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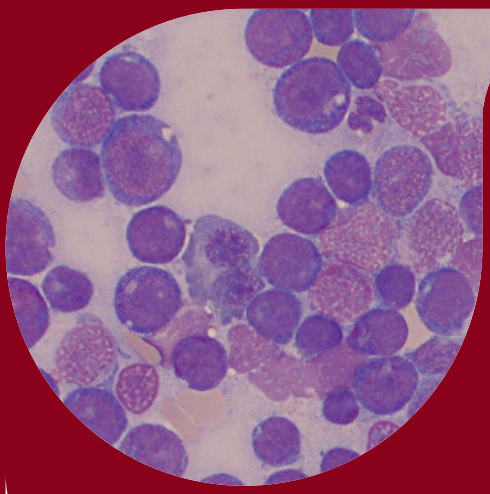
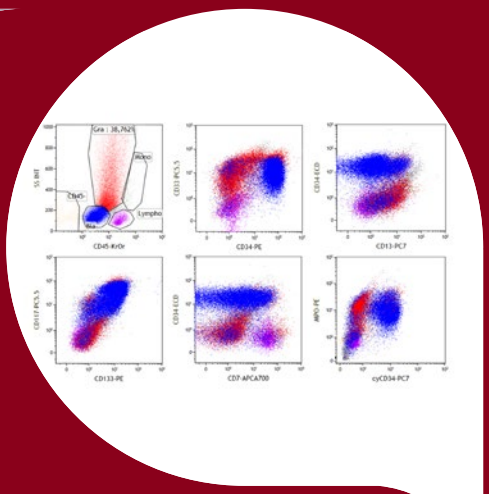
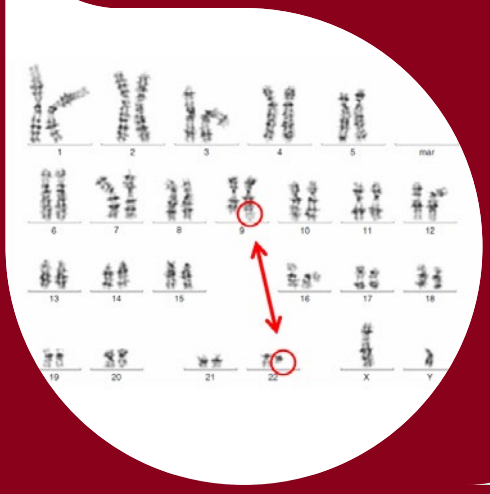
Veronika Ballová
Michele Ghielmini
Meletios-Athanasios Dimopoulos

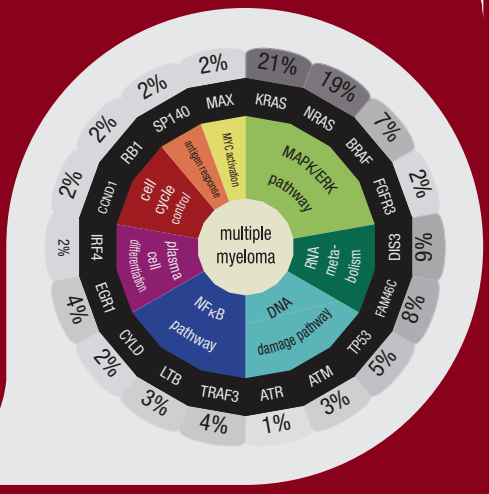
LEUKAEMIA AND MYELOMA

ESSENTIALS *for* CLINICIANS









ESMO Press

Leukaemia & Myeloma Essentials for Clinicians

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ESMO Press

First published in 2019 by ESMO Press

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

ISBN: 978-88-941795-6-9

For orders, corporate sales, foreign rights, and reprint permissions, please contact:

