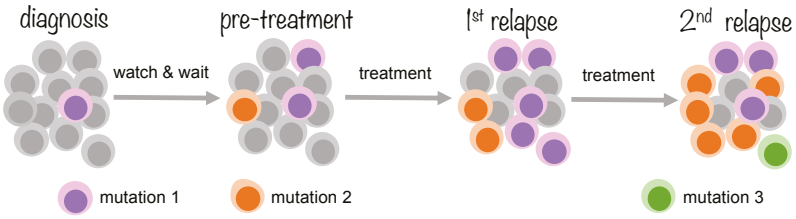


Fig. 16.9

REVISION QUESTIONS

1. What is ctDNA?
2. Are low frequency subclones of the tumour relevant?
3. Is it possible to therapeutically target somatic mutations?

Summary: Molecular biology of lymphomas

- Investigation of clonality is a helpful biomarker for diagnosis and disease monitoring
- Genomic aberrations are commonly harboured by lymphoma patients, and their detection, albeit seldom necessary for diagnosis, may be useful in outcome prediction or in differential diagnosis
- NGS identified novel genetic sub-entities with prognostic and potential therapeutic implications
- Lymphomas frequently exhibit deregulation of crucial processes including B-cell receptor, NF-κB, JAK/STAT, NOTCH signalling, chromatin remodelling, cell cycle, apoptosis and immune surveillance
- Genetic lesions, such as MYC-involving translocations or point mutations (e.g. *TP53*, *NOTCH1*, *BIRC3* and *SF3B1* in CLL) lead to adverse clinical outcomes
- Liquid biopsy enables non-invasive and real-time follow-up and opens promising possibilities in the detection of genetic and epigenetic aberrations, and in characterisation of tumour biology for personalised therapeutic approaches
- Mutational status of specific genes is included in the diagnostic work-up of lymphoma, but full implementation of NGS-based diagnostics in clinical routine is still in progress
- The introduction of NGS approaches in the clinical setting along with the development of new compounds targeting specific molecular lesions will hopefully lead to true personalised medicine

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Image sources: **All figures:** Institute of Oncology Research, Bellinzona, Switzerland.

17 Cutaneous lymphoma

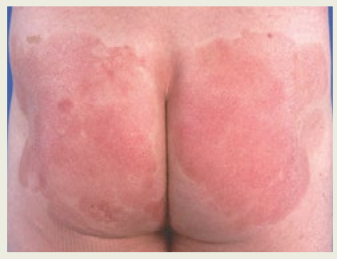
Cutaneous T-cell lymphomas: mycosis fungoides

Primary cutaneous lymphomas (PCLs) are non-Hodgkin lymphomas (NHLs) that present in the skin without evidence of extracutaneous involvement.

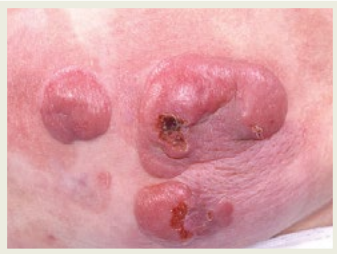
PCLs differ in clinical behaviour, prognosis and treatment from nodal lymphomas involving the skin secondarily, and are therefore classified separately.

The different types of cutaneous T-cell (CTCL) and cutaneous B-cell lymphoma (CBCL) have characteristic clinicopathological features and clinical behaviours.

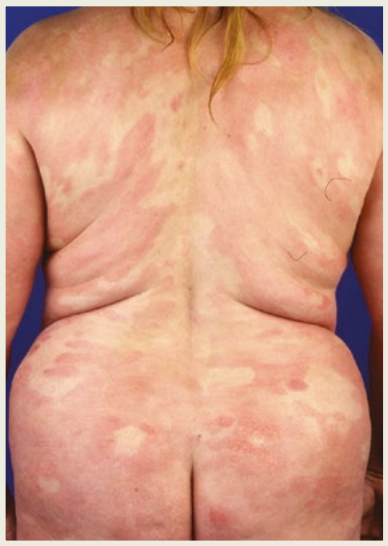
Mycosis fungoides: clinical presentation



Limited patches (stage IA)



Skin tumours (stage IIB)



Patches and plaques over >10% of skin surface (stage IB)

Fig. 17.1

Mycosis fungoides: epidermotropic T cells in early-stage disease

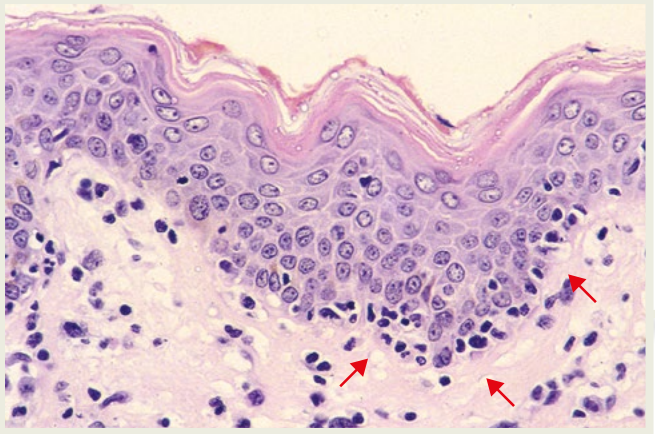


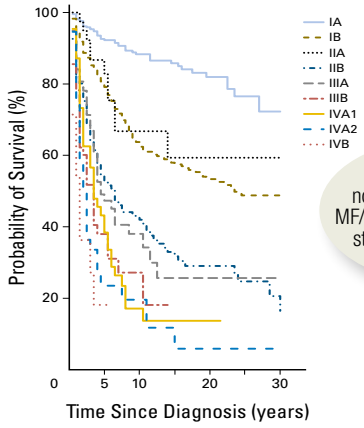
Fig. 17.2

Mycosis fungoides (MF) is the most common type of CTCL with an annual incidence of 0.3/100 000 persons. It mainly affects adults.

The course is indolent (years to decades) with slow progression from patches and plaques to tumours. Less than 25% of patients develop nodal or visceral disease.

Histologically, the early stages of MF show infiltration of atypical CD4+ T cells with convoluted and hyperchromatic nuclei into the epidermis (arrows).

Disease-specific survival of 1502 patients with MF and SS according to their clinical stage at diagnosis



Ann Arbor staging is not used in patients with MF/SS but there is a specific staging classification for MF/SS

MF, mycosis fungoides; SS, Sézary syndrome.

Fig. 17.3

Treatment and prognosis are dependent on stage, including type/extent of skin lesions (patch, plaque or tumour), and the presence of extracutaneous disease.

Skin-limited disease is treated with skin-directed therapies (SDTs), including topical steroids, topical nitrogen mustard, phototherapy (PUVA [psoralen plus ultraviolet-A], UVB [ultraviolet-B]) or radiotherapy (RT).

In refractory disease, SDTs are combined with IFN-α (interferon alpha) or retinoids. Systemic chemotherapy (ChT), targeted therapies and allogeneic stem-cell transplantation (alloSCT) are reserved for advanced disease.

REVISION QUESTIONS

1. Which type of skin lesions can be seen in MF?
2. What is the 10-year survival of patients with limited patches and plaques (stage IA)?
3. Which type of treatment is preferred in patients who present only with skin lesions?

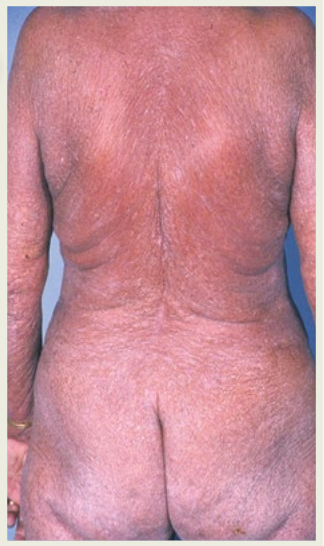
CTCLs other than MF

Sézary syndrome is a leukaemic form of CTCL defined by a pruritic erythroderma, enlarged lymph nodes and clonal CD4+ T cells in skin and blood (Sézary cells).

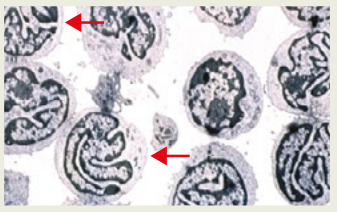
Differentiation from benign forms of erythroderma may be difficult. The prognosis is generally poor (5-year overall survival [OS]: 25%).

Treatment options are extracorporeal photopheresis (± IFN-α) or targeted therapies (mogamulizumab; low-dose alemtuzumab). AlloSCT has curative potential in selected patients.

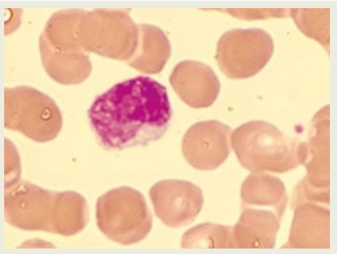
Sézary syndrome



Erythroderma



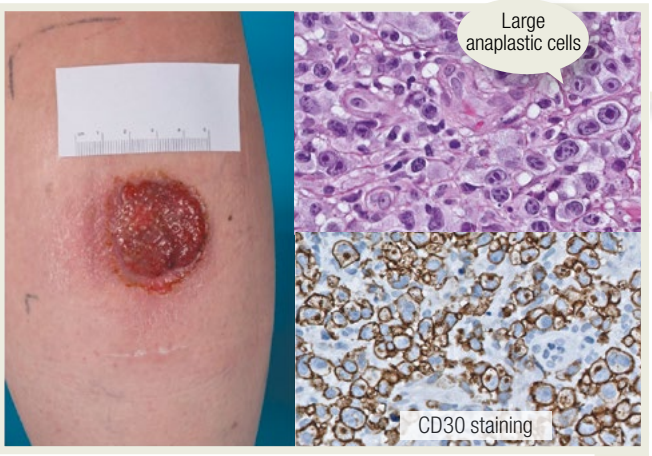
Sézary cells, cerebriform nucleus (electron micrograph)



Sézary cell (blood smear)

Fig. 17.4

C-ALCL presenting with a solitary tumour



C-ALCL, cutaneous anaplastic large cell lymphoma.

Fig. 17.5

Cutaneous anaplastic large cell lymphoma (C-ALCL) is a tumour of large anaplastic or pleomorphic CD30+ cells. Most patients present with a solitary (ulcerating) tumour.

A similar histology can be seen in lymphomatoid papulosis (recurrent, self-healing papules) and transformed MF. Thus, clinicopathological correlation is crucial.

The prognosis of C-ALCL is excellent (5-year OS: ~90%). Solitary lesions can be treated with RT or surgery, multifocal lesions with low-dose methotrexate (MTX) or brentuximab.

CTCLs other than MF, Sézary syndrome and primary cutaneous CD30+ T-cell lymphoproliferative disorders (LPDs) are rare and clinically heterogeneous.

Subcutaneous panniculitis-like T-cell lymphoma has a good prognosis (5-year OS: >80%) and should be treated first with prednisone or other immunosuppressive agents.

Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma and cutaneous gamma-delta (γδ) T-cell lymphoma are aggressive lymphomas (5-year OS: <20%).

Subcutaneous panniculitis-like T-cell lymphoma

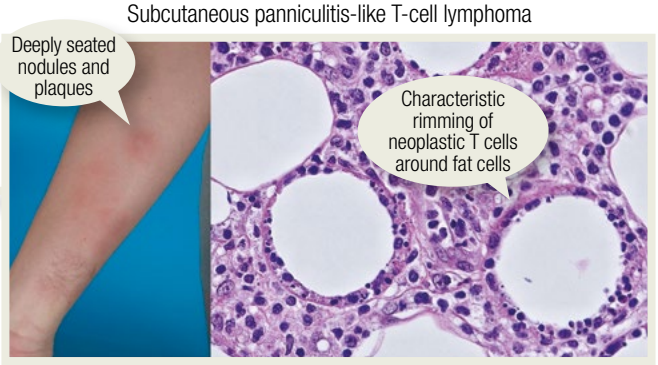


Fig. 17.6

REVISION QUESTIONS

1. What are the characteristic clinical features of Sézary syndrome?
2. What is the first-choice treatment of a primary C-ALCL presenting with a solitary skin tumour?
3. What is the first choice of treatment in patients with a subcutaneous panniculitis-like T-cell lymphoma?

Cutaneous B-cell lymphomas

Primary cutaneous marginal zone lymphoma may present with solitary, localised or multifocal lesions, often located on the trunk and arms.

Histologically, they are composed of small B cells, lymphoplasmacytoid cells, monotypic plasma cells, often follicles with reactive germinal centres, and an abundant T-cell infiltrate.

This is an indolent type of lymphoma, which can be managed easily by (intralesional) steroids, excision or low-dose RT. Extracutaneous dissemination is rare.

Primary cutaneous marginal zone lymphoma presenting with multiple lesions on the back

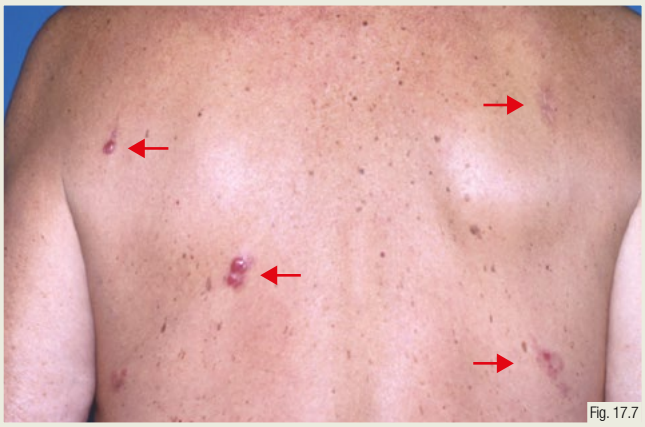
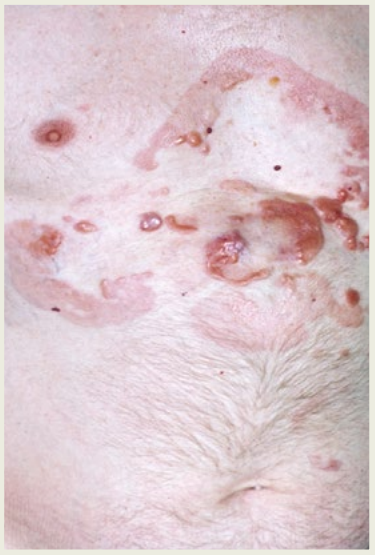
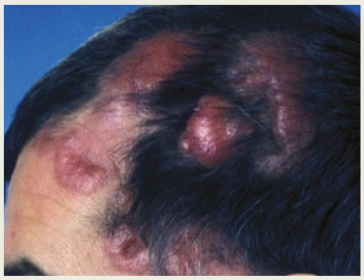
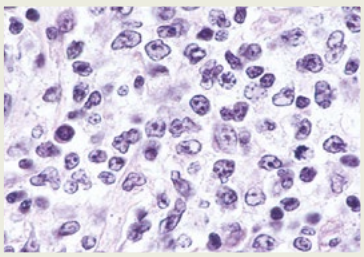


Fig. 17.7

Primary cutaneous follicle centre lymphoma presenting with localised lesions on the trunk or scalp







Large cells with cleaved nuclei

Fig. 17.8

Primary cutaneous follicle centre lymphoma generally presents with localised lesions on the trunk or scalp, and uncommonly with generalised skin lesions.

Histologically, it consists mainly of medium-sized to large centrocytes and variable numbers of centroblasts. The growth pattern may be diffuse, follicular or mixed.

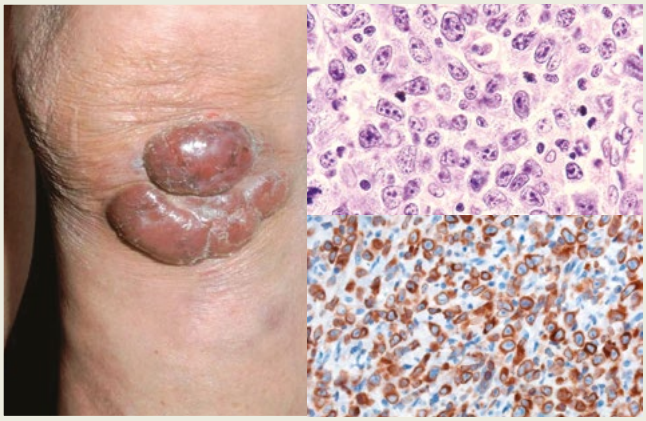
Local RT is the first choice of treatment. The prognosis is excellent with a 5-year OS >90%. Extracutaneous dissemination is uncommon.

Primary cutaneous diffuse large B-cell lymphoma, leg type.

Primary cutaneous diffuse large B-cell lymphoma, leg type characteristically presents with tumours on the (lower) legs in elderly patients, particularly in women.

Histology shows confluent sheets of large cells with round nuclei and prominent nucleoli (centroblasts and immunoblasts). B-cell lymphoma 2 (BCL2), MUM1 and immunoglobulin M (IgM) are strongly expressed.

MYD88 and/or CD79b mutations are present in 70%-75% of cases. R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone) is the first choice of treatment. The prognosis is intermediate with a 5-year OS ~50%.



BCL2, B-cell lymphoma 2. BCL2

Fig. 17.9

REVISION QUESTIONS

1. What is the characteristic clinical presentation for each of the three main types of CBCL?
2. What is the prognosis for each of the three main types of CBCL?
3. What is the preferred therapy in patients with primary cutaneous follicle centre lymphoma?

Summary: Cutaneous lymphoma

- The term 'primary cutaneous lymphoma' refers to NHLs presenting in the skin without evidence of extracutaneous disease at the time of diagnosis
- Different types of CTCL and CBCL have characteristic clinical features and courses
- MF is the most common type of CTCL
- Stage of disease in MF is important for first-choice treatment and for prognosis
- MF patients with only patches and plaques should be treated with SDTs
- Sézary syndrome is a leukaemic form of CTCL with a poor prognosis
- C-ALCL generally presents with solitary or localised skin lesions, which can easily be managed with RT
- Primary cutaneous marginal zone lymphoma and primary cutaneous follicle centre lymphoma are indolent types of CBCL and should not be treated with multiagent ChT
- Primary cutaneous diffuse large B-cell lymphoma, leg type should be treated with R-CHOP

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18 Rare NK/T-cell lymphomas

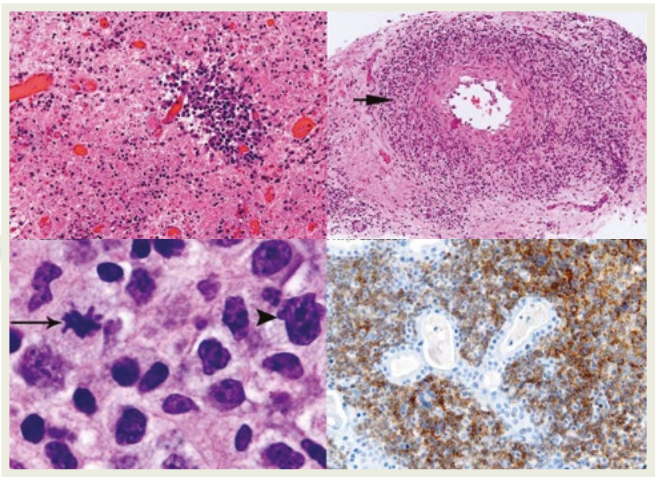
Pathology, biology and clinical features

Natural killer/T-cell lymphoma (NKTCL) is an Epstein–Barr virus (EBV)-associated lymphoma. It shows a geographical predilection for Asian and South American populations, with incidences of 5.2% and 3%, respectively (0.3% elsewhere).

NKTCL shows an angiocentric and angiodestructive pattern. Tumour cells are CD2+, CD5-, CD56+, cCD3+ and sCD3-, and express cytotoxic proteins.

NKTCL can be nodal (NNKTCL) or extranodal (ENKTCL); these represent clinically, pathophysiologically and genetically distinct entities.

NK/T-cell lymphoma



NK, natural killer.

Top left, necrosis is commonly present; Top right, angioinvasion (angiocentric lymphoma); Bottom left, tumour cells are large with irregular nuclei and can have frequent mitosis; Bottom right, tumour cells are CD56+.

Fig. 18.1

Comparison of the ENKTCL mutational landscape

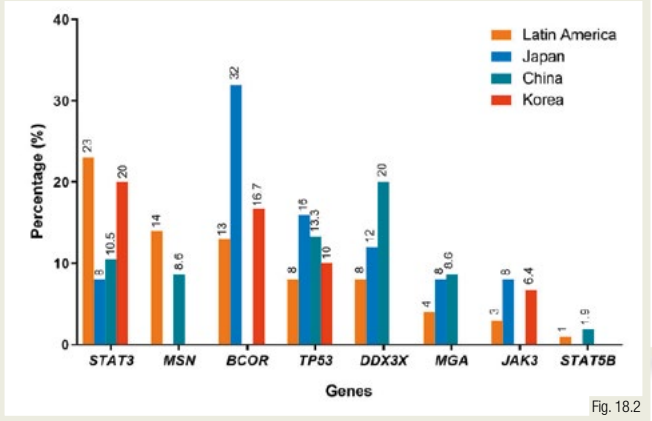


Fig. 18.2

ENKTCL, extranodal natural killer/T-cell lymphoma; JAK3, Janus kinase 3.

Frequency (%) of the most commonly altered genes in different populations from four different studies.

EBV infection and subsequent genetic alterations in infected cells are central to ENKTCL development. Positivity for EBV with *in situ* hybridisation (ISH) is necessary for diagnosis.

NK and T cells derive from the same lymphoid progenitor cell; most cases of ENKTCL have an NK cell origin, but a small minority is derived from T cells.

Cytogenetic abnormalities include del(6), del(8) and del(14); commonly mutated genes are *TP53*, Janus kinase 3 *(JAK 3)*, *STAT3*, *DDX3X*, *MGA*, *BCOR*, *ECSIT* and *MCL1*.