ESMO Head Office

Guidelines, Publishing and Online Education Department

Via Ginevra 4

6900 Lugano

Switzerland

Tel: +41 (0) 91 973 1900

Email: publication_support@esmo.org

www.esmo.org

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

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Preface

Based on the great success of the *Essentials for Clinicians* book series, focusing so far mostly on distinct solid cancer entities, the European Society for Medical Oncology (ESMO) has decided to extend this series further, presenting now the "Leukaemia & Myeloma" Essentials. This volume is published at the right time, as we are facing tremendous progress not only in understanding the biology but also in the clinical management of these diseases. Based on increasingly refined molecular diagnostics and accessibility to a plethora of new drugs targeting specific surface proteins or signal transduction pathways, personalised treatment is no longer only a vision but takes place in our daily clinical life. However, this great success substantially diversifies treatment approaches. In this situation, books such as this *Essentials for Clinicians*, which presents basic knowledge as well as deeper insight into novel therapeutic developments, are of immense value. Besides acute leukaemias and multiple myeloma, this volume also covers chronic myeloid leukaemia, myelodysplastic syndromes, myeloproliferative neoplasms and amyloidosis, thereby providing a comprehensive overview about leukaemias and myeloma as well as related or associated diseases. It informs the reader about biology, classification and treatment, including symptomatic therapy and management of complications. The concept to divide information into "What every oncologist/haematologist should know" and "More advanced knowledge" is brilliant and through this will address young as well as advanced haematologists/oncologists.

This *Essentials for Clinicians*, edited by the internationally recognised experts Drs Veronika Ballová, Michele Ghielmini and Meletios-Athanasios Dimopoulos, is an asset for the clinician dealing with haematological malignancies and will help to care for our patients in an optimal way.

Professor Christian Buske
Ulm, Germany

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Dr Veronika Ballová is a Senior Medical Oncologist at the Onkologie Kantonsspital in Baden, Switzerland. She graduated in medicine from the Comenius University of Bratislava, Slovakia, in 1992, and completed her specialist training in clinical oncology in 2001 at the National Cancer Institute in Bratislava. In 2003 she also completed an ESMO fellowship at the University Hospital in Cologne, Germany. Since then her career has mainly focused on haematological malignancies.

Dr Ballová has authored 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. She serves as a member of the European Society for Medical Oncology (ESMO) Publishing Working Group.

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Dr Dimopoulos is a Haematologist and Medical Oncologist, Chairman of the Department of Clinical Therapeutics and Rector of the National and Kapodistrian University of Athens, Greece. His main research interest is in plasma cell dyscrasias. He has authored more than 931 publications, has more than 53 000 citations and his h-index is 108.

Dr Dimopoulos serves on the Scientific Advisory Boards of several scientific societies and is a reviewer for numerous medical journals. He is a recipient of the Robert A. Kyle Award for outstanding contributions to research on Waldenström's macroglobulinaemia, of the Waldenström's Award for Myeloma Research of the International Myeloma Society, and of the COMy Excellence Award. In August 2017 he was given the title 'Officier dans l'Ordre des Palmes Académiques' of the French Republic. In May 2018 he was elected as a 'Membre Associé Etranger' of the French National Academy of Medicine.

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Professor Michele Ghielmini is Medical Director of the Oncology Institute of Southern Switzerland in Bellinzona and Head of the Medical Oncology Department, as well as Full Professor of Medicine at the University of Lugano and Honorary Professor at the University of Bern, Switzerland.

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Professor Ghielmini is a member and former Chair of the Lymphoma Section of the Swiss Group for Clinical Research Against Cancer (SAKK). He has been Chair of the European Society for Medical Oncology (ESMO) OncologyPRO Working Group and the ESMO Publishing Working Group, and a member of the ESMO Educational Committee. He has formerly sat on the Editorial Boards of *Annals of Oncology* and the *Journal of Clinical Oncology*.

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Abbreviations

AA	Alkylating agent
ABL1	Abelson
ACA	Additional cytogenetic aberration
aCML	Atypical chronic myeloid leukaemia
ADL	Activities of daily living
AE	Adverse event
aGvHD	Acute graft-versus-host disease
AL	Light chain amyloidosis
ALL	Acute lymphoblastic leukaemia
AlloSCT	Allogeneic stem cell transplantation
AML	Acute myeloid leukaemia
AP	Accelerated phase
APC	Antigen-presenting cell
APL	Acute promyelocytic leukaemia
ASCT	Autologous stem cell transplantation
ATO	Arsenic trioxide
ATRA	Al-trans retinoic acid
AYA	Adolescent and young adult
bAb	Bispecific antibody
B-ALL	B cell acute lymphoblastic leukaemia
BC	Blast crisis
BCR	Breakpoint cluster region
B-CLL	B cell chronic lymphocytic leukaemia
BCMA	B cell maturation antigen
BM	Bone marrow
BMPC	Bone marrow plasma cell
BP	Bisphosphonate
Btz	Bortezomib
BuCy	Busulfan and cyclophosphamide
CA	Chromosomal abnormality
CALR	Calreticulin
CAR	Chimeric antigen receptor
CAR-T cell	Chimeric antigen receptor-T cell
CB	Cord blood
CBC	Complete blood count
CCI	Charlson Comorbidity Index
CCND	Cyclin D
Cfz	Carfilzomib
CGH	Comparative genomic hybridisation
cGvHD	Chronic graft-versus-host disease
ChT	Chemotherapy
CI	Confidence interval
CLAG-Ida	CLAdribine, G-CSF-IDArubicin
CLL	Chronic lymphocytic leukaemia
CML	Chronic myeloid leukaemia
CMML	Chronic myelomonocytic leukaemia
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CP	Chronic phase
CPSS	CMML-specific prognostic scoring system
CR	Complete response
CRAB criteria	HyperCalcaemia, Renal insufficiency, Anaemia, Bone lesions
CRS	Cytokine-release syndrome
CSF	Cerebrospinal fluid
CT	Computed tomography
CyBorD	Cyclophosphamide/bortezomib/dexamethasone
DAC	Deacetylase
Dex	Dexamethasone
DIC	Disseminated intravascular coagulation
DIE	Disease-initiating event
DIPSS	Dynamic International Prognostic Scoring System
DLI	Donor lymphocyte infusion
DPE	Disease-progressing event
DRd	Daratumumab/lenalidomide/dexamethasone
DVd	Daratumumab/bortezomib/dexamethasone
eGFR	Estimated glomerular filtration rate
EGIL	European Group for the Immunological Characterization of Leukemias
ELN	European LeukemiaNet
ELO	Elotuzumab
ELTS	EUTOS long-term survival score
EMA	European Medicines Agency
EPO	Erythropoietin
ERd	Elotuzumab/lenalidomide/dexamethasone
ESA	Erythropoiesis-stimulating agent
ESMO	European Society for Medical Oncology
ET	Essential thrombocythaemia
EURO-SKI	European Stop Kinase Inhibitor
EUTOS	European Treatment and Outcome Study
FAB	French-American-British (classification)
FISH	Fluorescent *in situ* hybridisation
FLC	Free light chain
GC	Glucocorticoid
G-CSF	Granulocyte colony-stimulating factor
GEP	Gene expression profile
GI	Gastrointestinal
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GvHD	Graft-versus-host disease
GvL	Graft-versus-leukaemia
HAM	High-dose cytosine arabinoside and mitoxantrone
Hb	Haemoglobin
HD	Hyperdiploidy
HDAC	Histone deacetylase
HDACi	Histone deacetylase inhibitor
HD-Ara-C	High-dose cytarabine
HDM	High-dose melphalan
HDT	High-dose therapy
HLA	Human leukocyte antigen
HR	Hazard ratio
HSC	Haematopoietic stem cell
HSCT	Haematopoietic stem cell transplantation
HSPC	Haematopoietic stem or progenitor cell
5-HT3	5-Hydroxytryptamine
IADL	Instrumental activities of daily living
IChT	Intensive chemotherapy
ID-Ara-C	Intermediate-dose cytarabine
IDH	Isocitrate dehydrogenase
IFN	Interferon
IFNγ	Interferon gamma
Ig	Immunoglobulin
IgHtx	Immunoglobulin translocation
IL	Interleukin
IM	Imatinib
I-MAC	Intermediate-dose myeloablative conditioning
IMiD	Immunomodulatory drug
IMWG	International Myeloma Working Group
IO	Inotuzumab ozagamicin
IPSS	International Prognostic Scoring System
IPSS-R	Revised International Prognostic Scoring System
IRd	Ixazomib/lenalidomide/dexamethasone
IS	International Scale
ISS	International Staging System
ITD	Internal tandem duplication
i.v.	Intravenous
Ix	Ixazomib
JMML	Juvenile myelomonocytic leukaemia
Kd	Carfilzomib/dexamethasone
KRd	Carfilzomib/lenalidomide/dexamethasone
KT	Karyotype
LAIP	Leukaemia-associated (aberrant) immunophenotype
LD-Ara-C	Low-dose cytarabine
LDH	Lactate dehydrogenase
Len	Lenalidomide