More than two thirds of NKTCLs are localised at diagnosis and most frequently located in the nasal and upper airway region (nasal ENKTCL).

Nasal ENKTCL is more prevalent in men in their 5th decade. It presents with nasal obstruction, epistaxis and destructive lesions of the aerodigestive tract and mid-face.

Disseminated disease occurs in 10%-20% of ENKTCLs, involving sites such as testis, skin, intestine, soft tissue and bone marrow (rarely) and may be complicated by haemophagocytic syndrome (HPS).

Clinical presentation of nasal ENKTCL

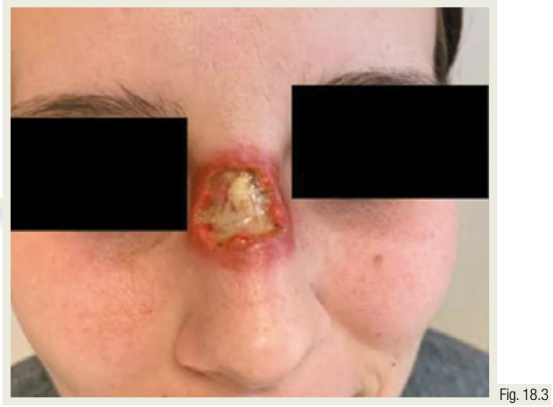


Fig. 18.3

ENKTCL, extranodal natural killer/T-cell lymphoma.

REVISION QUESTIONS

1. With which viral infection is ENKTCL often associated?
2. What are the pathological features of ENKTCL?
3. What is the typical immunophenotypic profile of NKTCL cells?

ENKTCL: Staging, prognosis and differential diagnosis

The Ann Arbor staging system (SS) is the most widely used for staging ENKTCL and is useful for planning radiotherapy (RT).

The Chinese Southwest Oncology Group and Asia Lymphoma Study Group SS considers site, local invasion and lymph node involvement and seems to be even more accurate in estimating survival.

The accuracy of SSs may be improved by positron emission tomography–computed tomography (PET–CT) and by quantification of plasma EBV-DNA, which gives an accurate measure of tumour burden and response to treatment.

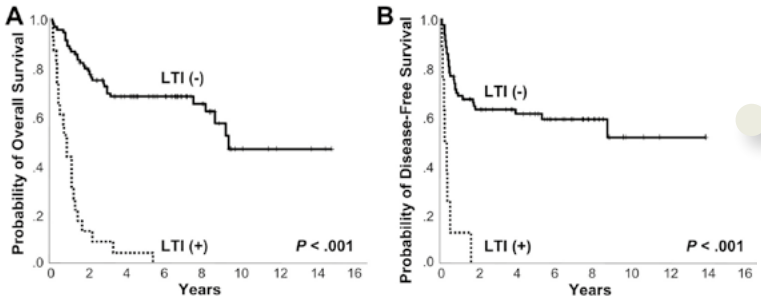
The Chinese Southwest Oncology Group and Asia Lymphoma Study Group (CA) ENKTCL staging system

Stage	Description
I	Lesions confined to the nasal cavity or nasopharynx No local invasion No lymph node involvement
II	Lesions confined to the nasal cavity or nasopharynx Local invasion No lymph node involvement Non-nasal disease
III	Lesions with regional lymph node involvement
IV	Non-regional lymph node involvement Lymph nodes above and below diaphragm Widespread disease

Fig. 18.4

ENKTCL, extranodal natural killer/T-cell lymphoma.

OS and DFS according to LTI



DFS, disease-free survival; LTI, local tumour invasiveness; OS, overall survival.

Fig. 18.5

The International Prognostic Index (IPI), Prognostic Index of NK Lymphoma (PINK) and nomogram-revised risk index (NRI) are the most widely used predictive models.

In nasal ENKTCL, some features of the tumour, such as size and local tumour invasiveness (LTI), are better predictors of outcome than the IPI.

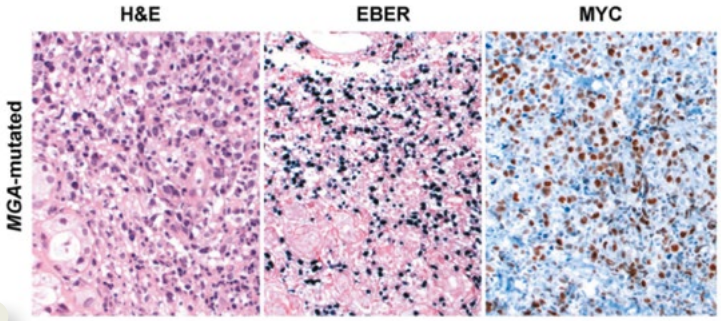
The NRI, a new prognostic index based on age >60 years, Eastern Cooperative Oncology Group (ECOG) score ≥2, lactate dehydrogenase (LDH), Ann Arbor stage (I/II vs III/IV) and LTI, is more accurate compared with the IPI or PINK.

The main differential diagnoses are other NK/T malignancies, EBV-associated disorders and infectious diseases including rhinoscleroma, cellulitis and deep mycoses.

The microscopic differential diagnosis includes diseases causing angiodestruction and necrosis, such as lymphomatoid granulomatosis or granulomatosis with polyangiitis (previously known as Wegener granulomatosis).

Positivity for EBV by ISH helps to differentiate it from peripheral T-cell lymphoma not otherwise specified (PTCL-NOS), which is EBV-negative.

In situ hybridisation for EBV-encoded RNA (EBER) in NKTCL



EBV, Epstein–Barr virus; H&E, haematoxylin and eosin; NKTCL, natural killer/T-cell lymphoma.

Fig. 18.6

REVISION QUESTIONS

1. What are the most important prognostic factors in nasal ENKTCL?
2. How can the accuracy of SSs be improved?
3. What are the differential diagnoses for ENKTCL?

ENKTCL: Treatment

Anthracycline-based chemotherapy (ChT) regimens were ineffective for ENKTCL. Various L-asparaginase, platinum and gemcitabine-based regimens have emerged as promising treatments.

Involved-site RT (ISRT [50-55 Gy]) alone or with ChT is effective for low-risk early-stage ENKTCL (NRI-defined risk stratification).

Concurrent, sequential or sandwiched chemoradiotherapy is the current standard treatment for intermediate-risk and high-risk early-stage I/II nasal ENKTCL.

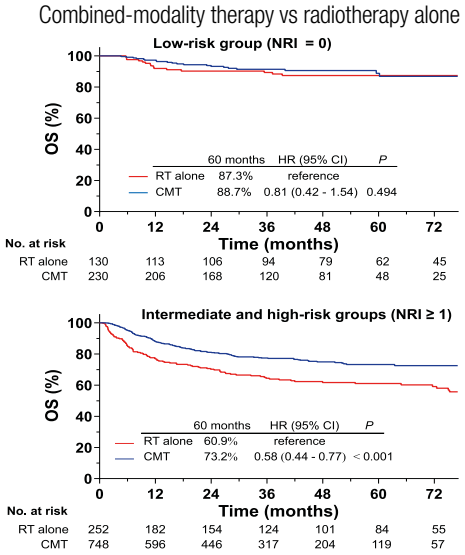


Fig. 18.7

CI, confidence interval; CMT, combined-modality therapy; HR, hazard ratio; NRI, nomogram-revised risk index; OS, overall survival; RT, radiotherapy.

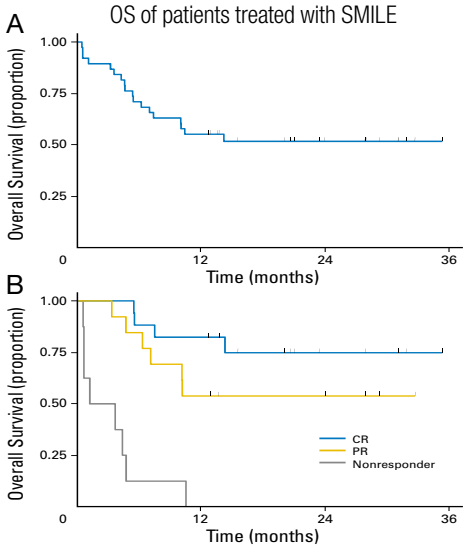


Fig. 18.8

CR, complete response; OS, overall survival; PR, partial response; SMILE, steroid, methotrexate, ifosfamide, L-asparaginase and etoposide.
A.OS of all patients; B. OS according to attained response.

Patients with advanced ENKTCL also benefit from combined RT and ChT, which can be given synchronously or metachronously in either order.

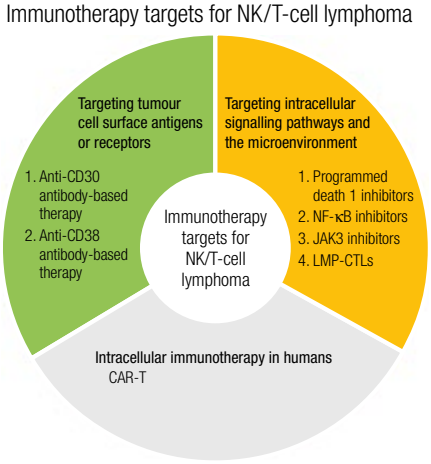
For stage III/IV ENKTCL, ChT with SMILE (steroid, methotrexate, ifosfamide, L-asparaginase and etoposide) is an effective but rather toxic option.

Several alternative regimens incorporating L-asparaginase, methotrexate, gemcitabine and oxaliplatin have shown similar efficacy and improved tolerability.

Some studies showed that autologous or allogeneic stem-cell therapy may improve survival in patients with extranasal or advanced nasal ENKTCL.

Immunotherapy regimens directed against NKTCL-associated targets such as immune checkpoint inhibitors and anti-CD30 and anti-CD38 antibodies are increasingly used.

Development of HPS is a rare but major complication that may dramatically reduce survival of ENKTCL patients.



CAR, chimeric antigen receptor; JAK3, Janus kinase 3; LMP-CTL, latent membrane protein-cytotoxic T lymphocyte; NF-κB, nuclear factor-kappa B; NK, natural killer.

Fig. 18.9

REVISION QUESTIONS

1. What is the role of RT in the treatment of ENKTCL?
2. What is the treatment for advanced ENKTCL?
3. Which monoclonal antibodies may be effective in ENKTCL therapy?

Summary: Rare NK/T-cell lymphomas

- ENKTCL is a rare, aggressive EBV-associated lymphoma with a poor prognosis in advanced stages
- ENKTCL is characterised by vascular damage and tissue destruction
- The majority of cases are located in the nasal and upper airway region and, rarely, in other sites such as testis, skin, intestine and soft tissue
- Local symptoms may include nasal obstruction, epistaxis and hard palate destruction
- Circulating EBV-DNA and PET–CT can predict the risk of treatment failure
- Combination ChT (e.g. SMILE) and early ISRT is recommended for localised nasal ENKTCL
- Multiagent innovative therapy shows promise for advanced nasal and extranasal ENKTCL
- Despite aggressive ChT, advanced-stage patients generally have a poor prognosis
- Immunotherapy regimens directed against ENKTCL-associated targets may be promising and are increasingly used

Further Reading

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19 Splenic and nodal marginal zone lymphomas

Marginal zone lymphomas and nodal marginal zone lymphomas

The name 'marginal zone lymphoma' (MZL) alludes to the fact that the neoplastic lymphocytes derive from and infiltrate the marginal zone of lymphoid follicles. MZLs are related to antigen stimuli.

The World Health Organization (WHO) classification includes three types: MZL of mucosa-associated lymphoid tissue (MALT), nodal MZL (NMZL) and splenic MZL (SMZL).

The main difference between MZL of MALT and NMZL is their primary origin: extranodal in MALT and nodal in NMZL. SMZL is a distinct clinicopathological entity.

Secondary lymphoid follicle, showing follicular centre and mantle and marginal zone areas

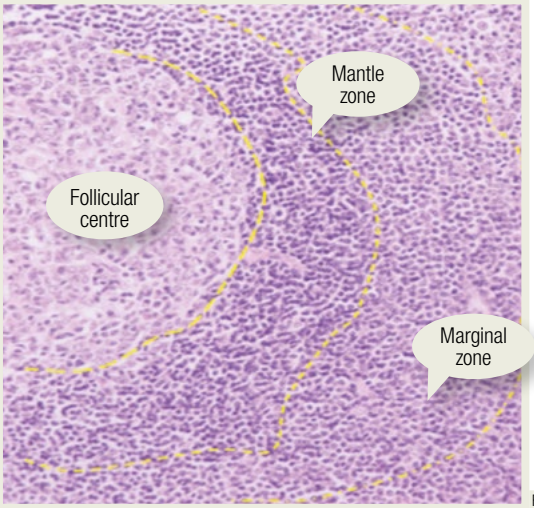


Fig. 19.1

Lymph node: infiltration by NMZL

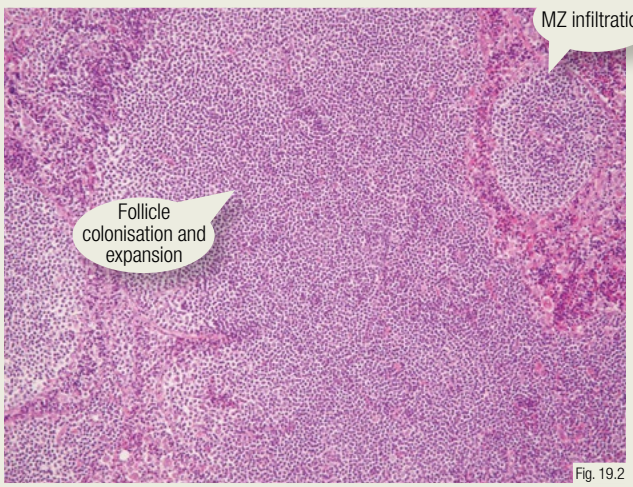


Fig. 19.2

MZ, marginal zone; NMZL, nodal marginal zone lymphoma.

In NMZL, the neoplastic lymphocytes infiltrate the marginal zone of the follicles, but also colonise reactive follicles and expand to interfollicular areas.

The infiltrate is composed of centrocyte-like lymphocytes (CD20+, CD5-, CD10-, CD23-, B-cell lymphoma 6 [BCL6], cyclin D1-) with variable plasma cell differentiation.

Histological features of lymph node (LN) involvement are indistinguishable in NMZL, SMZL and MALT lymphoma; the diagnosis of NMZL requires exclusion of primary extranodal involvement.

NMZL presents with localised or generalised enlarged LNs, with occasional bone marrow (BM; ~20%-40%) and peripheral blood (PB) involvement.

NMZL has an indolent course and many patients are asymptomatic, so treatment is required only when symptoms develop. It is occasionally associated with hepatitis C virus (HCV). Treatment is similar to that of SMZL.

Median overall survival (OS) is 8.6, 8.3 and 12.6 years for SMZL, NMZL and MALT lymphoma, respectively. Survival in NMZL and SMZL is inferior to that of matched general population.

Kaplan–Meier estimate of overall survival in the three types of MZL

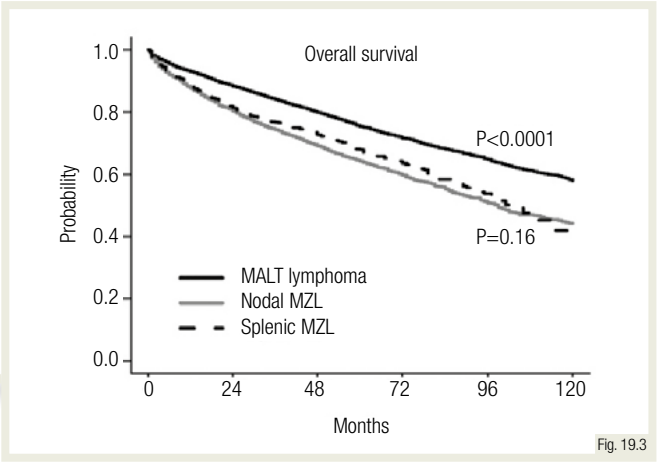


Fig. 19.3

MALT, mucosa-associated lymphoid tissue; MZL, marginal zone lymphoma.

REVISION QUESTIONS

1. How can NMZL be distinguished from MALT lymphoma with LN involvement?
2. What are the most important clinical features of NMZL?
3. What is the most usual course of NMZL?

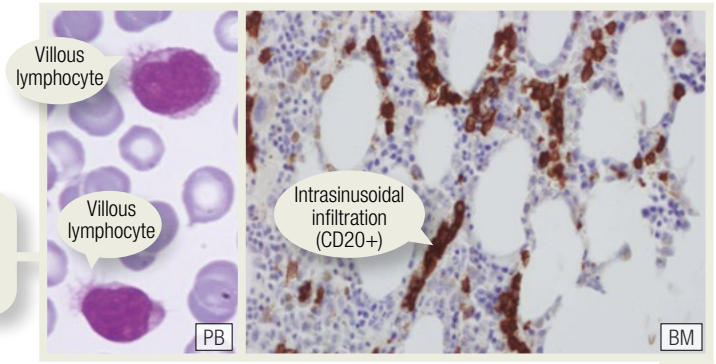
Splenic marginal zone lymphoma

SMZL is characterised by PB, BM and splenic infiltration by small lymphocytes: CD20+, CD79a+, CD5-, CD10-, CD23-, CD43-, cyclin D1-, annexin A1-, CD103- (chronic lymphocytic leukaemia [CLL] score ≤2). Villous lymphocytes can be found in the PB, but they are not specific to SMZL.

BM involvement may show intrasinusoidal, nodular, interstitial, diffuse or mixed infiltration patterns; the first is very characteristic of, but not exclusive to, SMZL.

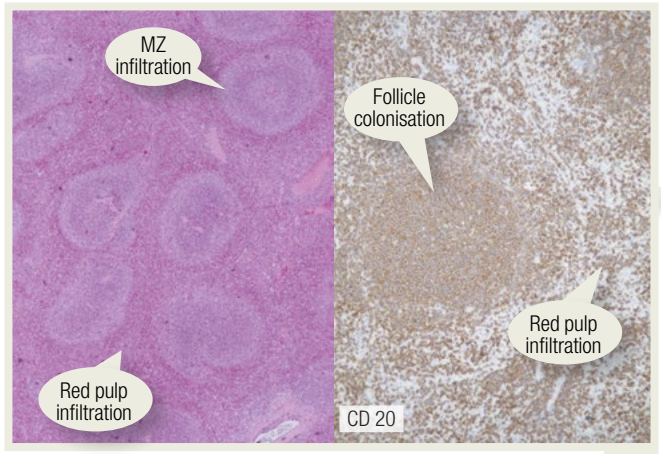
BM findings in SMZL are indistinct from those in splenic B-cell lymphoma/leukaemia unclassifiable types (splenic diffuse red pulp small B-cell lymphoma and hairy cell leukaemia-variant [HCLv]). Allelic loss of 7q31-32 is unique to SMZL.

Peripheral blood and bone marrow findings in SMZL



BM, bone marrow; PB, peripheral blood; SMZL, splenic marginal zone lymphoma. Fig. 19.4

SMZL. Spleen pathology



MZ, marginal zone; SMZL, splenic marginal zone lymphoma. Fig. 19.5

Spleen infiltration shows expansion of the white pulp with a macroscopic miliary-like aspect.

In the white pulp, small lymphocytes surround or replace reactive germinal centres infiltrating the marginal zone. The red pulp is also involved.

Splenectomy is not mandatory for the diagnosis of SMZL, which should be based on a combination of PB and BM morphology, histology, flow cytometry (FCM) and cytogenetics data.

Biological studies of SMZL spleen samples identified *NOTCH2*, *KLF2* and nuclear factor-kappa B (*NF-kB*) as the most frequently mutated genes.

A minimal set of 14 genes identifies two main and two additional clusters, and the expression of microenvironment genes identifies two (immunosuppressive and immunosilent) subsets.

The genetic and the microenvironment subsets are associated with different clinical outcomes. Mutations can be detected on PB and this may have practical implications.

Genetic and phenotypic attributes of SMZL

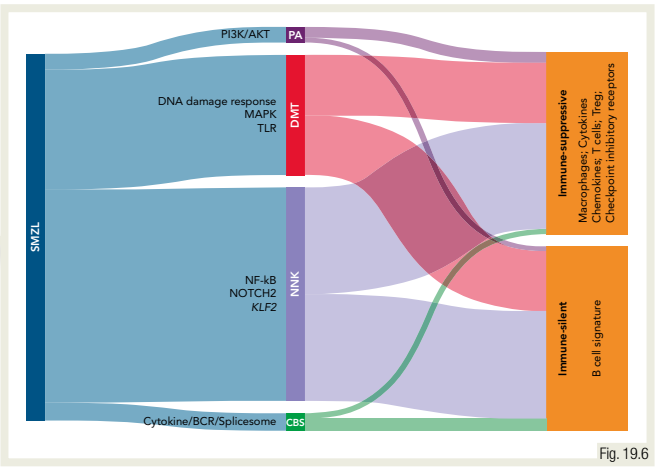


Fig. 19.6

BCR, B-cell receptor; MAPK, mitogen-activated protein kinase; NF-kB, nuclear factor-kappa B; PI3K, phosphoinositide 3-kinase; SMZL, splenic marginal zone lymphoma; TLR, toll-like receptor.

REVISION QUESTIONS

1. Are villous lymphocytes diagnostic of SMZL?
2. What is the most characteristic cytogenetic finding in SMZL?
3. Is a spleen examination, and therefore a splenectomy, required for the diagnosis of SMZL?

Splenic marginal zone lymphoma. Clinical features, prognosis and treatment

SMZL is an indolent lymphoma, occurring mostly in the elderly. At diagnosis, 25% are asymptomatic, but the disease tends to progress. A benign clonal CD5- lymphocytosis may precede SMZL.