Len-Dex	Lenalidomide/dexamethasone
M	Monoclonal
MA	Myeloablative
mAb	Monoclonal antibody
MAC	Myeloablative conditioning
MD-CMML	Myelodysplastic CMML
MDS	Myelodysplastic syndromes
MDS/MPN	Myelodysplastic/myeloproliferative neoplasms
MDS/MPN-RS-T	Myelodysplastic/myeloproliferative neoplasms with ring sideroblasts and thrombocytosis
MDS-RS	MDS with ringed sideroblasts
MDS-SLD	MDS with single lineage dysplasia
MDS-U	MDS unclassified
MF	Myelofibrosis
MFC	Multiparameter flow cytometry
MGUS	Monoclonal gammopathy of undetermined significance
MIL	Marrow-infiltrating lymphocyte
miRNA	microRNA
MM	Multiple myeloma
MO1	Classical monocytes
MP	Melphalan/prednisone
MP-CMML	Myeloproliferative chronic myelomonocytic leukaemia
MPN	Myeloproliferative neoplasm
MPO	Myeloperoxidase
MPT	Melphalan/prednisone/thalidomide
MR4	Molecular response 4
MRD	Minimal residual disease
MRI	Magnetic resonance imaging
mRNA	Messenger RNA
MTX	Methotrexate
ncRNA-seq	Non-coding RNA sequencing
NGS	Next generation sequencing
NIH	National Institutes of Health
NMA	Non-myeloablative
NR	Not reached
NT-proBNP	N-terminal pro-brain natriuretic peptide
ORR	Overall response rate
OS	Overall survival
PAD	Bortezomib/doxorubicin/dexamethasone
PanoVd	Panobinostat/bortezomib/dexamethasone
PBSC	Peripheral blood stem cell
PCD	Plasma cell disorder
PCR	Polymerase chain reaction
PD-1	Programmed cell death protein 1
PD-L1/L2	Programmed death-ligand 1/2
PET	Positron emission tomography
PFS	Progression-free survival
Ph	Philadelphia (chromosome)
PI	Proteasome inhibitor
Plt	Platelet
PNP	Peripheral neuropathy
PTEN	Phosphatase and tensin homologue
PV	Polycythaemia vera
RBC	Red blood cell
Rd	Lenalidomide/dexamethasone
Rd18	Lenalidomide/dexamethasone for 18 cycles
RIC	Reduced-intensity conditioning
R-ISS	Revised International Staging System
R-MCI	Revised-Myeloma Comorbidity Index
RRMM	Relapsed/refractory multiple myeloma
RT	Radiotherapy
RTqPCR	Reverse transcription quantitative polymerase chain reaction
SCT	Stem cell transplantation
sFLC	Serum free light chain
SMM	Smouldering multiple myeloma
SNP	Single nucleotide polymorphism
SSlow	Low side scatter
T-ALL	T cell acute lymphoblastic leukaemia
TCR	T cell receptor
TFR	Treatment-free remission
TKI	Tyrosine kinase inhibitor
TNF	Tumour necrosis factor
TPO	Thrombopoietin
TRM	Transplant-related mortality
VCD	Bortezomib/cyclophosphamide/dexamethasone
Vd	Bortezomib/dexamethasone
VDJ	Variable, diversity and joining
VGPR	Very good partial response
VMP	Bortezomib/melphalan/prednisone
VRd	Bortezomib/lenalidomide/dexamethasone
VTD	Bortezomib/thalidomide/dexamethasone
WBC	White blood cell
WES	Whole exome sequencing
WGS	Whole genome sequencing
WHO	World Health Organization
WMDA	World Marrow Donor Agency
wt	Wild-type