Cytopenias and splenomegaly (80%) are the leading symptoms. Lymphadenopathy is uncommon (13%-15%). A monoclonal IgM (immunoglobulin M) band, autoimmune haemolytic anaemia (AIHA) and other immune phenomena are common.

Nodal and extranodal dissemination or transformation to diffuse large B-cell lymphoma (DLBCL) may occasionally occur (10%-13%) at any moment and at any site during the evolution of SMZL.

Massive splenomegaly in the absence of lymphadenopathy in SMZL

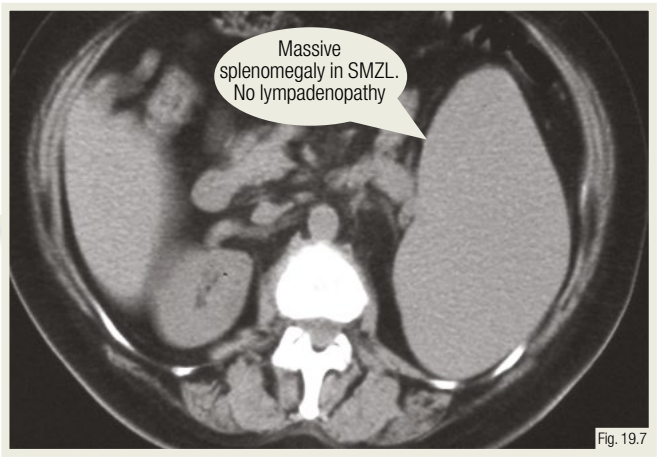


Fig. 19.7

SMZL, splenic marginal zone lymphoma.

HPLL/ABC: Simplified HPLL/ABC score for SMZL

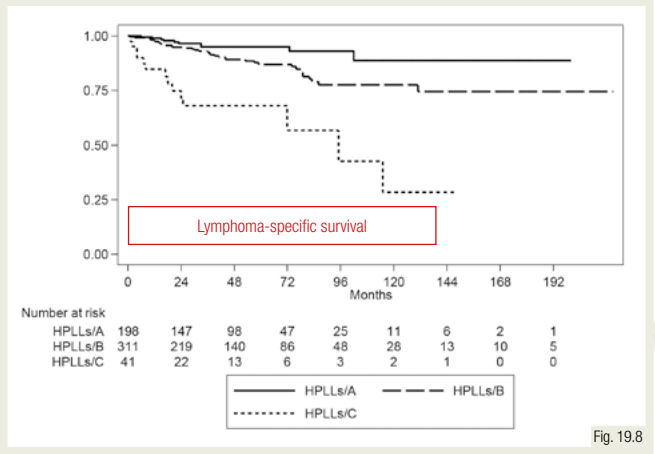


Fig. 19.8

HPLL, Haemoglobin, Platelets, Lactate dehydrogenase and extrahilar Lymphadenopathy; SMZL, splenic marginal zone lymphoma.

Treatment is required only when symptomatic painful splenomegaly, progressive cytopenias (haemoglobin [Hb] <10 g/dL, platelet count <80-100×10^3/μL), progressive LN or extranodal involvement occur.

As SMZL does not behave as a nodal lymphoma, Ann Arbor staging and the International Prognostic Index (IPI) or other indexes are not useful.

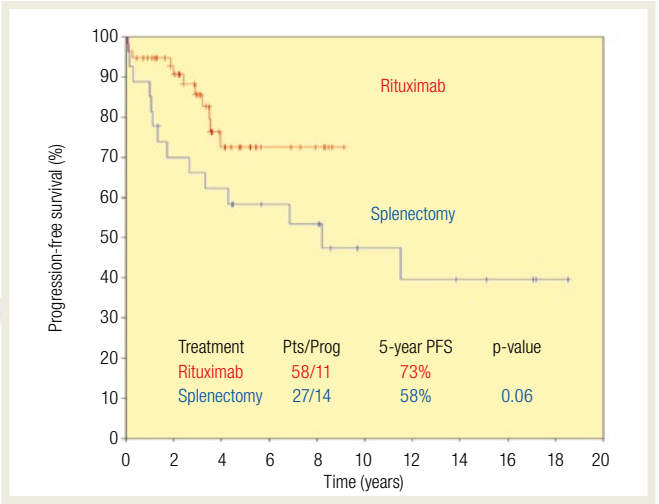
The combination of Hb <9.5 g/dL, platelet count <80×10^3/μL, high lactate dehydrogenase (LDH) and extrahilar lymphadenopathy results in a prognostic score (HPLL/ABC simplified score), where 0, 1-2 or 3-4 factors define three risk groups (A, B, C).

There is no standard treatment for SMZL. A watch-and-wait approach is a good option in stable situations. When present, treatment of HCV or malaria should precede other treatments.

Rituximab may achieve rapid clinical and molecular responses and is the first step of treatment, when needed. Whether the addition of chemotherapy (ChT) can improve its effect or just increase toxicity is not yet known.

Splenectomy has been the classical historical treatment, resulting in clinical but not molecular responses, and is no longer the best initial treatment.

Treatment of splenic marginal zone lymphoma: comparison of rituximab with splenectomy



PFS, progression-free survival; Prog, progression; Pts, patients.

Fig. 19.9

REVISION QUESTIONS

1. Should all patients with SMZL be treated at diagnosis?
2. What is the best prognostic factor for SMZL?
3. Is splenectomy still the first step of treatment for SMZL?

Summary: Splenic and nodal marginal zone lymphomas

- NMZL presents with lymphadenopathy and usually has an indolent course. Diagnosis requires the exclusion of extranodal involvement
- In endemic areas, HCV infection is associated with both NMZL and SMZL, and malaria with SMZL. Treatment of these infections may induce lymphoma response and should precede other systemic treatments
- SMZL is characterised by PB, BM and spleen involvement by CD5-negative lymphocytes and infrequent systemic lymphadenopathy
- Villous lymphocytes may occur in SMZL, but they are not specific for this type of lymphoma. 7q deletion is the specific cytogenetic finding in SMZL
- The diagnosis of SMZL should be the result of a combination of data obtained from the study of PB, BM and cytogenetics
- Splenectomy is not essential for the diagnosis of SMZL, although it is necessary for the diagnosis of splenic B-cell unclassifiable types
- Only symptomatic NMZL or SMZL patients require treatment
- Rituximab is the best first-line treatment for SMZL. It is not yet known whether adding ChT may improve the effect of rituximab or only increase toxicity
- Splenectomy is no longer the standard treatment for SMZL. It results in clinical but not molecular response
- The HPLL/ABC prognostic score for SMZL defines three groups (0, 1-2 or 3-4 factors) with different outcomes

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20 Waldenström macroglobulinaemia

Clinicopathological presentation

Waldenström macroglobulinaemia (WM) is a rare (~2% of all haematological malignancies), low-grade B-cell lymphoma characterised by bone marrow (BM) infiltration by a lymphoplasmacytic clone.

A somatic mutation in the *MYD88* gene (L265P) is found in >90% of cases.

Clonal cells produce a monoclonal immunoglobulin M (IgM) protein; however, there is no IgM threshold for diagnosis of WM.

Serum electrophoresis and immunofixation electrophoresis of a patient with WM

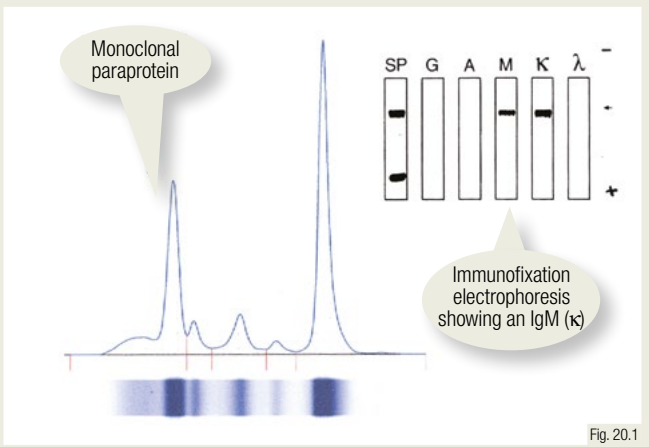


Fig. 20.1

IgM, immunoglobulin M; WM, Waldenström macroglobulinaemia.

Bone marrow biopsy

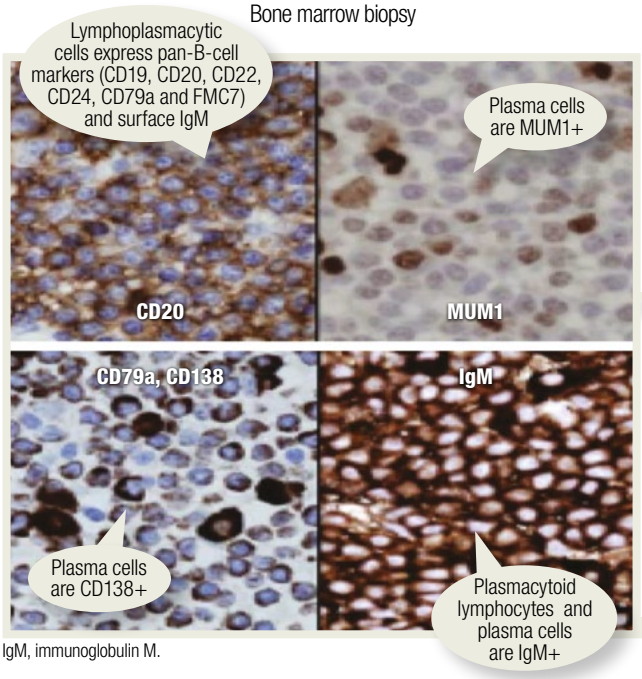


Fig. 20.2

IgM, immunoglobulin M.

A BM biopsy is required for diagnosis. Lymphoplasmacytic cells are small lymphocytes with plasmacytoid or plasma cell differentiation. An increased number of mast cells is frequent in the BM.

Clonal WM cells express pan-B markers (CD19, CD20, CD22, CD79, FMC7), are CD103- and CD11c-negative, but infrequently may be CD10- or CD5-positive. A small plasma cell clone is commonly also found.

Cytopenias (anaemia, less often thrombocytopenia) are common presenting symptoms. Liver, spleen or lymph node (LN) enlargement is found in ~50% of cases, usually by imaging.

Very high levels of IgM can cause hyperviscosity syndrome (HVS).

The IgM can have an auto-antibody (Ab) activity, such as anti-myelin-associated glycoprotein (MAG), causing a distal, symmetrical, chronic demyelinating peripheral neuropathy.

IgM may have cryoglobulin or cold-agglutinin properties causing clinical manifestations of cryoglobulinaemia, haemolysis, Raynaud syndrome and renal failure.

Hyperviscosity syndrome manifestations and Raynaud syndrome

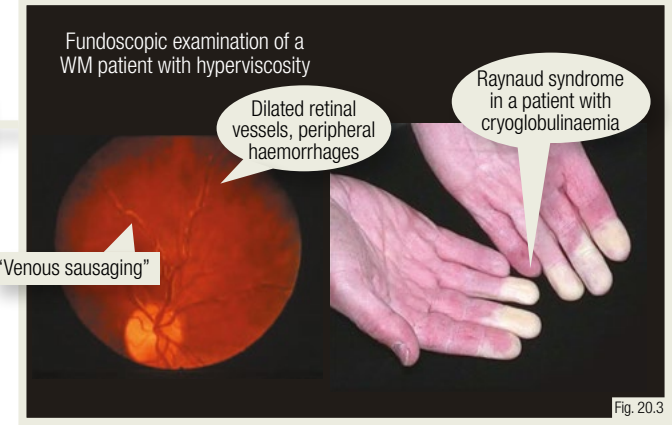


Fig. 20.3

WM, Waldenström macroglobulinaemia.

REVISION QUESTIONS

1. What is the most common somatic mutation in WM?
2. What is the typical immunophenotype of WM lymphoplasmacytic cells?
3. What is the threshold of IgM above which the diagnosis of WM is established?

Prognosis and treatment indications

A pre-existing IgM monoclonal gammopathy of undetermined significance (MGUS) is the most important risk factor for development of WM (with a 46-fold increase for the risk of WM). A familial predisposition exists.

WM is a chronic incurable disease but the median overall survival (OS) of patients with symptomatic WM exceeds 10 years and ~30%-50% of patients die of unrelated causes.

Patients with asymptomatic WM should not be treated, as they can remain stable for years.

Risk of progression to symptomatic disease for patients with asymptomatic WM

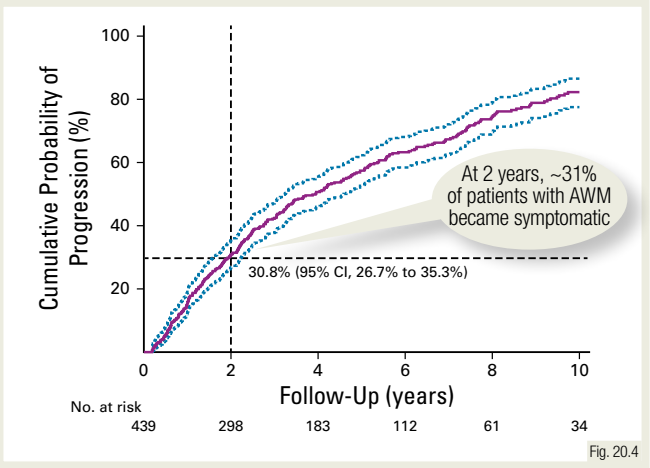


Fig. 20.4

AWM, asymptomatic WM; CI, confidence interval; WM, Waldenström macroglobulinaemia.

Survival after first treatment initiation according to the ISSWM

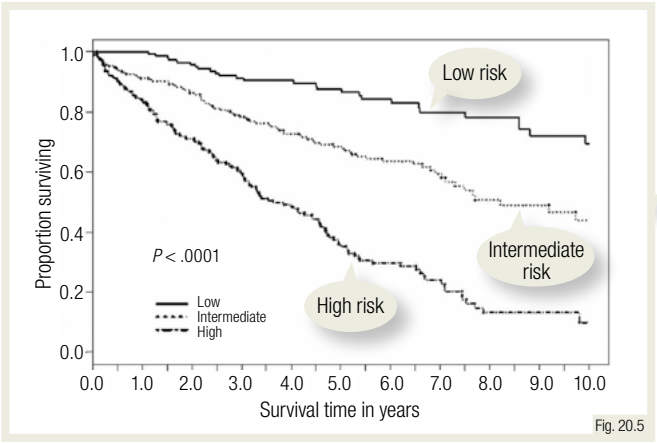


Fig. 20.5

ISSWM, International Prognostic Scoring System for Waldenström Macroglobulinaemia.

Indications to start treatment for WM include constitutional symptoms, IgM-related complications, bulky LNs or splenomegaly, cytopenias or evidence of histological transformation.

The International Prognostic Scoring System for Waldenström Macroglobulinaemia (ISSWM; age, haemoglobin [Hb], low platelets, β2-microglobulin, IgM) and the revised ISSWM (age, β2-microglobulin, serum albumin, lactate dehydrogenase [LDH]) discriminate risk groups.

Patients with an IgM-related disorder may require treatment to reduce circulating IgM levels and suppress IgM production by the malignant clone.

Association of IgM levels with HVS occurrence

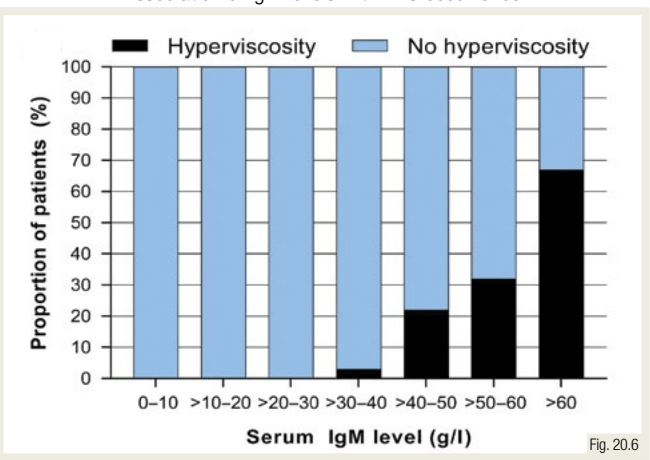


Fig. 20.6

HVS, hyperviscosity syndrome; IgM, immunoglobulin M.

Plasmapheresis may rapidly, but briefly, reduce IgM if it is necessary to manage IgM-related complications (as in HVS or cryoglobulinaemia).

Several agents have shown activity in WM: alkylators, nucleoside analogues, bendamustine, anti-CD20 monoclonal Abs (mAbs), proteasome inhibitors, Bruton tyrosine kinase (BTK) inhibitors and B-cell lymphoma 2 (BCL2) inhibitors.

Treatment should be adapted to the patient's characteristics (age, comorbidities) and clinical presentation (need for rapid IgM reduction, bulky disease, etc.).

REVISION QUESTIONS

1. Who is at risk for development of WM?
2. Are there any risk assessment tools for patients with WM?
3. How is HVS managed?

Treatment

First-line chemoimmunotherapy, either bendamustine-rituximab (B-R) or dexamethasone, rituximab and cyclophosphamide (DRC), offers prolonged remission (3-6 years).

Single-agent rituximab is safe but slow acting. It may be used for the management of some IgM-related disorders but a transient increase in serum IgM ('flare') is common (~50%).

Single-agent bortezomib can rapidly reduce IgM levels, but bortezomib added to DRC does not seem to offer significant benefit.

B-R in newly diagnosed WM achieves rapid responses

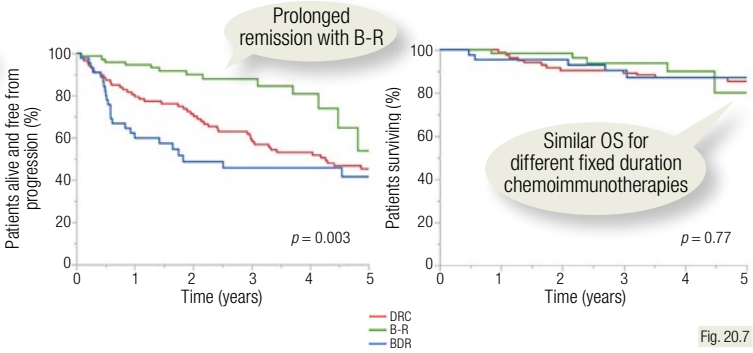
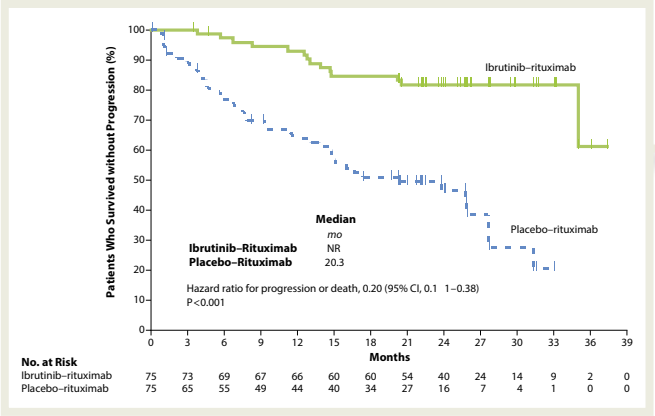


Fig. 20.7

B-R, bendamustine-rituximab; BDR, bortezomib, dexamethasone and rituximab; DRC, dexamethasone, rituximab and cyclophosphamide; OS, overall survival; WM, Waldenström macroglobulinaemia.

PFS of ibrutinib-rituximab vs placebo-extended dose rituximab in patients with WM



CI, confidence interval; NR, not reached; PFS, progression-free survival; WM, Waldenström macroglobulinaemia.

Fig. 20.8

MYD88 (L265P) somatic mutation causes constitutive stimulation of nuclear factor-kappa B (NF-κB) through BTK.

BTK inhibitors (ibrutinib, acalabrutinib and zanubrutinib) are the most active single agents in WM (overall response rate [ORR]: ~80%-95%) but continuous therapy is required.

Atrial fibrillation, haemorrhage, hypertension, diarrhoea and infections are the most common adverse events (AEs) associated with BTK inhibitors in WM.

Any of the drugs active in WM can be used at relapse, depending on prior exposure and duration of remission, comorbidities and clinical presentation.

The BCL2 inhibitor venetoclax has shown activity in relapsed/refractory WM (RRWM), including in patients refractory to ibrutinib.

High-dose therapy with autologous stem-cell transplantation has a very limited role in the era of targeted therapies.

Activity of venetoclax in RRWM

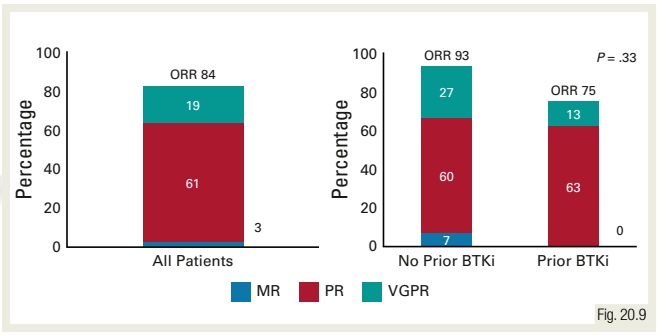


Fig. 20.9

BTKi, Bruton tyrosine kinase inhibitor; MR, minor response; ORR, overall response rate; PR, partial response; RRWM, relapsed/refractory Waldenström macroglobulinaemia; VGPR, very good partial response.

REVISION QUESTIONS

1. What are the primary options for first-line therapy in WM?
2. What are the treatment options for patients who relapse after DRC or B-R?
3. What are the most common toxicities of BTK inhibitors in WM?

Summary: Waldenström macroglobulinaemia

- Histology: lymphoplasmacytic cells which express pan–B-cell surface markers and surface IgM
- A somatic mutation in *MYD88* (L265P) is found in >90% of cases
- Cytopenias (more often anaemia) are the most common presenting features
- Prognostic scores include ISSWM and revised ISSWM
- The median OS for patients with symptomatic WM is >10 years
- Asymptomatic patients should be observed without treatment
- HVS is managed with plasmapheresis
- First-line chemoimmunotherapy offers prolonged remission (3-6 years)
- BTK inhibitors are the most active single agents in WM but require continuous therapy
- The BCL2 inhibitor venetoclax has shown activity in RRWM, including patients refractory to ibrutinib

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21 Burkitt Lymphoma

Morphology, biology and epidemiology

Burkitt lymphoma (BL) is a mature aggressive B-cell neoplasm, with a doubling time of 24-48 hours and histologically a characteristic 'starry sky' morphology with a high proliferation index (Ki-67: 100%).

The proliferation is composed of monomorphic, medium-sized cells with basophilic cytoplasm and multiple small nucleoli.

The proliferation has a germinal-centre phenotype in immunohistochemistry with CD10, B-cell lymphoma 6 (BCL6), immunoglobulin M (IgM) and MYC nuclear expression (80%+), whereas BCL2 and cyclin D1 are usually negative.

Morphology in Burkitt lymphoma (starry sky and Ki-67 strongly positive)

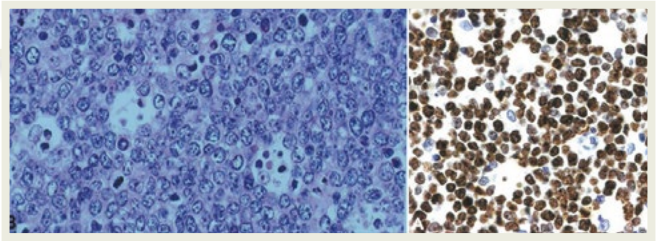


Fig. 21.1

Characteristics of the three clinical subtypes

Stage	Endemic	Sporadic	HIV-associated
Areas	Holoendemic malaria in Africa and Papua New Guinea	Europe, America, East Asia	–
Incidence	5 per 10^5 subjects/year	2–3 per 10^6 subjects/year	25%-35% of HIV-associated NHL, CD4+ >0.2 x 10^9/L
Age	**Children** → adults	Children → adults	Adults
Localisation	Extranodal **Jaw** → abdomen	Extranodal **Ileum, caecum, intra-abdominal LN** → head and neck	Frequently extranodal (gut, BM)
BM infiltration/ leukaemic presentation	Rare	30%	30%
CNS involvement	30%-40% (15% sudden paraplegia)	20%	20%-30%
EBV/malaria	**> 90%/frequent**	**20%/absent**	**20%-40%/absent**
cMYC	Identical in all types: 80% t(8;14), 15% t(2;8), 5% t(8;22)		

Fig. 21.2

BM, bone marrow; CNS, central nervous system; EBV, Epstein–Barr virus; HIV, human immunodeficiency virus; LN, lymph node; NHL, non-Hodgkin lymphoma.

Three clinical subtypes of BL are described based on epidemiology and geography: the most frequent is 'endemic', followed by 'sporadic' and 'immunodeficiency-associated' (mainly human immunodeficiency virus [HIV]-related).

Each subtype is associated with a distinct age, epidemiology, biology and clinical presentation, although a high tumour burden is a common feature.

Recent data suggest that Epstein–Barr virus (EBV)-positive BL and EBV-negative BL form distinct groups with particular molecular features superseding the epidemiological subtyping.

The hallmark of BL is a translocation, juxtaposing the *MYC* oncogene (on 8q24), next to one of the three Ig loci: IgH (heavy; t[8;14]), IgK (kappa; t[2;8]) or IgL (lambda; t[8;22]), leading to constitutive MYC overexpression.

In EBV-negative BL, recurrent mutations in genes controlling cell proliferation, growth and survival have been identified, such as *TCF3* and *ID3* mutations, *CCND3* or *TP53*.

EBV-positive BLs have particular molecular features, with an increased number of non-coding activation-induced deaminase (AID)-driven mutations and fewer driver events compared with EBV-negative cases, especially within apoptosis-related genes.

The main signalling pathways in BL

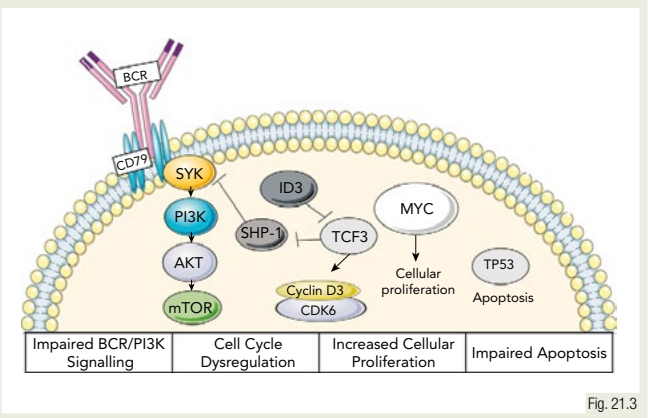


Fig. 21.3

BCR, B-cell receptor; BL, Burkitt lymphoma; CDK6, cyclin-dependent kinase 6; mTOR, mammalian target of rapamycin; PI3K, phosphoinositide 3-kinase.

REVISION QUESTIONS

1. What are the three clinical subtypes of BL?
2. What is the genomic hallmark of BL?
3. Which infectious diseases are associated with BL?

Staging, prognosis and initial treatment approach

The prognosis of BL patients differs. Low-risk patients have a 2-year overall survival (OS) rate of 80%-100%. High-risk patients have a 2-year OS rate of ~70%-75%.

Different risk classifications have been used. In most prospective studies, low-risk patients meet all of the following criteria: World Health Organization (WHO) performance status (PS) ≤1, Ann Arbor stage I/II(E), normal lactate dehydrogenase (LDH), tumour mass <7 cm.

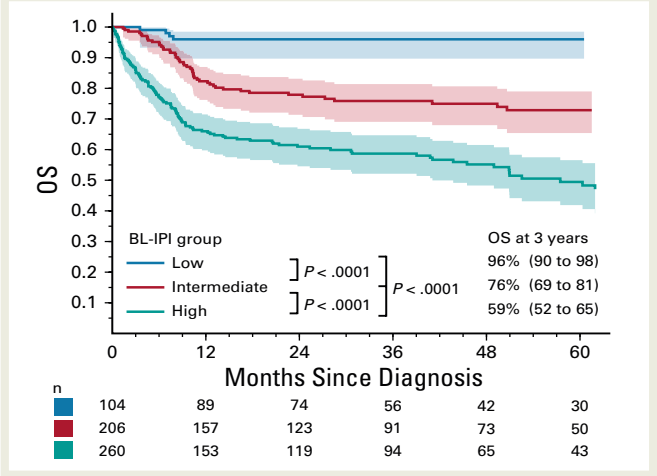
All other patients (including those with central nervous system [CNS] and bone marrow [BM] involvement) should be considered as high risk.

Risk classification factors used in different prospective studies

	Prospective studies					
	R-CODOX-M/R-IVAC (modified Magrath)			LMB	DA-EPOCH-R	
	Magrath JCO 1996	Mead Ann Oncol 2002	Mead Blood 2008	Divine Ann Oncol 2005	Dunleavy NEJM 2013	Roschewski JCO 2020
Low Risk	All: -Normal LDH -Resected abdominal mass	All: -Normal LDH -WHO PS 0 or 1 -AA stage I/II -No mass ≥10 cm	3 out of 4: -Normal LDH -WHO PS 0 or 1 -AA stage I/II -EN ≤1	Group A: Resected stage 1 and abdominal stage 2	-Resected stage I/II	All: -AA stage ≤2 -ECOG PS ≤1 -Normal LDH -Tumour <7 cm
Intermediate Risk	X	X	X	Group B: No CNS, no BM	All others	X
High Risk	All others	All others	All others	Group C: CNS and/or BM involvement	-CNS localisation or -BM involvement >25%	All others

AA, Ann Arbor; BM, bone marrow; CNS, central nervous system; DA, dose-adjusted; ECOG, Eastern Cooperative Oncology Group; EN, extranodal; EPOCH-R, etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin plus rituximab; LDH, lactate dehydrogenase; LMB, Lymphomes Malins B; PS, performance status; R-CODOX-M, rituximab, cyclophosphamide, doxorubicin, vincristine and methotrexate; R-IVAC, rituximab, ifosfamide, etoposide and cytarabine; WHO, World Health Organization. Fig. 21.4

Prognostic score by BL-IPI



BL, Burkitt lymphoma; IPI, International Prognostic Index; OS, overall survival. Fig. 21.5

For a more distinctive prognostic estimate of an individual patient, the recently developed BL International Prognostic Index (BL-IPI) score is recommended.

The BL-IPI score is based on retrospective data and consists of the following factors: age >40 years, PS ≥2, LDH >3× upper limit of normal (ULN), CNS localisation.

Classification by BL-IPI: Low risk: 0 factors. Intermediate risk: 1 factor. High risk: 2, 3 or 4 factors. This subdivision shows a 3-year progression-free survival (PFS) of 92%, 72%, 53% and OS of 96%, 76%, 59%, respectively.

Patients with BL often present with high tumour burden. Immediate treatment can induce tumour lysis syndrome (TLS), which is seen in <42% (laboratory TLS) and 6% (clinical TLS) of patients.

TLS prophylaxis with hydration, allopurinol or rasburicase is important. TLS laboratory values should be determined before therapy, and every 4-6 hours for the first 48-72 hours after therapy initiation.

Other supportive care such as infectious prophylaxis (antibacterial, antiviral, ± antifungal), growth factor support and transfusion are needed in almost all patients.

Tumour lysis syndrome definitions

Laboratory TLS: 2 or more present	
Uric acid	≥476 µmol/L (8 mg/dL) or 25% increase from baseline
Potassium	≥6.0 mmol/L (6 mEq/L) or 25% increase from baseline
Phosphorous	≥2.1 mmol/L (children) or ≥1.45 mmol/L (adults) or 25% increase from baseline
Calcium	≤1.75 mmol/L or 25% decrease from baseline
Clinical TLS: laboratory TLS + 1 of the following	
(1) Creatinine ≥1.5 ULN (age adjusted)	
(2) Cardiac arrhythmia/sudden death	
(3) Seizure	

Fig. 21.6

Cairo-Bishop definition of laboratory TLS and clinical TLS
TLS, tumour lysis syndrome; ULN, upper limit of normal.

REVISION QUESTIONS

1. Is the prognosis equal for all BL patients?
2. Which prognostic factors are part of the BL-IPI?
3. Which supportive measures have to be applied at the time of therapy initiation?

Treatment of patients with BL

For low- and high-risk BL, different treatment approaches exist. Choose between R-CODOX-M (rituximab, cyclophosphamide, doxorubicin, vincristine and methotrexate)/R-IVAC (rituximab, ifosfamide, etoposide and cytarabine), dose-adjusted (DA)-EPOCH-R (etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin plus rituximab), or Lymphomes Malins B (LMB). DA-EPOCH-R is not recommended in patients with CNS involvement.

The addition of rituximab has improved the outcome for BL patients.

All patients should receive CNS prophylaxis according to their risk stratification.

First-line strategies in Burkitt lymphoma

Modified Magrath *(Mead, Blood 2008)*	Low risk	R-CODOX-M × 3
	High risk	R-CODOX-M & R-IVAC × 2
LMB *(Ribrag, Lancet 2016)*	Group A/B (BM and CNS-)	COP R-COPADM 1 and 2 (R D1, D6) CYM 1 and 2 M1
	Group C	COP R-COPADM 1 and 2 (R D1, D6) CYVE 1 and 2 M1* (cranial radiation if CNS) M2-M3-M4
DA-EPOCH-R *(Roschewski, J Clin Oncol 2020)*	Low risk	DA-EPOCH-RR × 2 PET-CT -ve: DA-EPOCH-R × 1 PET-CT +ve: DA-EPOCH-R + IT MTX × 6
	High risk	DA-EPOCH-R + IT MTX × 6

Fig. 21.7

For the definitions of the risk groups see Fig. 21.4.

BM, bone marrow; CNS, central nervous system; COP, low-dose vincristine and cyclophosphamide; CT, computed tomography; CYM, cytarabine and methotrexate; CYVE, cytarabine and etoposide; DA-EPOCH-R, dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin plus rituximab; DA-EPOCH-RR, DA-EPOCH-R rituximab on days 1 and 5; IT MTX, intrathecal methotrexate; LMB, Lymphomes Malins B; M, maintenance; PET, positron emission tomography; R-CODOX-M, rituximab, cyclophosphamide, doxorubicin, vincristine and methotrexate; R-COPADM, rituximab, cyclophosphamide, vincristine, prednisone, doxorubicin and high-dose methotrexate; R-IVAC, rituximab, ifosfamide, etoposide and cytarabine; RT, radiotherapy.

OS of HIV-positive and HIV-negative BL patients

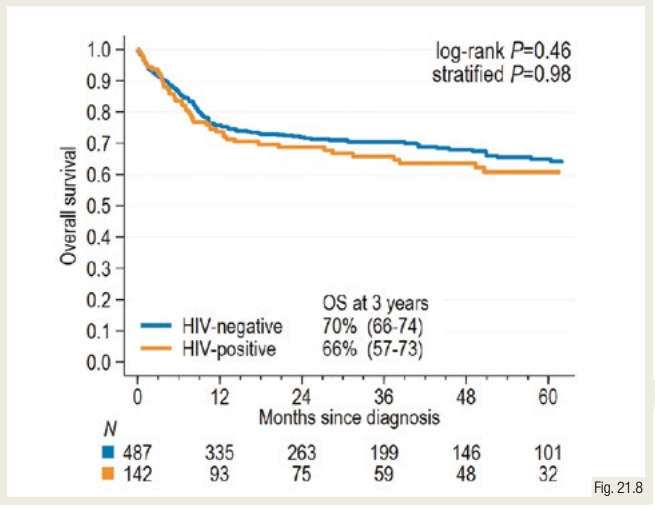


Fig. 21.8

BL, Burkitt lymphoma; HIV, human immunodeficiency virus; OS, overall survival.

Patients with HIV have a 10%-20% lifetime risk of developing BL independent of treatment with antiretroviral therapy (ART). HIV-associated BL often presents with nodal involvement and B symptoms.

ART should be individualised but can be administered concurrently with lymphoma treatment in most patients.

Outcomes in HIV-positive and HIV-negative BL patients are similar. Prognostic factors for HIV-positive BL patient outcomes are associated with BL characteristics, rather than HIV-related features.

Outcome in patients with a relapsed/refractory (R/R) BL is extremely poor, with median OS post-relapse of ~6 months, and estimated 5-year OS of ~30% in children.

Autologous or allogeneic stem-cell transplantation may be an option if a complete response can be reached after salvage therapy, leading to a median OS of 5 years.

Since 2017, chimeric antigen receptor (CAR)-T cell therapies have been investigated in clinical trials and may offer another therapeutic option in this unmet medical need.

Post-relapse OS in children treated with the LMB protocols

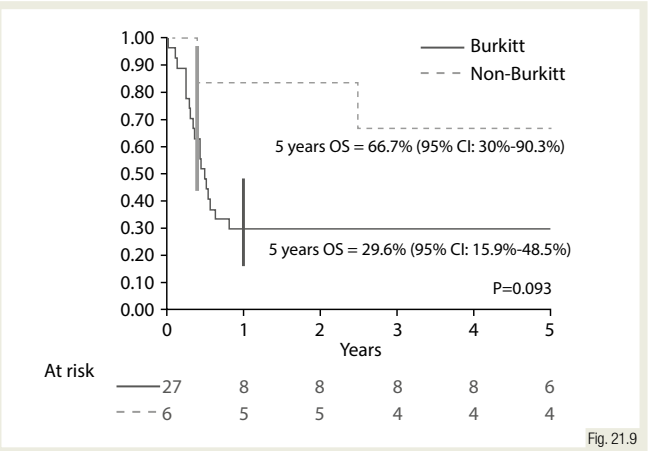


Fig. 21.9

CI, confidence interval; LMB, Lymphomes Malins B; OS, overall survival.

REVISION QUESTIONS

1. What is the most life-threatening complication at time of treatment initiation in BL?
2. Is the outcome of HIV-positive BL patients different from the outcome of HIV-negative patients?
3. What is the median OS for patients with R/R BL?

Summary: Burkitt Lymphoma

- BL is a mature aggressive B-cell neoplasm, with a doubling time of 24-48 hours and histologically a characteristic 'starry sky' morphology
- Three clinical subtypes of BL are described based on epidemiological context and geographical region: 'endemic', 'sporadic' and 'immunodeficiency-associated'
- EBV positivity is found in >90% of endemic cases versus 20% of sporadic cases
- The hallmark of BL is a translocation, involving the *MYC* oncogene on chromosome 8q24
- Prognosis of BL patients differs. Low-risk patients have a 2-year OS rate of 80%-100%. High-risk patients have a 2-year OS rate of ~70%-75%
- Low-risk patients meet all of the following criteria: WHO PS ≤1, Ann Arbor stage I/II(E), normal LDH, tumour mass <7 cm
- For a distinctive prognostic estimate of an individual patient, the BL-IPI score is recommended
- Different treatment approaches exist. Choose between R-CODOX-M/R-IVAC, DA-EPOCH-R or LMB according to risk classification and the presence of CNS disease
- Outcome of HIV-positive BL patients is not different when compared with HIV-negative BL patients. Individualised ART can be given concurrently with lymphoma treatment in most patients
- Outcome of patients with R/R BL is extremely poor, with a median OS post-relapse of ~6 months, warranting new treatment options

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22 Primary central nervous system lymphoma

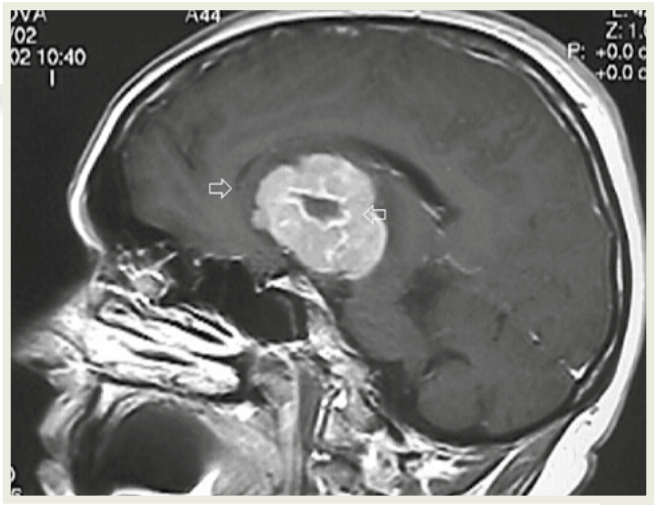
Definition and presentation

In the 5th edition of the World Health Organization Classification of Haematolymphoid Tumours (WHO-HAEM5), primary central nervous system lymphoma (PCNSL) is classified in the 'Large B-cell lymphomas of immune-privileged sites' group, whereas it is considered a specific entity in the 2022 International Consensus Classification of Mature Lymphoid Neoplasms (ICC).

It is an aggressive neoplasm; the disease is limited to the central nervous system (CNS) both at presentation and relapse, with rare cases of systemic dissemination.

PCNSL accounts for 2% of all primary CNS tumours and 4%-6% of extranodal lymphomas, with an incidence of 0.43/100 000 persons/year.

A case of PCNSL



PCNSL, primary central nervous system lymphoma. Fig. 22.1

Incidence of PCNSL according to year of diagnosis and age

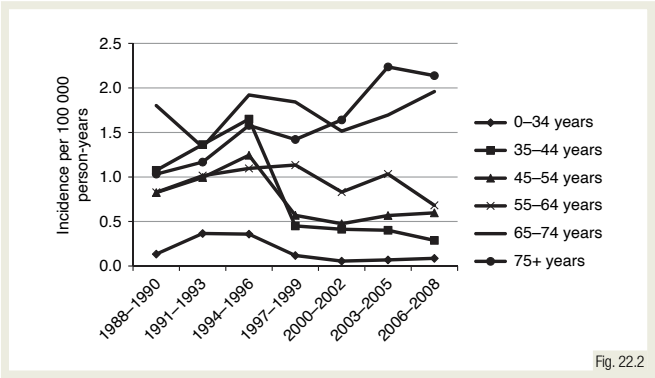


Fig. 22.2

PCNSL, primary central nervous system lymphoma.

PCNSL is most commonly diagnosed in the 6th or 7th decade of life (median age: 68 years); its incidence is increasing, mostly in subjects >60 years old.

Patients usually present with neurological or neuropsychiatric symptoms; the range corresponds to the location and extent of the tumour.

Systemic symptoms (fever, night sweats and weight loss) are exceptionally rare.

The brain is the most common localisation; frontal lobe and periventricular areas are more frequently involved. Nearly half of patients have multifocal disease.

The eye (vitreous and retina) is involved in 15%-20% of patients; blurred vision or floaters occur in half of them, while the residual ones are asymptomatic.

Leptomeningeal involvement, often asymptomatic, is detected by conventional cerebrospinal fluid (CSF) cytological examination in 16% of patients; isolated leptomeningeal lymphoma is exceptional.

Tumour infiltration of the vitreous fluid (arrows)

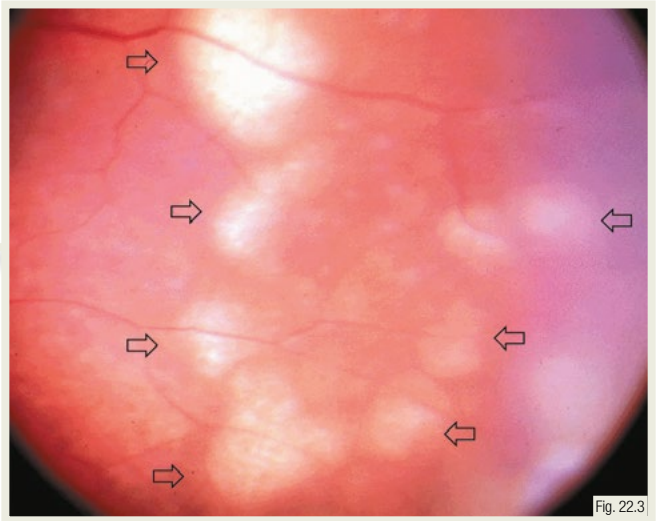


Fig. 22.3

REVISION QUESTIONS

1. Which are the entity-defining characteristics of PCNSL?
2. Which are the most likely CNS-involved anatomical sites in patients with personality changes or ataxia?
3. Which are the most commonly involved sites in PCNSL?