Acknowledgements

We would like to thank all the authors for their dedication and contribution to this publication and the members of the ESMO Publishing Working Group and Educational Committee for supporting this initiative.

We also wish to thank Aude Galli, Claire Bramley and Nicki Peters of ESMO for their support in the preparation of this publication.

Veronika Ballová, Michele Ghielmini and Meletios-Athanasios Dimopoulos

A

What every oncologist should know

1 Diagnosis and classification of leukaemias

Diagnosis of leukaemias – conventional techniques

An abnormal complete blood count (CBC) raises the suspicion of acute myeloid/lymphoblastic leukaemia (AML/ALL), chronic myeloid leukaemia (CML) or myelodysplastic syndrome (MDS).

In leukaemia patients, white blood cell counts can be either elevated or depleted.

Bone marrow aspirate and histology are mandatory to establish the diagnosis.

Diagnostic tests include cytomorphology, immunophenotyping, cytogenetics and molecular analyses

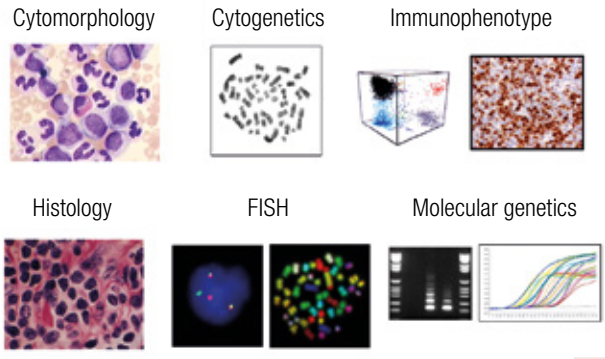
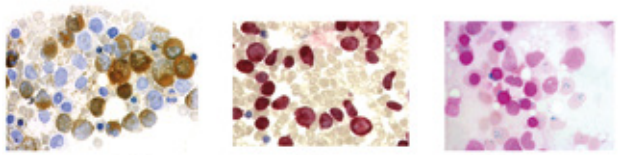


Fig. 1.1

FISH, Fluorescent *in situ* hybridisation.

Typical cytochemistry staining includes myeloperoxidase (MPO) to differentiate myeloid from lymphoid cells, nonspecific esterase (NSE) to detect monocytic cells and iron staining (FE) to assess iron storage



MPO	NSE	FE
Myeloid cell dysplasia	Monocytic cells	Iron storage Ring sideroblasts (MDS)

Fig. 1.2

MDS, Myelodysplastic syndrome.

Cytomorphology is a rapid but observer-dependent technique that allows the diagnosis of most AML and MDS cases.

Morphology is used to quantify blasts in peripheral blood and bone marrow, where ≥20% is the World Health Organization (WHO) cut off to diagnose acute leukaemia.

Cytochemistry is used to subspecify cells and to assess the iron storage, which is especially helpful in discriminating MDS subtypes.