Diagnosis and staging

The preferred neuroimaging diagnostic method is contrast-enhanced magnetic resonance imaging (MRI), including diffusion- and perfusion-weighted scans, with volumetric protocols according to International PCNSL Collaborative Group (IPCG) guidelines.

PCNSL shows strongly, homogeneously enhancing lesions with diffusion characteristics reflecting hypercellularity. Haemorrhages and necrosis are classically absent.

Perilesional oedema is less extensive than in malignant gliomas. Proton magnetic resonance (MR) spectroscopy findings may suggest a PCNSL diagnosis.

Multifocal PCNSL on MRI (arrows)

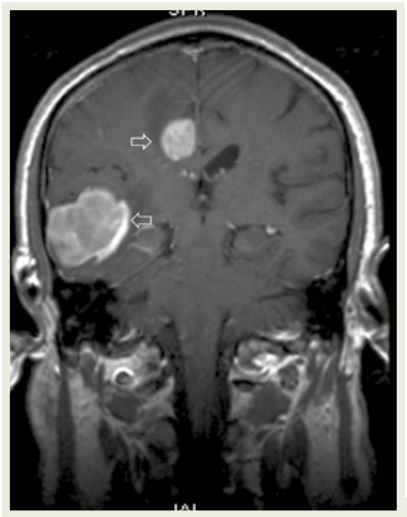


Fig. 22.4

MRI, magnetic resonance imaging; PCNSL, primary central nervous system lymphoma.

PCNSL at the microscope

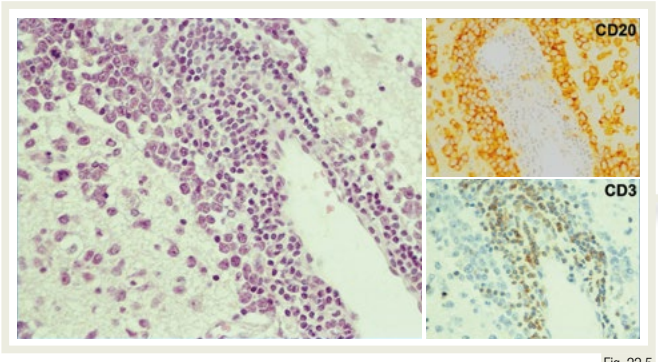


Fig. 22.5

PCNSL, primary central nervous system lymphoma.

The gold-standard diagnostic method relies on the histopathological examination of specimens obtained by stereotactic biopsy.

At the microscope, a diffuse, dense arrangement of large neoplastic B-lymphocytes resembling centroblasts is observed; perivascular cuffing of lymphomatous cells is common.

Most PCNSLs express B-cell markers and display a non-germinal centre (GC) phenotype. Perivascular infiltration of small reactive T-lymphocytes is observed in one third of cases in addition to the usual interstitial one.

Staging work-up is mandatory and aims to determine both the spread within the CNS areas and the occurrence of systemic disease.

CNS structures are evaluated with neurological examination, MRI of the brain, CSF analysis and ophthalmological investigation.

Extra-CNS dissemination is evaluated by ^{18}F-fluorodeoxyglucose (^{18}FDG)–positron emission tomography (PET)–computed tomography (CT) and symptom-driven specific exams. PCNSL patients should be stratified according to prognostic scores.

IELSG prognostic score and variables

Using the variables reported (left), three risk groups can be distinguished (right)

Variable	0	1
Age	≤60 ys	>60 ys
ECOG-PS	0-1	2-4
LDH	Normal	Elevated
CSF protein	Normal	Elevated
Deep lesions	No	Yes

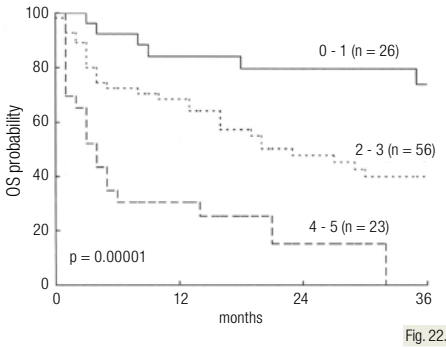


Fig. 22.6

CSF, cerebrospinal fluid; ECOG, Eastern Cooperative Oncology Group; IELSG, International Extranodal Lymphoma Study Group; LDH, lactate dehydrogenase; OS, overall survival; PS, performance status.

REVISION QUESTIONS

1. Which is the main differential diagnosis of PCNSL on MRI?
2. Which is the most common cell-of-origin phenotype in PCNSL?
3. What is the expected 3-year overall survival (OS) of patients with low-risk disease according to the International Extranodal Lymphoma Study Group (IELSG) score?

Treatment and prognosis

Patients should be enrolled in prospective trials, if available. Routine treatment consists of induction and consolidation phases. Age should not be used as a single parameter to select treatment intensity.

High-dose methotrexate (HD-MTX) combined with an alkylating agent, rituximab ± high-dose cytarabine (HD-AraC) is the standard induction treatment. Combinations tested in randomised trials are suggested.

Intrathecal and intravitreal chemotherapies (ChTs) are not used in routine practice, except for patients with persistence of disease at the end of first-line treatment.

OS according to induction polychemotherapy

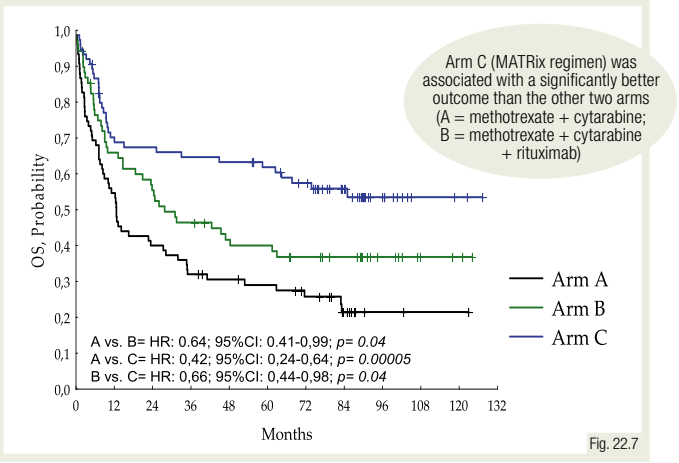


Fig. 22.7

CI, confidence interval; HR, hazard ratio; MATRix, methotrexate, cytarabine, thiotepa and rituximab; OS, overall survival.

OS of patients treated with MATRix followed by ASCT or WBRT

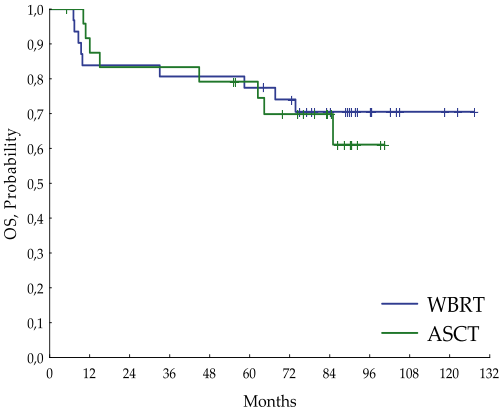


Fig. 22.8

ASCT, autologous stem-cell transplantation; MATRix, methotrexate, cytarabine, thiotepa and rituximab; OS, overall survival; WBRT, whole-brain radiotherapy.

Autologous stem-cell transplantation (ASCT) is recommended as consolidation in fit patients with responsive/stable disease after induction. Thiotepa-based conditioning regimens should be used.

Consolidation whole-brain radiotherapy (WBRT) is recommended in young patients who are not suitable candidates for ASCT. Its use in older patients is limited by risk of neurotoxicity.

Patients treated with HD-MTX-based ChT and consolidative ASCT/WBRT exhibit a 7-year OS rate of 70%.

Despite these achievements, 16%-26% of patients ≤70 years old are chemorefractory and 25% experience relapse after response. These rates are higher among older patients.

Patients with relapsed/refractory (R/R) PCNSL should be enrolled in a prospective trial, if available. In routine practice, HD-AraC- or HD-ifosfamide (HD-IFO)-based therapy followed by ASCT is an option for fit patients.

After relapse, HD-MTX rechallenge can result in a second durable remission. Patients with contraindications to ChT can be treated with salvage WBRT. Patients with extra-CNS relapses receive R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone).

Survival after relapse according to salvage therapy

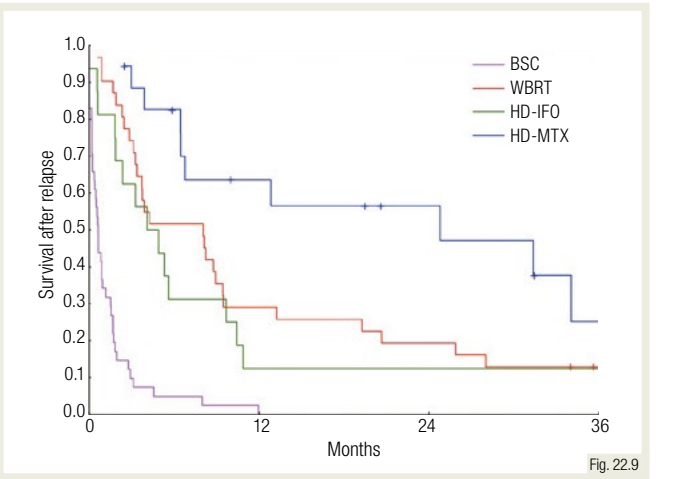


Fig. 22.9

BSC, best supportive care; HD-IFO, high-dose ifosfamide; HD-MTX, high-dose methotrexate; WBRT, whole-brain radiotherapy.

REVISION QUESTIONS

1. How do you treat a young and fit patient with newly diagnosed PCNSL?
2. What 5-year OS rate would you expect in cases responding to induction chemoimmunotherapy?
3. How do you treat a patient with PCNSL relapsed after 4 years from four courses of MATRix (methotrexate, cytarabine, thiotepa and rituximab) and ASCT?

Summary: Primary central nervous system lymphoma

- PCNSL is an aggressive malignancy limited to the CNS, with rare cases of systemic relapse
- It is typically diagnosed in the 6th or 7th decade of life, usually presenting with a range of neurological or neuropsychiatric symptoms
- Contrast-enhanced MRI including diffusion- and perfusion-weighted scans with volumetric protocols is the preferred procedure to assess areas of brain involvement
- Histopathological examination of specimens obtained by stereotactic biopsy is the gold-standard diagnostic method
- Staging work-up is mandatory to determine both the compartments involved within the CNS and to rule out the presence of concomitant systemic disease
- All patients should be offered enrolment in a prospective trial, if available. Routine treatment consists of induction and consolidation phases
- HD-MTX combined with an alkylating agent, rituximab ± HD-AraC is the standard induction treatment
- ASCT is recommended as consolidation in fit patients with responsive/stable disease after induction; consolidation WBRT is recommended in patients unsuitable for ASCT
- Patients treated with HD-MTX-based ChT and consolidative ASCT/WBRT exhibit a 7-year OS of 70%
- Despite therapeutic progress, half of patients experience relapse. Patients with R/R PCNSL should be enrolled in a prospective trial, if available

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23 Lymphomas in the immunocompromised patient

Lymphomas in people living with HIV

In the era of highly active antiretroviral therapy (HAART), one third of people living with human immunodeficiency virus (HIV; PLHIV) will die of cancer, with non-Hodgkin lymphoma (NHL) being the most common.

The incidence of lymphoma is significantly increased in PLHIV compared with the general population: NHL ~100× and classical Hodgkin lymphoma (cHL) ~10-20× (pre-HAART era).

The incidence of acquired immunodeficiency syndrome (AIDS)-related NHL is associated with low CD4 count and has significantly decreased since the introduction of HAART (NHL ~18-48×).

NHL incidence and HAART use in HIV-infected patients

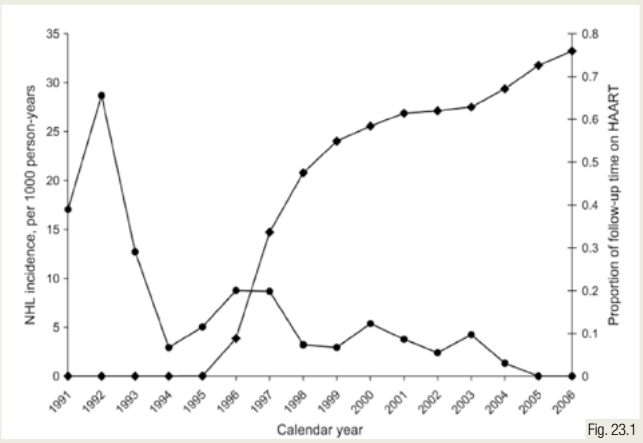


Fig. 23.1

HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; NHL, non-Hodgkin lymphoma.

WHO-HAEM5 classification

Lymphoid proliferations and lymphomas associated with immune deficiency and dysregulation
Hyperplasias arising in immune deficiency/dysregulation
Polymorphic lymphoproliferative disorders arising in immune deficiency/dysregulation
EBV-positive mucocutaneous ulcer
Lymphomas arising in immune deficiency/dysregulation (includes lymphomas associated with HIV infection)
Inborn error of immunity-associated lymphoid proliferations and lymphomas

Fig. 23.2

EBV, Epstein–Barr virus; HIV, human immunodeficiency virus; WHO-HAEM5, World Health Organization Classification of Haematolymphoid Tumours, 5th edition.

NHL is an AIDS-defining malignancy that includes several entities, as newly defined in the 5th edition of the World Health Organization Classification of Haematolymphoid Tumours (WHO-HAEM5).

Diffuse large B-cell lymphoma (DLBCL) and Burkitt lymphoma (BL) are the most frequent subtypes. The incidence of primary central nervous system lymphoma (PCNSL) has significantly decreased in the HAART era.

Immunosuppression, chronic antigen stimulation, cytokine dysregulation and coinfection with oncogenic viruses (human herpes virus 8 [HHV8] and Epstein–Barr virus [EBV]) contribute to lymphomagenesis.

NHL and cHL in PLHIV present with aggressive clinical features including poor performance status (PS), extranodal disease and high-risk International Prognostic Index/International Prognostic Score (IPI/IPS) scores.

Following the introduction of HAART, the outcome of PLHIV with NHL/Hodgkin lymphoma (HL) has significantly improved and is similar to the outcome in HIV-negative patients.

PLHIV and lymphoma should be managed in combination with the HIV team and receive HAART and prophylactic antibiotics during chemotherapy (ChT).

Kaplan–Meier plots on overall survival with respect to HAART use

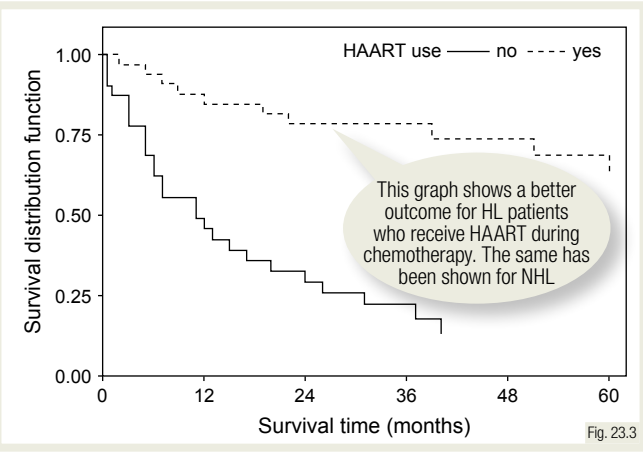


Fig. 23.3

HAART, highly active antiretroviral therapy; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma.

REVISION QUESTIONS

1. What specific features of PLHIV are associated with a higher incidence of lymphoma?
2. What are the most common subtypes of NHL in PLHIV?
3. How has the introduction of HAART impacted on the incidence and outcome of lymphoma in PLHIV?

Lymphomas in PLHIV (continued)

The IPI remains an important prognostic factor for PLHIV with DLBCL; the CD4 count is not associated with outcome in the contemporary era.

Standard first-line therapy for DLBCL is R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone), as in HIV-negative patients. Other protocols used are infusional regimens such as dose-adjusted (DA) EPOCH-R (etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin plus rituximab).

As in HIV-negative patients, the standard therapy for DLBCL at relapse or not in complete response (CR) after first-line is salvage ChT followed by autologous stem-cell transplantation (ASCT).

OS for HIV-infected and non-infected patients

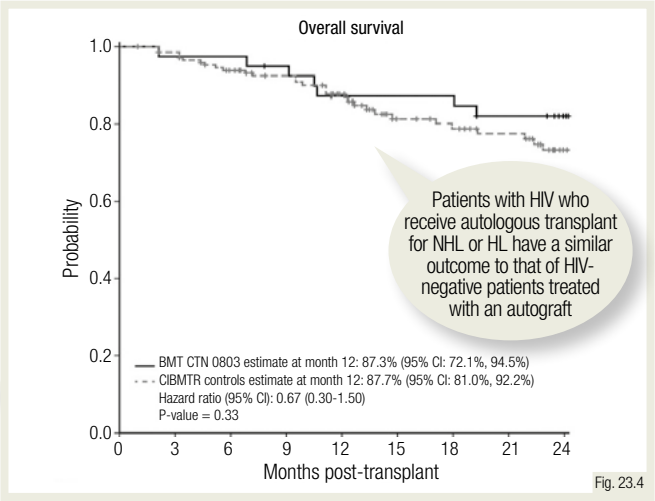


Fig. 23.4

BMT CTN, Blood and Marrow Transplant Clinical Trials Network; CI, confidence interval; CIBMTR, Center for International Blood and Marrow Transplant Research; HIV, human immunodeficiency virus; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma; OS, overall survival.

Outcomes of patients with BL treated with intensive chemotherapy according to HIV status

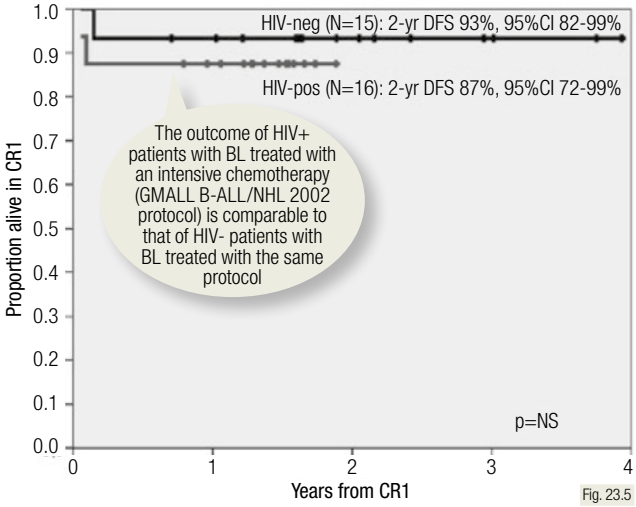


Fig. 23.5

B-ALL, B-cell acute lymphoblastic leukaemia; BL, Burkitt lymphoma; CI, confidence interval; CR1, complete response 1; DFS, disease-free survival; GMALL, German Multicenter Study Group for Adult Acute Lymphoblastic Leukemia; HIV, human immunodeficiency virus; neg, negative; NHL, non-Hodgkin lymphoma; NS, not specified; pos, positive.

The prognosis of PLHIV and BL depends on lymphoma characteristics (PS, central nervous system [CNS] infiltration, lactate dehydrogenase [LDH] level, extranodal sites) rather than on HIV-related features.

Front-line intensive ChT in PLHIV with BL has comparable outcomes to those in the general population.

The addition of rituximab to CODOX-M/IVAC (cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate/ifosfamide, etoposide and high-dose cytarabine) does not increase toxicity and results in a 2 year-overall survival (OS) of ~75%.

Moderate (rather than severe) immunosuppression is associated with HL; hence, the incidence of HL may be increasing in the HAART era.

HL presents in PLHIV with B symptoms, advanced stage, extranodal disease and high-risk IPS more frequently than in HIV-negative patients.

The outcome of PLHIV and HL treated with doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) ChT is similar to that of the general population.

OS according to HIV status in patients with HL treated with ABVD chemotherapy

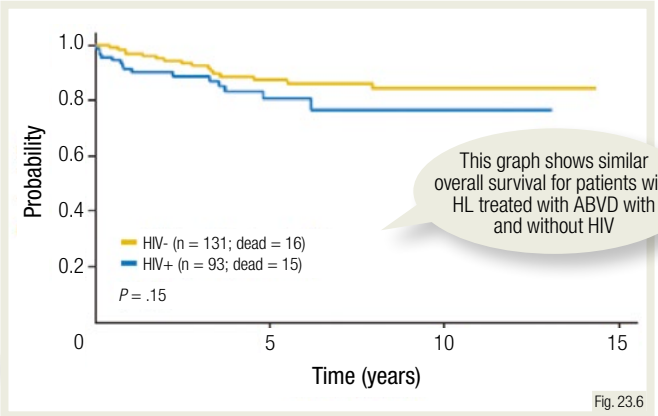


Fig. 23.6

ABVD, doxorubicin, bleomycin, vinblastine and dacarbazine; HIV, human immunodeficiency virus; HL; Hodgkin lymphoma, OS, overall survival.

REVISION QUESTIONS

1. What is the standard treatment for patients with HIV and relapsed lymphoma?
2. Should patients with BL and HIV infection be treated with DLBCL regimens or with intensive ChT?
3. How does the outcome of HL treated with ABVD in PLHIV compare with the outcome of HL in the general population?

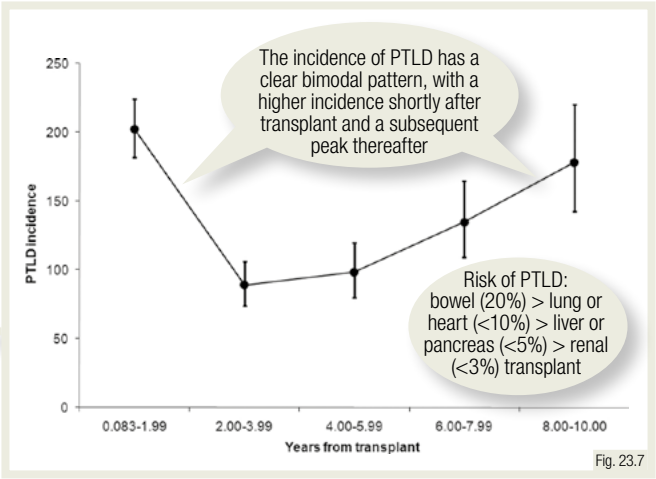
Post-transplant lymphoproliferative disorders

Post-transplant lymphoproliferative disorders (PTLDs) are lymphomas arising in patients who are immunosuppressed following a solid organ transplant (SOT) or a bone marrow transplant (BMT).

They are heterogeneous with varied morphology, phenotype and EBV status. The most important risk factors for PTLD are EBV seronegativity and intense immunosuppression.

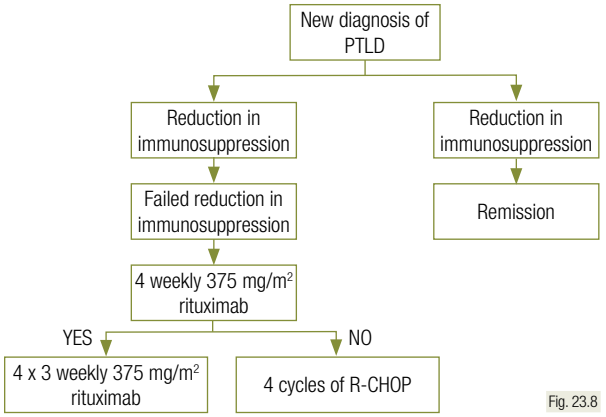
Early PTLD (<12 months) is often EBV-driven while late-onset PTLD is usually EBV-negative. The risk of PTLD is higher in children, related to EBV primary infection.

Incidence of PTLD among kidney recipients,1999–2007



PTLD, post-transplant lymphoproliferative disorder.

Pathway for front-line treatment of systemic monomorphic B-cell PTLD



PTLD, post-transplant lymphoproliferative disorder; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone.

Reduction of immunosuppression (RI) is the first step in the management of PTLD, with a higher response rate seen in early lesions compared with monomorphic PTLD.

Low-risk patients not responding to RI can be treated with rituximab monotherapy with excellent results, as it kills the EBV-infected B cells, thus eliminating EBV.

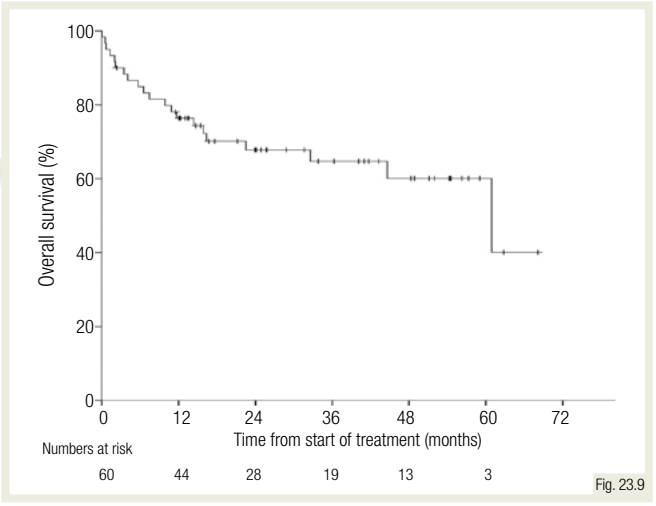
The PTLD-1 and PTLD-2 trials have both outlined a risk-stratified, sequential approach to chemoimmunotherapy.

In the PTLD-2 trial, 2-year time to progression and OS were 78% and 68%, respectively. Two-year OS in the low-risk group was 100%.

In addition to clinical characteristics (PS, extranodal disease), other poor prognostic factors include EBV negativity, graft involvement and monomorphic subtype.

Very high-risk patients with thoracic SOT and progressive disease after rituximab induction have a poor prognosis despite chemoimmunotherapy consolidation with median OS estimates of <1 year.

OS in the intention-to-treat population of the PTLD-2 trial (median time of follow-up 2.8 years)



OS, overall survival; PTLD, post-transplant lymphoproliferative disorder.

REVISION QUESTIONS

1. What are the most important risk factors for PTLD?
2. Cite some of the poor prognostic factors in PTLD.
3. What is the first step in the management of PTLD?

Summary: Lymphomas in the immunocompromised patient

- Incidence of NHL and HL is increased in PLHIV
- The introduction of HAART has decreased the incidence of some types of NHL
- DLBCL and BL are the most common types of NHL in PLHIV
- Patients with HIV and DLBCL or HL have more aggressive disease with poor risk features in comparison with non-HIV patients with DLBCL or BL
- The outcome of patients with HIV and lymphoma has significantly improved in the HAART era
- The outcome of HIV patients with lymphoma is similar to that of HIV-negative patients treated with the same ChT schedules
- Management of relapsed lymphoma in HIV patients includes ASCT, as in the general population
- PTLD is diagnosed more frequently following SOT than following BMT
- Prognosis of patients with PTLD depends on the presence of clinically aggressive characteristics
- Treatment of PTLD includes RI and rituximab (with or without ChT)

Further Reading

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Image sources: **Fig. 23.1.** Engels EA, et al. J Acquir Immune Defic Syndr 2010;54:78-84; **23.2.** courtesy of the authors; **23.3.** Hentrich M, et al. Ann Oncol 2006;17:914-919; **23.4.** Alvarnas JC, et al. Blood 2016;128:1050-1058; **23.5.** Oriol A, et al. Cancer 2008;113:117-125; **23.6.** Montoto S, et al. J Clin Oncol 2012;30:4111-4116; **23.7.** Quinlan SC, et al. Am J Hematol 2011;86:206-209; **23.8.** adapted from Shah N, et al. Br J Haematol 2021;193:727-740; **23.9.** Zimmermann H, et al. Leukemia 2022;36:2468-2478.

Appendix 1: Comparison of the ICC and the WHO-HAEM5 lymphoma classifications

INTERNATIONAL CONSENSUS CLASSIFICATION#	WHO CLASSIFICATION, 5th EDITION
MATURE B-CELL LYMPHOMAS	
SMALL B-CELL LYMPHOMAS	
Chronic lymphocytic leukaemia/small lymphocytic lymphoma	Chronic lymphocytic leukaemia/small lymphocytic lymphoma
Monoclonal B-cell lymphocytosis	Monoclonal B-cell lymphocytosis
B-cell prolymphocytic leukaemia	**Entity deleted**
Splenic marginal zone lymphoma	Splenic marginal zone lymphoma
Hairy cell leukaemia	Hairy cell leukaemia
Splenic B-cell lymphoma/leukaemia, unclassifiable - *Splenic diffuse red pulp small B-cell lymphoma* - *Hairy cell leukaemia-variant*	Splenic diffuse red pulp small B-cell lymphoma **Splenic B-cell lymphoma/leukaemia with prominent nucleoli** (Encompasses hairy cell leukaemia-variant and some cases of B-cell prolymphocytic leukaemia)
Lymphoplasmacytic lymphoma - Waldenström macroglobulinaemia	Lymphoplasmacytic lymphoma - Waldenström macroglobulinaemia
Immunoglubulin M (IgM) monoclonal gammopathy of undetermined significance (MGUS) **- IgM MGUS, plasma cell type*** **- IgM MGUS, NOS***	IgM monoclonal gammopathy of undetermined significance (MGUS)
Primary cold agglutinin disease	**Cold agglutinin disease**
HEAVY CHAIN DISEASES	
Mu heavy chain disease	Mu heavy chain disease
Gamma heavy chain disease	Gamma heavy chain disease
Alpha heavy chain disease	Alpha heavy chain disease
PLASMA CELL NEOPLASMS	
Non-IgM MGUS	Non-IgM MGUS
	Monoclonal gammopathy of renal significance
Multiple myeloma (Plasma cell myeloma) **- Multiple myeloma (MM), NOS** **- MM with recurrent genetic abnormality*** **- MM with *CCND* family translocation** **- MM with *MAF* family translocation** **- MM with *NSD2* translocation** **- MM with hyperdiploidy**	Plasma cell myeloma
Solitary plasmacytoma of bone	Solitary plasmacytoma of bone
Extraosseous plasmacytoma	Extraosseous plasmacytoma
Monoclonal immunoglobulin (Ig) deposition diseases **- Ig light chain amyloidosis (AL)** **- Localised AL amyloidosis** - Light chain and heavy chain deposition disease	Monoclonal Ig deposition diseases **- Ig-related (AL) amyloidosis** **- Monoclonal Ig deposition disease**
NODAL AND EXTRANODAL B-CELL NEOPLASMS	
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)	Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
Primary cutaneous marginal zone lymphoproliferative disorder (LPD)	**Primary cutaneous marginal zone lymphoma**
Nodal marginal zone lymphoma - Paediatric nodal marginal zone lymphoma	Nodal marginal zone lymphoma - Paediatric nodal marginal zone lymphoma
Follicular lymphoma - Grade 1-2 and 3A - Grade 3B - *In situ* follicular neoplasia - Duodenal-type follicular lymphoma	Follicular lymphoma **- Classic follicular lymphoma** **- Follicular large B-cell lymphoma** - *In situ* follicular B-cell neoplasm - Duodenal-type follicular lymphoma - Testicular follicular lymphoma **- Follicular lymphoma with uncommon features** **- Follicular lymphoma with "blastoid" or "large centrocytes"** **- Diffuse follicular lymphoma**
BCL2-R-negative, CD23-positive follicle centre lymphoma* (RELATED BUT NOT EQUIVALENT to the diffuse variant of follicular lymphoma in the WHO classification)	
Primary cutaneous follicle centre lymphoma	Primary cutaneous follicle centre lymphoma
Paediatric-type follicular lymphoma	Paediatric-type follicular lymphoma
Testicular follicular lymphoma	
Large B-cell lymphoma with *IRF4* rearrangement **(LISTED WITH FOLLICULAR LYMPHOMA)**	
Mantle cell lymphoma - *In situ* mantle cell neoplasia	Mantle cell lymphoma - *In situ* mantle cell neoplasm
- Leukaemic non-nodal mantle cell lymphoma	- Leukaemic non-nodal mantle cell lymphoma

LARGE B-CELL LYMPHOMAS	
Diffuse large B-cell lymphoma (DLBCL), NOS - Germinal centre B-cell subtype - Activated B-cell subtype	Diffuse large B-cell lymphoma, NOS - Germinal centre B-cell subtype - Activated B-cell subtype
Large B-cell lymphoma with 11q aberration	**High-grade B-cell lymphoma with 11q aberrations**
Nodular lymphocyte-predominant B-cell lymphoma (no longer considered a Hodgkin subtype of lymphoma)	
T-cell/histiocyte-rich large B-cell lymphoma	T-cell/histiocyte-rich large B-cell lymphoma
	Large B-cell lymphoma with IRF4 rearrangement **(LISTED WITH LARGE B-CELL LYMPHOMAS)**
Primary DLBCL of the central nervous system	**Primary large B-cell lymphoma of immune-privileged sites (includes central nervous system, testis and vitreoretinal)**
Primary DLBCL of the testis	
Primary cutaneous DLBCL, leg type	Primary cutaneous DLBCL, leg type
Intravascular large B-cell lymphoma	Intravascular large B-cell lymphoma
HHV8 and EBV-negative primary effusion-based lymphoma	**Fluid overload-associated large B-cell lymphoma**
EBV-positive mucocutaneous ulcer	EBV-positive mucocutaneous ulcer
EBV-positive DLBCL, NOS	EBV-positive DLBCL
DLBCL associated with chronic inflammation - Fibrin-associated DLBCL	DLBCL associated with chronic inflammation
	Fibrin-associated large B-cell lymphoma
Lymphomatoid granulomatosis	Lymphomatoid granulomatosis
EBV-positive polymorphic B-cell LPD, NOS*	
ALK-positive large B-cell lymphoma	ALK-positive large B-cell lymphoma
Burkitt lymphoma	Burkitt lymphoma
High-grade B-cell lymphoma, with *MYC* and *BCL2* rearrangements	**Diffuse large B-cell lymphoma / high-grade B-cell lymphoma with *MYC* and *BCL2* rearrangements**
High-grade B-cell lymphoma with MYC and BCL6 rearrangements	**(Cases with *MYC* and *BCL6* rearrangements are classified either as a subtype of DLBCL, NOS or HGBL, NOS according to their cytomorphological features)**
High-grade B-cell lymphoma, NOS	High-grade B-cell lymphoma, NOS
Primary mediastinal large B-cell lymphoma	Primary mediastinal large B-cell lymphoma
Mediastinal grey-zone lymphoma	**Mediastinal grey-zone lymphoma**
Plasmablastic lymphoma	Plasmablastic lymphoma
HHV8-associated lymphoproliferative disorders - Multicentric Castleman disease - HHV8-positive germinotropic LPD - HHV8-positive DLBCL, NOS - Primary effusion lymphoma	KSHV/HHV8-associated B-cell lymphoid proliferations and lymphomas - KSHV/HHV8-associated multicentric Castleman disease - KSHV/HHV8-positive germinotropic LPD - KSHV/HHV8-positive DLBCL - Primary effusion lymphoma
MATURE T-CELL AND NK-CELL LYMPHOMAS	
MATURE T-CELL LEUKAEMIAS	
T-prolymphocytic leukaemia	T-prolymphocytic leukaemia
T-cell large granular lymphocytic leukaemia	T-large granular lymphocytic leukaemia
Chronic LPD of NK cells	**NK-large granular lymphocytic leukaemia**
Adult T-cell leukaemia/lymphoma	Adult T-cell leukaemia/lymphoma
Sézary syndrome	Sézary syndrome
EBV-POSITIVE NK/T-CELL NEOPLASMS	
Extranodal NK/T-cell lymphoma, nasal type	**Extranodal NK/T-cell lymphoma**
Aggressive NK-cell leukaemia	Aggressive NK-cell leukaemia
Primary nodal EBV-positive T/NK-cell lymphoma	**EBV-positive nodal T- and NK-cell lymphoma**
EBV-POSITIVE NK/T LPD OF CHILDHOOD	
Hydroa vacciniforme LPD Classic Systemic	**Hydroa vacciniforme LPD** Classic Systemic
Severe mosquito bite allergy	Severe mosquito bite allergy
Chronic active EBV disease, systemic (T- and NK-cell phenotype)	**Systemic chronic active EBV disease**
Systemic EBV-positive T-cell lymphoma of childhood	Systemic EBV-positive T-cell lymphoma of childhood

PRIMARY CUTANEOUS T-CELL LYMPHOMAS	
Primary cutaneous CD4-positive small or medium T-cell LPD	Primary cutaneous CD4-positive small or medium T-cell LPD
Primary cutaneous acral CD8-positive T-cell LPD	**Primary cutaneous acral CD8-positive LPD**
Mycosis fungoides	Mycosis fungoides
Primary cutaneous CD30-positive T-cell LPD - Lymphomatoid papulosis - Primary cutaneous anaplastic large cell lymphoma	Primary cutaneous CD30-positive T-cell LPD - Lymphomatoid papulosis - Primary cutaneous anaplastic large cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma	Subcutaneous panniculitis-like T-cell lymphoma
Primary cutaneous gamma/delta T-cell lymphoma	Primary cutaneous gamma/delta T-cell lymphoma
Primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma	Primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma
	Primary cutaneous peripheral T-cell lymphoma, NOS
INTESTINAL T-CELL AND NK-CELL LYMPHOID PROLIFERATIONS AND LYMPHOMAS	
Indolent clonal T-cell LPD of the gastrointestinal tract	**Indolent T-cell lymphoma of the gastrointestinal tract**
Indolent NK-cell LPD of the gastrointestinal tract	**Indolent NK-cell LPD of the gastrointestinal tract**
Type II refractory coeliac disease*	
Enteropathy-associated T-cell lymphoma	Enteropathy-associated T-cell lymphoma
Monomorphic epitheliotropic intestinal T-cell lymphoma	Monomorphic epitheliotropic intestinal T-cell lymphoma
Intestinal T-cell lymphoma, NOS	Intestinal T-cell lymphoma, NOS
Hepatosplenic T-cell lymphoma	Hepatosplenic T-cell lymphoma
Peripheral T-cell lymphoma, NOS	Peripheral T-cell lymphoma, NOS
Follicular helper T-cell lymphoma **- Follicular helper T-cell lymphoma, angioimmunoblastic type** **- Follicular helper T-cell lymphoma, follicular type** **- Follicular helper T-cell lymphoma, NOS**	**Nodal T-follicular helper (TFH) cell lymphoma** **- Nodal TFH cell lymphoma, angioimmunoblastic-type** **- Nodal TFH cell lymphoma, follicular-type** **- Nodal TFH cell lymphoma, NOS**
Anaplastic large cell lymphoma, ALK-positive	ALK-positive anaplastic large cell lymphoma
Anaplastic large cell lymphoma, ALK-negative	ALK-negative anaplastic large cell lymphoma
Breast implant-associated anaplastic large cell lymphoma	Breast implant-associated anaplastic large cell lymphoma

HODGKIN LYMPHOMA	
Nodular sclerosis classic Hodgkin lymphoma	Nodular sclerosis classic Hodgkin lymphoma
Lymphocyte-rich classic Hodgkin lymphoma	Lymphocyte-rich classic Hodgkin lymphoma
Mixed cellularity classic Hodgkin lymphoma	Mixed cellularity classic Hodgkin lymphoma
Lymphocyte-depleted classic Hodgkin lymphoma	Lymphocyte-depleted classic Hodgkin lymphoma
No longer a Hodgkin lymphoma subtype (named Nodular lymphocyte-predominant B-cell lymphoma)	Nodular lymphocyte-predominant Hodgkin lymphoma

IMMUNODEFICIENCY-ASSOCIATED LYMPHOPROLIFERATIVE DISORDERS	LYMPHOID PROLIFERATIONS AND LYMPHOMAS ASSOCIATED WITH IMMUNE DEFICIENCY AND DYSREGULATION†
Post-transplant lymphoproliferative disorders (PTLDs) - Non-destructive PTLD - Plasmacytic hyperplasia PTLD - Infectious mononucleosis PTLD - Florid follicular hyperplasia PTLD	**Hyperplasias arising in immune deficiency/dysregulation**
- Polymorphic PTLD - Monomorphic PTLD - Classic Hodgkin lymphoma PTLD	**Polymorphic lymphoproliferative disorders arising in immune deficiency/dysregulation†**
Other iatrogenic immunodeficiency-associated LPD	**Lymphomas arising in immune deficiency/dysregulation†**
Lymphoproliferative diseases associated with primary immune disorders	**Inborn error of immunity-associated lymphoid proliferations and lymphomas**

Coloured text indicates those entities that differ between the International Consensus Classification (red text) and the World Health Organization (WHO), 5th edition (blue text).
In **bold** are highlighted those entities that introduce significant changes with respect to the WHO, 4th edition revised classification.
In *italics*, the provisional entities from the International Consensus Classification.
#The ICC has been developed by the European Association for Haematopathology (EAHP) and the Society for Hematopathology (SH) together with clinicians and scientists through a joint Clinical Advisory Committee.
*Entities only present in the International Consensus Classification.
†The 5th edition of the WHO lymphoma classification adopts the nomenclature proposed at the 'Workshop on Immunodeficiency and Dysregulation' organised by the SH and the EAHP in 2015. In this classification, the nomenclature of lymphomas and lymphoid proliferations associated with immunodeficiency and dysregulation is constructed based on a three-tier structure as follows:

1. Histological diagnosis according to accepted criteria and terminology
2. Presence or absence of one or more oncogenic virus(es)
3. The clinical setting/immunodeficiency background.

Abbreviations: ALK, anaplastic lymphoma kinase; EBV, Epstein–Barr virus; HGBL, high-grade B-cell lymphoma; HHV, human herpes virus; ICC, International Consensus Conference; KSHV, Kaposi's sarcoma-associated herpes virus; NK, natural killer; NOS, not otherwise specified; WHO, World Health Organization; WHO-HAEM5, World Health Organization of Haematolymphoid Tumours, 5th edition.