Flow cytometry using fluorochrome antibody conjugates identifies blast cells and is a valuable tool to differentiate AML from ALL.

Typically, AML blasts have low side scatter (SSlow), show low expression of CD45 (CD45low), express CD34, CD13, CD117, CD133, MPO (myeloperoxidase) and can have aberrant expression of CD2, CD5, CD7, CD56, CD11b and CD15.

The leukaemia-associated (aberrant) immunophenotype (LAIP) is a valuable tool to detect minimal residual disease (MRD) following treatment.

Typical immunophenotype of an AML sample. Here SSlow and CD45low blast cells (gate in blue) express CD34, CD13, CD117, CD133, partially CD7 and MPO

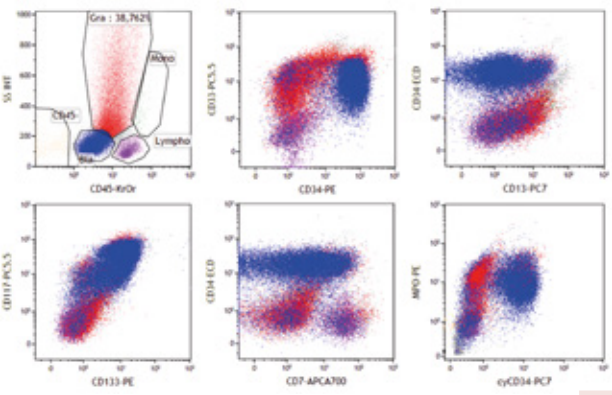


Fig. 1.3

REVISION QUESTIONS

1. What is the first diagnostic test used for leukaemia or MDS?
2. Does a white blood cell count of 1000/µL rule out leukaemia?
3. What is the main indication for flow cytometry in leukaemia diagnosis?

Diagnosis of leukaemias – cytogenetic techniques

Following a short period of culturing the diagnostic sample, metaphase chromosomes are analysed to establish the karyotype. This assay requires a fresh heparinised bone marrow or blood sample.

Giemsa-banded metaphase after capture by an automated microscope reveals a classical *t(9;22)* translocation, as in CML (A).

Complex karyotypes are hard to decipher by standard banding, and 24-colour fluorescent *in situ* hybridisation (FISH) on the identical metaphase helps to resolve complex rearrangements (B).

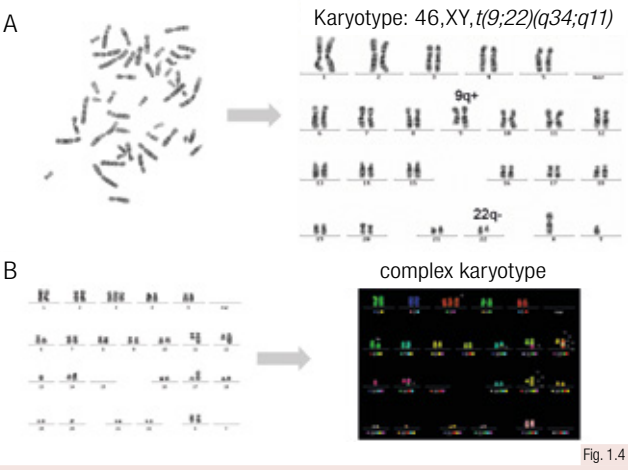


Fig. 1.4

Workflow for AML diagnosis: A. Cytomorphology showing typical blast cells with Auer rods. B. Immunophenotype with aberrant expression of CD56 and CD19. C. Karyogram showing translocation *t(8;21)*