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Appendix 2: Prognostic indices

CLL-IPI: International Prognostic Index for Chronic Lymphocytic Leukaemia [1]

Risk group	Number of adverse factors	% of patients	5-year OS
Low risk	0-1	28%	93.2%
Intermediate risk	2-3	39%	79.3%
High risk	4-6	28%	63.3%
Very high risk	7-10	5%	23.3%

Risk factors: age ≥65; clinical stage Binet B-C or Rai I-IV; β2-microglobulin >3.5 mg/L; IGHV unmutated; deletion 17p (FISH) and/or TP53 mutation (sequencing)

FLIPI: Follicular Lymphoma International Prognostic Index [2]

Risk group	Number of adverse factors	% of patients	5-year OS
Low risk	0-1	36%	91%
Intermediate risk	2	37%	78%
High risk	3-5	27%	52%

Risk factors: age ≥60; LDH >ULN; stage III-IV; Hb <120 g/L; number nodal areas ≥5

FLIPI 2: Follicular Lymphoma International Prognostic Index 2 [3]

Risk group	Number of adverse factors	% of patients	5-year PFS	5-year OS
Low risk	0	20%	79%	98%
Intermediate risk	1-2	53%	51%	88%
High risk	3-5	27%	20%	77%

Risk factors: age >60; β2-microglobulin >ULN; BM involvement; Hb <120 g/L; longest diameter of largest node >6 cm

IELSG (International Extranodal Lymphoma Study Group) Prognostic Score for Central Nervous System Lymphoma [4]

Risk group	Number of adverse factors	Number of patients	5-year OS
Low risk	0-1	n = 26	80%±8%
Intermediate risk	2-3	n = 56	48%±7%
High risk	4-5	n = 23	15%±7%

Risk factors: age >60; ECOG ≥2; LDH >ULN; cerebrospinal fluid protein >ULN; deep structures involved (basal ganglia, corpus callosum, brain stem, cerebellum)

IPI: International Prognostic Index for Patients with Aggressive Lymphoma [5,6]

Risk group	Number of adverse factors	% of patients	4-year PFS*	4-year OS*
Low risk	0-1	28%	85%	82%
Intermediate-low	2	27%	80%	81%
Intermediate-high	3	21%	57%	49%
High risk	4-5	24%	51%	59%

**Data on patients treated with R-CHOP*
Risk factors: age >60; LDH >ULN; stage III-IV; PS ECOG ≥2; extranodal sites ≥2

NCCN-IPI: National Comprehensive Cancer Network International Prognostic Index [7]

Risk group	Number of adverse factors	% of patients	5-year PFS	5-year OS
Low risk	0-1	38%	91%	96%
Low-intermediate	2-3	26%	74%	82%
High-intermediate	4-5	22%	51%	64%
High risk	≥6	41%	30%	33%

Risk factors: age >40-60, >60-75, ≥75; ECOG ≥2; LDH ≤3× ULN, >3× ULN; stage III/IV; extranodal sites (bone marrow, CNS, liver/GI tract, lung)

IPS: International Prognostic Score for Advanced Hodgkin Lymphoma (Hasenclever Index) [8]

Number of adverse factors	% of patients	5-year PFS	5-year OS
0	7%	84%	89%
1	22%	77%	90%
2	29%	67%	81%
3	23%	60%	78%
4	12%	51%	61%
≥5	7%	42%	56%

Risk factors: age ≥45; male gender; stage IV; Hb <105 g/L; lymphocyte count <0.6 × 10^9/L; leukocyte count ≥15 × 10^9/L; albumin <40 g/L

ISSWM: International Prognostic Scoring System for Waldenström Macroglobulinaemia [9]

Risk group	Number of adverse factors	% of patients	5-year OS
Low risk	0-1 and age <65y	27%	87%
Intermediate risk	2 or age ≥65y	38%	68%
High risk	≥3	35%	36%

Risk factors: age ≥65; Hb ≤115 g/L; platelets ≤100 × 10^9/L; β2-microglobulin >3 mg/L; IgM >70 g/L

MIPI: Mantle Cell Lymphoma International Prognostic Index [10]

MIPI score: 0.03535 × age (years) + 0.6978 (if ECOG >1) + 1.367 × $\log_{10}$(LDH/ULN) + 0.9393 × $\log_{10}$(WBC count)
Online calculator of MIPI score: https://www.german-lymphoma-alliance.de/Scores.html (date last accessed, 12 January 2024)

Simplified MIPI [10]

Points	Age (years)	ECOG	LDH/ULN	WBC, 10^9/L
0	<50	0-1	<0.67	<6.7
1	50-59	-	0.67-0.99	6.7-9.99
2	60-69	2-4	1-1.49	10-14.99
3	≥70	-	≥1.5	≥15

Risk group	Number of adverse factors	% of patients	Median OS
Low risk	0-3	44%	Not reached
Intermediate	4-5	35%	51 months
High risk	6-11	21%	29 months

Risk factors: age; ECOG; LDH; WBC

MALT-IPI: MALT-lymphoma International Prognostic Index [11]

Risk group	Number of adverse factors	Number of patients	5-year PFS	5-year OS
Low risk	0	n = 167	76%	98.7%
Intermediate risk	1	n = 165	63.1%	93.1%
High risk	≥2	n = 68	32.5%	64.3%

Risk factors: age ≥70; LDH >ULN; stage III/IV

PINK: Prognostic Index of Natural Killer Lymphoma [12]

Risk group	Number of adverse factors	Number of patients	3-year OS
Low risk	0	n = 108	81%
Intermediate risk	1	n = 78	62%
High risk	≥2	n = 70	25%

Risk factors: age >60; stage III/IV; non-nasal primary localisation; distant lymph node involvement

PIT: Prognostic index for Peripheral T-cell Lymphoma Unspecified [13]

Risk group	Number of adverse factors	% of patients	5-year OS
Group 1	0	20%	62%
Group 2	1	33%	53%
Group 3	2	26%	33%
Group 4	3-4	21%	18%

Risk factors: age >60; LDH >ULN; ECOG PS ≥2; BM infiltration

Abbreviations: BM, bone marrow; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; FISH, fluorescent *in situ* hybridisation; GI, gastrointestinal; Hb, haemoglobin; IGHV, immunoglobulin heavy chain variable; IgM, immunoglobulin M; LDH, lactate dehydrogenase; MALT, mucosa-associated lymphoid tissue; OS, overall survival; PFS, progression-free survival; PS, performance status; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; ULN, upper limit of normal; WBC, white blood cell.

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Appendix 3: Selected treatment schedules

Burkitt lymphoma (BL)

First line

CODOX-M/IVAC (Magrath)* [1-3]**				
CODOX-M (Cycles 1 and 3)				
Cyclophosphamide	800 mg/m²	i.v.	d1	
Cyclophosphamide	200 mg/m²/d	i.v.	d2–5	
Vincristine	1.5 mg/m² (max. 2 mg)	i.v.	d1 + d8, cycle 1 d1 + d8 + d15, cycle 3	
Methotrexate*	300 mg/m² loading dose the 1st hour followed by 2700 mg/m² for the next 23 hours	i.v.	d10	
Rituximab	375 mg/m²	i.v.	d1	
G-CSF	5 µg/kg/d	s.c.	from d13	
Cytarabine	70 mg	i.t.	d1 + d3	
Methotrexate	12 mg	i.t.	d15	
Leucovorin	15 mg/dose	p.o.	d16	**

** leucovorin rescue*
*** next cycle on the day that the unsupported ANC is >1.0 × 10^9/L, with an unsupported platelet count >75 × 10^9/L*
**** for patients <65 years old*

IVAC (Cycles 2 and 4)				
Ifosfamide	1500 mg/m²/d	i.v.	d1–5	
Mesna	1500 mg/m²/d	i.v.	d1–5	
Etoposide	60 mg/m²/d	i.v.	d1–5	
Cytarabine	2 g/m² × 2/d	i.v.	d1 + d2	
G-CSF	5 µg/kg/d	s.c.	from d7	
Methotrexate	12 mg	i.t.	d5	
Leucovorin	15 mg/dose	p.o.	d16	**

*** next cycle on the day that the unsupported ANC is >1.0 × 10^9/L, with an unsupported platelet count >75 × 10^9/L*

GMALL B-ALL/NHL 2002 *(patients 18-55 years)* [4]				
Cycle A				
Rituximab	375 mg/m²	i.v.	d1	
Dexamethasone	10 mg/m²	p.o.	d2–6	
Vincristine	2 mg	i.v.	d2	
Ifosfamide	800 mg/m²	i.v.	d2–6	
Methotrexate	1500 mg/m² (150 mg/m² loading)	i.v.	d2	
Etoposide	100 mg/m²	i.v.	d5–6	
Cytarabine	2 ×150 mg/m²	i.v.	d5–6	
G-CSF	5 µg/kg/d	s.c.	from d8	
Cycle B				
Rituximab	375 mg/m²	i.v.	d1	
Dexamethasone	10 mg/m²	p.o.	d2–6	
Vincristine	2 mg	i.v.	d2	
Cyclophosphamide	200 mg/m²	i.v.	d2–6	
Methotrexate	1500 mg/m² (150 mg/m² loading)	i.v.	d2	
Adriamycin	25 mg/m²	i.v.	d5–6	
G-CSF	5 µg/kg/d	s.c.	from d8	
Cycle C				
Rituximab	375 mg/m²	i.v.	d1	
Dexamethasone	10 mg/m²	p.o.	d2–6	
Vindesine	3 mg/m² (max. 5 mg)	i.v.	d2	
Methotrexate	1500 mg/m² (150 mg/m² loading)	i.v.	d2	
Etoposide	250 mg/m²	i.v.	d5–6	
Cytarabine	2 × 2000 mg/m²	i.v.	d6	
G-CSF	5 µg/kg/d	s.c.	from d8	

R-Hyper-CVAD [5]				
Cycles 1, 3, 5, 7				
Cyclophosphamide	300 mg/m² C.I./3 h × 2/d	i.v.	d1–3	
Mesna	600 mg/m²/d C.I.	i.v.	d1–3	
Vincristine	2 mg	i.v.	d4 + d11	
Doxorubicin	50 mg/m² C.I. over 24 h*	i.v.	d4	
Dexamethasone	40 mg/d	p.o.	d1–4, d11–14	
Rituximab	375 mg/m²	i.v.	d1 + d11	
G-CSF	10 µg/kg/d	s.c.	from d6	q 3 wks***
Methotrexate	12 mg	i.t.	d2	
Cytarabine	100 mg	i.t.	d7	
Cycles 2, 4, 6, 8				
Methotrexate**	1000 mg/m² C.I. over 24 h	i.v.	d2–3	
Cytarabine	3000 mg/m² × 2/d	i.v.	d2 + d3	
Rituximab	375 mg/m²	i.v.	d2 + d8	
G-CSF	10 µg/kg/d	s.c.	from d5	q 3 wks***

** via central venous catheter*
*** leucovorin rescue*
**** or earlier if count recovery occurred (at least 14 days apart)*

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Chronic lymphocytic leukaemia (CLL)

First line

Acalabrutinib [1]				
Acalabrutinib	100 mg/d	p.o.	daily	

2-CDA [2,3]				
Cladribine	0.1 mg/kg/d	s.c.	d1–5	q 4 wks

Chlorambucil + obinutuzumab [4]				
Chlorambucil	0.5 mg/kg	p.o.	d1 + d15	
Obinutuzumab	100 mg 900 mg 1000 mg 1000 mg	i.v.	d1, cycle 1 d2, cycle 1 d8 + d15, cycle 1 d1, from cycle 2–6	 q 4 wks q 4 wks

(R-)FC [5-7]				
Fludarabine	25-30 mg/m^2/d	i.v.	d1–3	
Cyclophosphamide	250-300 mg/m^2/d	i.v.	d1–3	
Rituximab	375-500* mg/m^2	i.v.	d1	q 4 wks

** 500 mg/m^2 only for CLL*

Ibrutinib [8] (also registered in relapsed MCL and WM)				
Ibrutinib	420 mg/d	p.o.	daily	

Venetoclax-obinutuzumab/rituximab [9]				
Venetoclax	400 mg/d*	p.o.	daily	
Obinutuzumab	100 mg 900 mg 1000 mg 1000 mg	i.v.	d1, cycle 1 d2, cycle 1 d8 + d15, cycle 1 d1, from cycle 2-6	q 4 wks
OR rituximab	375 mg/m^2 500 mg/m^2	i.v.	d1, cycle 1 d1, cycle 2-6	

** after a 5-week ramp-up phase from d22 in cycle 1*

Zanubrutinib [10] (also registered in relapsed MZL and WM)				
Zanubrutinib	320 mg/d	p.o.	daily	

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CNS lymphoma

First line

MATRix [1], *up to 4 cycles*				
Rituximab	375 mg/m^2	i.v.	d1	
Methotrexate*	3500 mg/m^2	i.v.	d2	
Cytarabine	2000 mg × 2/d	i.v.	d3–4	
Thiotepa	30 mg/m^2	i.v.	d5	q 3 wks

** leucovorin rescue*

Methotrexate (MTX) / Cytarabine [2]				
Methotrexate*	3500 mg/m^2	i.v.	d1	
Cytarabine	2000 mg × 2/d	i.v.	d2–3	q 3 wks

** leucovorin rescue*

MTX High dose [3-5]				
Methotrexate*	3500/8000 mg/m^2	i.v.	d1	q 2 wks

** leucovorin rescue*

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Diffuse large B-cell lymphoma (DLBCL)

First line

R-ACVBP [1]				
Induction phase				
Rituximab	375 mg/m²	i.v.	d1	
Doxorubicin	75 mg/m²	i.v.	d1	
Cyclophosphamide	1200 mg/m²	i.v.	d1	
Vindesine	2 mg/m²	i.v.	d1 + d5	
Bleomycin	10 U/m²	i.v.	d1 + d5	
Prednisone	60 mg/m²	p.o.	d1–5	
G-CSF	5 µg/kg/d	s.c.	from d6	
Methotrexate	15 mg	i.t.	d1	q 2 wks
Consolidation phase 1				
Methotrexate*	3 g/m²	i.v.	d1	q 2 wks
Consolidation phase 2				
Rituximab	375 mg/m²	i.v.	d1	
Etoposide	300 mg/m²	i.v.	d1	
Ifosfamide	1500 mg/m²	i.v.	d1	q 2 wks
Consolidation phase 3				
Cytarabine	100 mg/m²	s.c.	d1–4	q 2 wks

** leucovorin rescue*

(R-)CHOEP [2,3]				
Doxorubicin	50 mg/m²	i.v.	d1	
Cyclophosphamide	750 mg/m²	i.v.	d1	
Vincristine	1.4 mg/m²	i.v.	d1	
Prednisone	100 mg/d	p.o.	d1–5	
Etoposide	100 mg/m²/d	i.v.	d1–3	
± Rituximab*	375 mg/m²	i.v.	d1	q 3 wks

** without rituximab for T-NHL or CD20-negative NHL*

(R-)CHOP-21 [4-6]				
Doxorubicin	50 mg/m²	i.v.	d1	
Cyclophosphamide	750 mg/m²	i.v.	d1	
Vincristine	1.4 mg/m²	i.v.	d1	
Prednisone	100 mg/d	p.o.	d1–5	
± Rituximab*	375 mg/m²	i.v.	d1	q 3 wks

** without rituximab for T-NHL or CD20-negative NHL*

Dose-adjusted EPOCH-(R) [7,8]				
Doxorubicin**	10 mg/m²/d C.I.	i.v.	d1–4	
Etoposide**	50 mg/m²/d C.I.	i.v.	d1–4	
Vincristine	0.4 mg/m²/d C.I.	i.v.	d1–4	
Cyclophosphamide**	750 mg/m²	i.v.	d5	
Prednisone	60 mg/m²/d	p.o.	d1–5	
± Rituximab*	375 mg/m²	i.v.	d1	
Filgrastim	300 mg	s.c.	from d5 until ANC >5000/µL	q 3 wks

** without rituximab for T-NHL or CD20-negative NHL*
****

- *if nadir ANC at least 0.5 × 10⁹/L: 20% increase in etoposide, doxorubicin and cyclophosphamide above last cycle*
- *if nadir ANC less than 0.5 × 10⁹/L on 1 or 2 measurements: same dose(s) as last cycle*
- *if nadir ANC less than 0.5 × 10⁹/L on at least 3 measurements: 20% decrease in etoposide, doxorubicin and cyclophosphamide below last cycle*
- *if nadir platelet count less than 25 × 10⁹/L on 1 measurement: 20% decrease in etoposide, doxorubicin and cyclophosphamide below last cycle*

Pola-R-CHP [9]				
Doxorubicin	50 mg/m²	i.v.	d1	
Cyclophosphamide	750 mg/m²	i.v.	d1	
Prednisone	100 mg/d	p.o.	d1–5	
Polatuzumab vedotin	1.8 mg/kg	i.v.	d1	
Rituximab	375 mg/m²	i.v.	d1	q 3 wks

First line, frail/elderly patients

R-miniCHOP [10]				
Doxorubicin	25 mg/m²	i.v.	d1	
Cyclophosphamide	400 mg/m²	i.v.	d1	
Prednisone	40 mg/m²	p.o.	d1–5	
Vincristine	1 mg	s.c.	d1	
Rituximab	375 mg/m²	i.v.	d1	q 3 wks

Relapse

R-DHAOx [11]				
Dexamethasone	40 mg/d	i.v.	d1–4	
Cytarabine	2000 mg/m² × 2	i.v.	d2	
Oxaliplatin	130 mg/m²	i.v.	d1	
Rituximab	375 mg/m²	i.v.	d1	q 3-4 wks

(R-)DHAP [12]				
Dexamethasone	40 mg/d	i.v.	d1–4	
Cytarabine	2000 mg/m² × 2	i.v.	d2	
Cisplatin	100 mg/m²	i.v.	d1	
± Rituximab*	375 mg/m²	i.v.	d1	q 3-4 wks

** without rituximab for T-NHL or CD20-negative NHL and HL*

(R-)ESHAP [13,14]				
Etoposide	40 mg/m²/d	i.v.	d1–4	
Cytarabine	2000 mg/m²	i.v.	d5	
Cisplatin	25 mg/m²/d C.I.	i.v.	d1–4	
Methylprednisolone	250–500 mg/d	i.v.	d1–4	
± Rituximab*	375 mg/m²	i.v.	d1	q 3 wks

** without rituximab for T-NHL or CD20-negative NHL and HL*

(R-)GDP [15]				
Gemcitabine	1000 mg/m²	i.v.	d1 + d8	
Dexamethasone	40 mg/d	i.v.	d1–4	
Cisplatin	75 mg/m²	i.v.	d1	
± Rituximab*	375 mg/m²	i.v.	d1	q 3 wks

** without rituximab for T-NHL or CD20-negative NHL*

R-GEMOX [16]				
Rituximab	375 mg/m²	i.v.	d1	
Gemcitabine	1000 mg/m²	i.v.	d1	
Oxaliplatin	100 mg/m²	i.v.	d1	q 3 wks

(R-)ICE [17,18]				
Etoposide	100 mg/m²/d	i.v.	d1–3	
Ifosfamide	5000 mg/m² C.I. over 24 h	i.v.	d2	
Mesna	5000 mg/m² C.I. over 24 h	i.v.	d2	
Carboplatin	AUC = 5 (max. 800 mg)	i.v.	d2	
± Rituximab*	375 mg/m²	i.v.	d1	
G-CSF	5 µg/kg/d	s.c.	from d7	q 2-3 wks

** without rituximab for T-NHL or CD20-negative NHL and HL*

Pola-B-R [19]				
Bendamustine	90 mg/m²	i.v.	d1–2	
Rituximab	375 mg/m²	i.v.	d1	
Polatuzumab vedotin	1.8 mg/kg	i.v.	d1	q 3 wks

Tafa-len [20]				
Lenalidomide	25 mg/d	p.o.	d1–21	
Tafasitamab	12 mg/kg	i.v.	d1 + d4 + d8 + d15 + d22, cycle 1 d1 + d8 + d15 + d22, cycle 2–3 d1 + d15, from cycle 4	q 4 wks

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Follicular lymphoma (FL)

First line

Bendamustine-Rituximab/Obinutuzumab (B-R/O) [1,2]				
Bendamustine	70-90 mg/m²	i.v.	d1–2	
Rituximab	375 mg/m²	i.v.	d1	q 4 wks
OR Obinutuzumab	100 mg 900 mg 1000 mg 1000 mg	i.v.	d1, cycle 1 d2, cycle 1 d8 + d15, cycle 1 d1, from cycle 2–6	 q 4 wks q 4 wks

R/O-CHOP-21 [3]				
Doxorubicin	50 mg/m²	i.v.	d1	
Cyclophosphamide	750 mg/m²	i.v.	d1	
Vincristine	1.4 mg/m²	i.v.	d1	
Prednisone	100 mg/d	p.o.	d1–5	
Rituximab	375 mg/m²	i.v.	d1	q 3 wks
OR Obinutuzumab	100 mg 900 mg 1000 mg 1000 mg	i.v.	d1, cycle 1 d2, cycle 1 d8 + d15, cycle 1 d1, from cycle 2–6	 q 4 wks q 4 wks

R/O-CVP [3,4]				
Cyclophosphamide	750 mg/m²	i.v.	d1	
Vincristine	1.4 mg/m²	i.v.	d1	
Prednisone	40 mg/d	p.o.	d1–5	
Rituximab	375 mg/m²	i.v.	d1	q 3 wks
OR Obinutuzumab	100 mg 900 mg 1000 mg 1000 mg	i.v.	d1, cycle 1 d2, cycle 1 d8 + d15, cycle 1 d1, from cycle 2–6	 q 4 wks q 4 wks

R [5]				
Rituximab	375 mg/m²	i.v.	d1	weekly × 4 then every 2 months × 4

Relapse

R² [6]				
Lenalidomide	20 mg/d	p.o.	d1–21	
Rituximab	375 mg/m² 375 mg/m²	i.v.	d1 + d8 + d15 + d22, cycle 1 d1, from cycle 2–5	 q 4 wks

Mosunetuzumab [7]				
Mosunetuzumab	1 mg 2 mg 60 mg 60 mg 30 mg	i.v.	d1 d8 d15, cycle 1 d1, cycle 2 d1, from cycle 3	 q 3 wks

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Hodgkin lymphoma (HL)

First line

ABVD [1]				
Doxorubicin	25 mg/m²	i.v.	d1 + d15	
Bleomycin	10 mg/m²	i.v.	d1 + d15	
Vinblastine	6 mg/m²	i.v.	d1 + d15	
DTIC (Dacarbazine)	375 mg/m²	i.v.	d1 + d15	q 4 wks

BEACOPP escalated [2,3]				
Bleomycin	10 mg/m²	i.v.	d8	
Etoposide	200 mg/m²/d	i.v.	d1–3	
Doxorubicin	35 mg/m²	i.v.	d1	
Cyclophosphamide	1250 mg/m²	i.v.	d1	
Vincristine	1.4 mg/m²	i.v.	d8	
Procarbazine	100 mg/m²/d	p.o.	d1–7	
Prednisone	40 mg/m²/d	p.o.	d1–14	
Lenograstim **OR** Pegfilgrastim	150 µg/m²/d 6 mg	s.c. s.c.	from d4 d4	q 3 wks

BV-AVD [4]				
Doxorubicin	25 mg/m²	i.v.	d1 + d15	
Brentuximab vedotin	1.2 mg/kg	i.v.	d1 + d15	
Vinblastine	6 mg/m²	i.v.	d1 + d15	
DTIC (Dacarbazine)	375 mg/m²	i.v.	d1 + d15	q 4 wks

Relapse

Brentuximab vedotin (BV) [5] (also registered in ALCL, T-cell [NOS])				
Brentuximab vedotin	1.8 mg/kg	i.v.	d1	q 3 wks

Gem [6] (also registered in T-cell lymphoma)				
Gemcitabine	1000 mg/m²	i.v.	d1+ d8 + d15	q 4 wks

IGEV [7]				
Gemcitabine	800 mg/m²/d	i.v.	d1 + d4	
Ifosfamide	2000 mg/m²/d	i.v.	d1–4	
Mesna	2600 mg/m²/d	i.v.	d1–4	
Vinorelbine	20 mg/m²	i.v.	d1	
Prednisolone	100 mg/m²/d	p.o.	d1–4	
G-CSF	5 µg/kg/d	s.c.	d7–14	q 3 wks

Nivolumab [8]				
Nivolumab	240 mg	i.v.	d1	q 2 wks

Pembrolizumab [9]				
Pembrolizumab	200 mg	i.v.	d1	q 3 wks

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Mantle cell lymphoma (MCL)

First line

Bendamustine-Rituximab (B-R) [1] (also referenced in MZL and WM)				
Bendamustine	70–90 mg/m²	i.v.	d1–2	
Rituximab	375 mg/m²	i.v.	d1	q 4 wks

R-CHOP + Ibrutinib / R-DHAP [2]				
Cycles 1,3,5				
Doxorubicin	50 mg/m²	i.v.	d1	
Cyclophosphamide	750 mg/m²	i.v.	d1	
Vincristine	1.4 mg/m²	i.v.	d1	
Prednisone	100 mg/d	p.o.	d1–5	
Rituximab	375 mg/m²	i.v.	d1	
Ibrutinib	560 mg/d	p.o	d1–21	q 3 wks
Cycles 2,4,6				
Dexamethasone	40 mg/d	i.v.	d1–4	
Cytarabine	2000 mg/m² × 2	i.v.	d2	
Cisplatin	100 mg/m²	i.v.	d1	
Rituximab	375 mg/m²	i.v.	d1	q 3 wks

R-Hyper-CVAD [3]				
Cycles 1,3,5				
Cyclophosphamide	300 mg/m² C.I./3 h × 2/d	i.v.	d1–3	
Mesna	600 mg/m²/d C.I.	i.v.	d1–3	
Vincristine	1.4 mg	i.v.	d4 + d11	
Doxorubicin	16.6 mg/m²/d C.I. over 72 h*	i.v.	d4–6	
Dexamethasone	40 mg/d	p.o.	d1–4, d11–14	
Rituximab	375 mg/m²	i.v.	d1	q 3 wks
G-CSF	5 µg/kg/d	s.c.	from d6	

** via central venous catheter*

Cycles 2, 4, 6				
Methotrexate**	1000 mg/m² C.I. over 24 h	i.v.	d1	
Cytarabine	3000 mg/m² × 2/d	i.v.	d2 + d3	
Rituximab	375 mg/m²	i.v.	d1	
G-CSF	5 µg/kg/d	s.c.	from d5	q 3 wks

*** leucovorin rescue*

VR-CAP [4]				
Doxorubicin	50 mg/m²	i.v.	d1	
Cyclophosphamide	750 mg/m²	i.v.	d1	
Prednisone	100 mg/d	p.o.	d1–5	
Bortezomib	1.3 mg/kg	s.c.	d1, d4, d8, d11	
Rituximab	375 mg/m²	i.v.	d1	q 3 wks

Relapse

Ibrutinib [5]				
Ibrutinib	560 mg/d	p.o.	daily	

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1. Rummel MJ, Niederle N, Maschmeyer G, et al; Study group indolent Lymphomas (StiL). Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. Lancet 2013; 381:1203–1210.
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Marginal zone lymphoma (MZL)

First line

B-R
see Mantle cell lymphoma (MCL)

Relapse

Zanubrutinib
see Chronic lymphocytic leukaemia (CLL)

T-cell lymphoma

First line

Anaplastic large cell lymphoma (ALCL) and CD30-positive peripheral T-cell lymphoma (CD30+ PTCL)				
BV-CHP [1]				
Doxorubicin	50 mg/m^2	i.v.	d1	
Cyclophosphamide	750 mg/m^2	i.v.	d1	
Prednisone	100 mg/d	p.o.	d1–5	
Brentuximab vedotin	1.8 mg/kg	i.v.	d1	

Natural killer (NK)/T-cell lymphoma, nasal type				
SMILE [2]				
Methotrexate*	2 g/m^2	i.v.	d1	
Ifosfamide	1.5 g/m^2	i.v.	d2, d3, d4	
Mesna	300 mg/m^2 × 3/d	i.v.	d2, d3, d4	
Dexamethasone	40 mg/d	i.v. or p.o.	d2, d3, d4	
Etoposide	100 g/m^2	i.v.	d2, d3, d4	
L-asparaginase *(Escherichia coli)*	6000 U/m^2	i.v.	d8, d10, d12, d14, d16, d18, d20	
G-CSF	5 µg/kg/d	s.c.	from d6	

** leucovorin rescue*

T-cell lymphoma (not otherwise specified, NOS)
CHOP or CHOEP
see Diffuse large B-cell lymphoma (DLBCL)

Relapse

ALCL, T-cell (NOS)
BV
see Hodgkin lymphoma (HL), Relapsed

Cutaneous T-cell lymphoma				
Romidepsin [3,4]				
Romidepsin	14 mg/m^2	i.v.	d1, d8, d15	q 4 wks

T-cell lymphoma (NOS)
Gem
see Hodgkin lymphoma (HL), Relapsed

Pralatrexate [5]				
Pralatrexate	30 mg/m^2	i.v.	weekly	

References:

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Waldenström macroglobulinaemia (WM)

First line

Acalabrutinib
see Chronic lymphocytic leukaemia (CLL)

B-R
see Mantle cell lymphoma (MCL)

DRC [1]				
Dexamethasone	20 mg	i.v.	d1	
Cyclophosphamide	100 mg/m^2 × 2/d	p.o.	d1–5	
Rituximab	375 mg/m^2	i.v.	d1	q 3 wks

Ibrutinib
see Chronic lymphocytic leukaemia (CLL)

Zanubrutinib
see Chronic lymphocytic leukaemia (CLL)

Reference:

1. Dimopoulos MA, Anagnostopoulos A, Kyrtsonis MC, et al. Primary treatment of Waldenström macroglobulinemia with dexamethasone, rituximab, and cyclophosphamide. J Clin Oncol 2007; 25:3344–3349.

Abbreviations:
2/d, twice a day; ALCL, anaplastic large cell lymphoma; ANC, absolute neutrophil count; AUC, area under the curve; B-ALL, B-cell acute lymphoblastic leukaemia; C.I., continuous infusion; CNS, central nervous system; d, day; G-CSF, granulocyte-colony stimulating factor; HL, Hodgkin lymphoma; i.t., intrathecal; i.v., intravenous; MCL, mantle cell lymphoma; MTX, methotrexate; MZL, marginal zone lymphoma; NHL, non-Hodgkin lymphoma; NOS, not otherwise specified; p.o., oral; q x wks, every x weeks; s.c., subcutaneous; wk, week; WM, Waldenström macroglobulinaemia.

Appendix 4: List of targeted agents (including EMA approval)

Principle	Mode of action	Drugs	Phase II or III trials completed / *active*	EMA approval	Indication (expected)
B-cell receptor pathway	BTK	Ibrutinib	CLL, WM, FL LBCL, *MZL, MCL, CNS*	X	MCL, CLL, WM
		Acalabrutinib	*CLL, MCL, MZL, LBCL, CNS*	X	CLL
		Zanubrutinib	CLL, WM, FL, *MZL, MCL, DLBCL, CNS*	X	WM (MZL)
		Pirtobrutinib	CLL, MCL		(MCL, CLL)
	PI3K	Idelalisib	*CLL*, iNHL	X	iNHL, CLL
		Copanlisib	*DLBCL, FL, MZL*		Pending
		Duvelisib	*T-NHL, CLL, FL*		
		Umbralisib	*FL, MCL, CLL*, WM		
	mTOR	Temsirolimus	MCL	X	MCL
Antiapoptotic drugs	BCL2	Venetoclax	CLL, FL, DLBCL, MCL, WM	X	CLL
	EZH2	Tazemetostat	*FL, DLBCL*		(FL)
	XPO-1	Selinexor	*DLBCL, MZL*, CTCL		
	CDK 6	Abemaciclib	MCL		
		Palbociclib	*MCL*		
	PKCβ	Enzastaurin	LBCL		
HDAC		Romidepsin	*T-NHL*		
		Belinostat	*PTCL, T-cell leukaemia-lymphoma*		
		Vorinostat	Different NHL		
NF-κB	Proteasome	Bortezomib	MCL, LBCL	X	MCL
		Carfilzomib	MCL, MZL, WM, T-NHL, HL		
Immune modulators		Lenalidomide	CLL, MCL, WM, DLBCL, FL	X	MCL, FL
	RXR-selective retinoids	Bexarotene	CTCL	X	CTCL
Immune checkpoint regulators		Nivolumab	LBCL, T-NHL	X	HL
		Ipilimumab	LBCL, HL, MZL		
		Pembrolizumab	*PMBCL*, T-NHL	X	HL
Monoclonal antibodies		Rituximab	All B-cell lymphomas	X	LBCL, FL, CLL
		Obinutuzumab	MCL, *MZL, FL, CNS*	X	FL, CLL
		Tafasitamab	*FL, MZL, CNS*	X	LBCL
		Mogamulizumab-kpkc	*T-NHL*	X	T-NHL
	Drug conjugates	Brentuximab vedotin	HL, *T-NHL, FL*	X	HL, ALCL
		Polatuzumab vedotin	*FL, DLBCL*	X	LBCL
		Inotuzumab ozogamicin	*ALL*	Stopped	
		Loncastuximab tesirine	*MCL, MZL, FL, DLBCL*	Pending	
	Bispecific antibodies	Blinatumomab	ALL, mixed	ALL	
		Mosunetuzumab	*FL, MZL*, LBCL	X	FL
		Glofitamab	*LBCL, different NHL*	Pending	
		Epcoritamab	*FL, LBCL, MZL*	Pending	
		Odronextamab	Mixed	Pending	
Antineoplastic agents		Pixantrone		X	B-NHL
Others	ALK inhibitors	Crizotinib, brigatinib, ceritinib	ALK-positive ALCL		
	Aurora kinase inhibitors	Alisertib	DLBCL, MCL, anaplastic LBL, T-NHL	Stopped	
CAR-T cell therapy*		Lisocabtagene maraleucel		X	DLBCL, PMBCL, FL
		Axicabtagene ciloleucel		X	DLBCL, PMBCL
		Tisagenlecleucel		X	B-ALL, DLBCL, FL
		Brexucabtagene autoleucel		X	MCL

**Cellular therapy*
(Table prepared April 2023)

Abbreviations: ALCL, anaplastic large cell lymphoma; ALK, anaplastic lymphoma kinase; ALL, acute lymphoblastic leukaemia; B-ALL, B-cell acute lymphoblastic leukaemia; BCL2, B-cell lymphoma 2; B-NHL, B-cell non-Hodgkin lymphoma; BTK, Bruton tyrosine kinase; CAR, chimeric antigen receptor; CDK6, cyclin-dependent kinase 6; CLL, chronic lymphoblastic leukaemia; CNS, central nervous system; CTCL, cutaneous T-cell lymphoma; DLBCL, diffuse large B-cell lymphoma; EMA, European Medicines Agency; EZH2, enhancer of zeste homologue 2; FL, follicular lymphoma; HDAC, histone deacetylase; HL, Hodgkin lymphoma; iNHL, indolent non-Hodgkin lymphoma; LBL, lymphoblastic lymphoma; LBCL, large B-cell lymphoma; MCL, mantle cell lymphoma; mTOR, mammalian target of rapamycin; MZL, marginal zone lymphoma; NF-κB, nuclear factor-kappa B; NHL, non-Hodgkin lymphoma; PI3K, phosphoinositide 3-kinase; PKCβ, protein kinase C beta; PMBCL, primary mediastinal large B-cell lymphoma; PTCL, peripheral T-cell lymphoma; RXR, retinoid X receptor; T-NHL, T-cell non-Hodgkin lymphoma; WM, Waldenström macroglobulinaemia; XPO-1, exportin 1.

Declarations of interest

S Araf: No conflict of interest.

A Arribas: Travel grants: AstraZeneca.

V Ballova: Institutional advisory board honoraria: AbbVie, BMS, Janssen, Sanofi Aventis.

Y Benavente: No conflict of interest.

F Bertoni: Institutional consultancy fees: Helsinn, Menarini; institutional funding: ADC Therapeutics, Bayer AG, Cellestia, Helsinn, Immunogen, Menarini Ricerche, NEOMED Therapeutics 1, Nordic Nanovector ASA, PIQUR Therapeutics AG, Oncology Therapeutic Development; institutional research grant: Spexis. Co-inventor of patent WO2019185117A1 for the Fondazione per l'Istituto Oncologico di Ricerca (IOR). Travel grants: Amgen, AstraZeneca, Jazz Pharmaceuticals, iOnctura SA. Institution product samples: HTG.

M Blanco: No conflict of interest.

P Borchmann: Personal advisory board honoraria: Takeda Oncology, Roche; expert testimony honoraria: BMS, MSD, Novartis, Miltenyi Biotech, Incyte. Institute received funding for his work as coordinating principal investigator from Takeda Oncology, Roche, Novartis, MSD, Amgen, Miltenyi Biotech.

A Borra: No conflict of interest.

E Campo: Personal invited speaker honoraria: Janssen, EUSA Pharma, BMS; personal advisory board honoraria: Takeda; institutional fees for consulting of cases in a clinical trial: Genmab; potential licensing fees paid to his institute: Diagnostica Longwood; personal and institutional research grant for his role as principal investigator: AstraZeneca.

D Casabonne: No conflict of interest.

MED Chamuleau: Institutional advisory board honoraria: Novartis; institutional research funding: BMS, AbbVie, Gilead.

A Chiappella: Personal advisory board honoraria: Gilead Sciences, Roche, Takeda, Ideogen; personal invited speaker honoraria: Gilead Sciences, Janssen, Roche, AstraZeneca, Takeda, Incyte, Novartis.

F d'Amore: Institutional research grant for his role as coordinating principal investigator: Servier; institutional Steering Committee Member fee: Nordic Nanovector. Chairman of the Nordic Lymphoma Group (NLG) T-cell Lymphoma working group (1988-2021); member of the Clinical Advisory Committee of the World Health Organization (WHO) Classification of Tumours of the Haematopoietic and Lymphoid Tissues; member of the scientific committee of the European School of Haematology; Principal Investigator for the RESILIENCE trial (financed by the European HORIZON 2022 program) at Aarhus University Hospital, Denmark.

A Davies: Personal fees as an advisory board member: Abbvie, Acerta Pharma, AstraZeneca, BMS/Celgene, Genmab, Gilead, Incyte, Karyopharm, Kite Pharma, Regeneron, Roche, Sobi, Takeda; personal fees as an invited speaker: AstraZeneca, Gilead, Roche; institutional research grants for conduct of commercial research and funding of IST: Acerta Pharma, Roche; institutional research grants for conduct of commercial research: ADC Therapeutics, AstraZeneca, BMS/Celgene, Gilead, Pfizer; institutional research grant: MSD (no financial interest); non-renumerated leadership role, member and UK Board representative: Precision Medicine in Aggressive Lymphoma Consortium of the International Extranodal Lymphoma Study Group; advisory role and international advisor: Swiss SAKK Lymphoma Project Group and member of the UK National Cancer Research Institute's High Grade Lymphoma Study Group.

MA Dimopoulos: Institution advisory board honoraria: Amgen, Takeda, Janssen, BeiGene, BMS, Sanofi, Abbvie, Pharmacyclics Inc, GSK, Karyopharm, Pfizer.

M Dreyling: Personal advisory board honoraria: AstraZeneca, Bayer, BMS/Celgene, BeiGene, Genmab, Gilead, Incyte, Janssen, Novartis, Roche, Lilly/Loxo, MorphoSys; personal speaker's honoraria: Amgen, AstraZeneca, Bayer, Celgene, Gilead/Kite, Incyte, Janssen, Novartis, Roche; institutional research grants for academic trials: AbbVie, Bayer, Celgene, Janssen, Roche.

DA Eichenauer: Speaker honoraria: Takeda.

AJM Ferreri: Personal advisory board honoraria: Abbvie, AstraZeneca, BMS, Genmab, Gilead, Incyte, Juno, Novartis, PletixaPharm, Roche; institutional honoraria for his work as a local principal investigator: ADC Therapeutics, Abbvie, Amgen, BMS, BeiGene, Genmab, Gilead, Hutchison MediPharma, Incyte, Janssen, Novartis, Pfizer, Pharmacyclics, Takeda; research grant: BTG Therapeutics; institutional funding: Roche. He is the President of Fondazione Italiana Linfomi, and member of the European Hematology Association Global Outreach Committee. He is the Inventor of patents on NGR-hTNF/RCHOP in relapsed or refractory primary CNS lymphoma and SNGR-hTNF and treatment in brain tumours with the IRCCS Ospedale San Raffaele srl.

G Frigola: No conflict of interest.

A Gallamini: Personal invited speaker honoraria: Takeda International.

M Ghielmini: No conflict of interest.

G Hess: Clinical research grants: Gilead/Kite, Incyte, Janssen, MorphoSys, Pfizer, Roche, Abbvie; consulting fees: Abbvie, ADC Therapeutics, AstraZeneca, BMS, Genmab, Gilead/Kite, Incyte, Janssen, Miltenyi, Novartis, Roche, Lilly; honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events: Abbvie, AstraZeneca, BeiGene, BMS, Genmab, Gilead, Incyte, Janssen, Lilly, Roche; support for attending meetings and/or travel: Janssen, Gilead/Kite. Participation on a Data Safety Monitoring Board or Advisory Board: Miltenyi.

M Hutchings: Personal advisory board honoraria: AbbVie, Genmab, Janssen, Roche, Takeda, AstraZeneca, Merck; institutional funding for his work as coordinating principal investigator: Genmab, Janssen, Merck, Novartis, Roche, Takeda, AstraZeneca.

E Kastritis: Personal advisory board honoraria: Amgen, Janssen; personal speaker honoraria: Genesis Pharma, Janssen, Takeda, Pfizer, Integris, GSK; institutional funding for his work as coordinating principal investigator: Janssen; institutional funding: Jansen, Amgen, Pfizer.

M Kättström: Institutional funding for her work as local principal investigator: AstraZeneca; academic studies such as the German CLL Study Group and research funding: Region Örebro County and Uppsala-Örebro Regional Research Council.

E Kimby: Personal advisory board honoraria: Pierre Fabre, Beigene; personal public speaker fee: AbbVie; personal consultancy fee: Celgene; she has received honoraria from Janssen for chairing educational meetings, and from Genmab for participating in independent data safety monitoring committees (IDMC). She has been the chair of the Indolent Lymphoma Group of the Nordic Lymphoma Group.

L Mazzucchelli: No conflict of interest.

A Moccia: Personal advisory board honoraria: Janssen, Takeda.

C Montalban: No conflict of interest.

S Montoto: Personal honoraria as a member of the Data Monitoring Committee: Bayer.

A Muntañola: No conflict of interest.

MB Pedersen: No conflict of interest.

L Petrikova: No conflict of interest.

M Ponzoni: Personal speaker honoraria: Novartis, BeiGene; personal expert testimony honoraria: Ventana Roche.

M Provencio: Personal advisory board honoraria: BMS, MSD, Bayer, Lilly, Roche, Takeda, Janssen; he is President of the Spanish Lung Cancer Group and Director of the Insutituto Investigación Sanitaria Puerta de Hierro.

KD Quint: Consultancy: Kyowa Kirin.

C. Sarkozy: Personal speaker honoraria: Abbvie; institutional honoraria for an expert testimony (DLBCL): Incyte; institutional advisory board honoraria: Janssen; institutional congress fees; Takeda, Gilead; institutional research funding; Roche; institutional speaker honoraria: Lilly.

D Scott: No conflict of interest.

D Soldini: No conflict of interest.

C Thieblemont: No conflict of interest.

M-K Tilch: No conflict of interest.

U Vitolo: Personal advisory board honoraria: Bayer, Genmab, Constellation Pharmaceuticals, Gilead, Abbvie; personal invited speaker honoraria: Janssen, Incyte, Abbvie, Roche; institutional funding for his work as coordinating principal investigator: MorphoSys. Member of the board of directors of the Fondazione Italiana Linfomi.

T Weiglein: No conflict of interest.

R Willemze: Personal advisory board honoraria: Helsinn.

E Zucca: Personal advisory board honoraria: Beigene, BMS, Curis, Eli/Lilly, Incyte, Ipsen, Janssen, Merck, Roche, Miltenyi Biomedicine; institutional travel grants: Abbvie, BeiGene, Roche. Institution received research grants (IELSG trials) from AstraZeneca, Celgene/BMS, Incyte, Janssen, Roche.

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