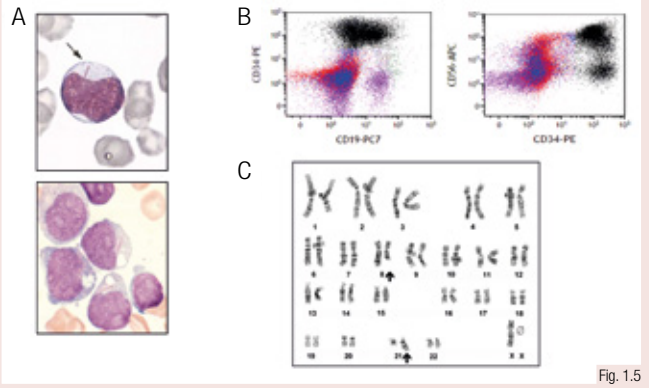


Fig. 1.5

In a routine workflow, cytomorphology and flow cytometry are rapid techniques that usually yield results within a few hours.

The typical morphology and immunophenotype can raise suspicion for certain subtypes of AML, which need further specification.

A conventional karyogram then returns the final diagnosis, e.g. an AML with a recurrent cytogenetic aberration: a *t(8;21)* translocation.

FISH is a tool to detect specific chromosomal aberrations. It can be applied to interphase nucleoli or metaphases after cell culture.

Probes are designed to bind specific genomic regions and allow the detection of trisomy (A), deletions (B) and translocations (C).

FISH is more sensitive than karyotyping and, in cases of specific translocations, can detect 1 in 200 cells (0.5%).

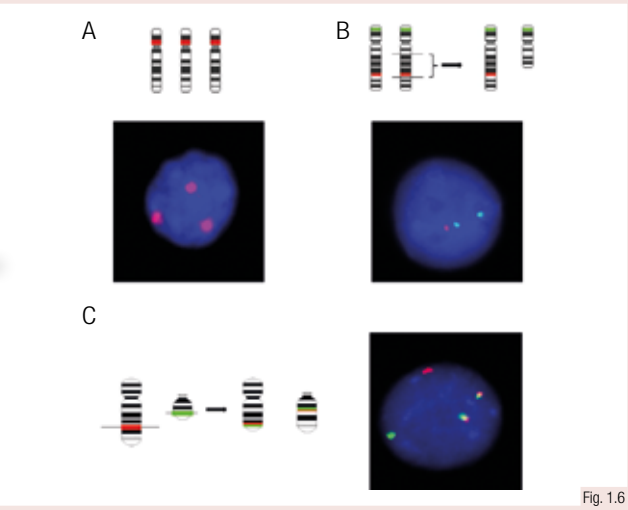


Fig. 1.6

REVISION QUESTIONS

1. What is the purpose of conventional cytogenetics?
2. What material (i.e. fresh or fixed) can be used for a cytogenetic workup?
3. What is the lower sensitivity level of FISH?

Diagnosis of leukaemias – molecular techniques

Polymerase chain reaction (PCR) is a method used for the detection of specific gene regions, e.g. specifically after rearrangement.

After gel electrophoresis, PCR products are visualised by DNA staining. Different PCR products of 9 patients of the rearranged fusion gene *BCR-ABL1* in CML discriminate the breakpoint (A).

Quantitative PCR (qPCR) (B) is a highly sensitive method to detect even low levels of tumour burden. In certain AML and CML, qPCR is validated for MRD detection.

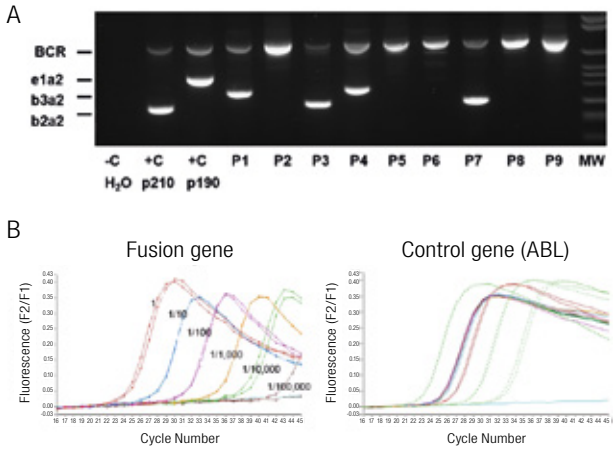


Fig. 1.7

Overview of NGS (next generation sequencing) instruments launched since 2005 from Roche(454), Illumina, Ion Torrent and Qiagen; illustrating the development of NGS with increasing sequencing capacities

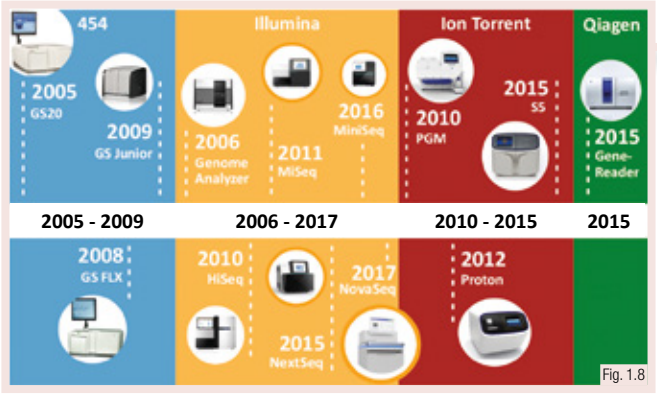


Fig. 1.8

Molecular sequencing techniques have enabled fast and accurate analysis from single genes to whole genomes.

The first cancer genome reported was an AML genome published in *Nature* in 2008.

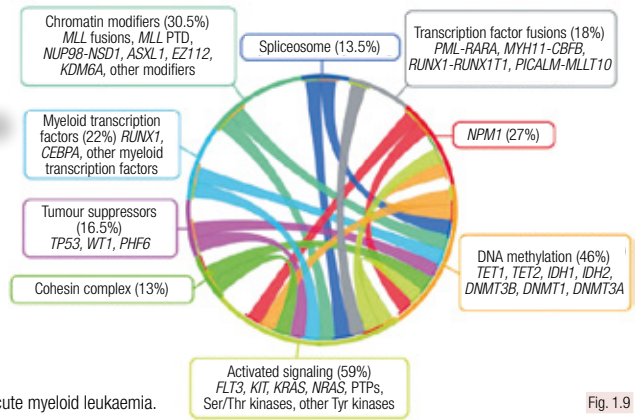
The Cancer Genome Atlas project has added numerous AML genomes, identifying driver and passenger mutations.

Those analyses have shown that AML is a disease with only few recurrent mutations.

Genetic events in AML occur in 9 different functional classes. Some mutations are strongly associated with each other, while others are mutually exclusive (Chen et al. 2013).

Gene panel sequencing is on its way to becoming a routine measure in the diagnosis of leukaemias and MDS, and is of diagnostic and prognostic value.

Circos plot showing genetic events leading to AML. Ribbons connecting distinct categories reflect the associations between mutations. Mutual exclusive alterations are not connected



AML, Acute myeloid leukaemia.

Fig. 1.9

REVISION QUESTIONS

1. Which molecular techniques are used in leukaemia diagnosis?
2. What is the role of real-time PCR in molecular diagnostics?
3. What is the role of gene sequencing in establishing the diagnosis?

Classification of AML and CML

The French-American-British (FAB) classification for AML was based on cytomorphologic features and has been replaced by the WHO 2001/2008 and 2016 classifications.

The European LeukemiaNet (ELN) defines 3 risk groups according to genetic abnormalities (Döhner et al. 2017).

Certain AML subgroups such as acute promyelocytic leukaemia (APL) (*PML-RARA*, *t[15;17]*) benefit from targeted treatment and have an excellent prognosis.

2017 ELN risk stratification by genetics

Risk category	Genetic abnormality
Favourable	*t(8;21)(q22;q22.1); RUNX1-RUNX1T1* *inv(16)(p13.1q22)* or *t(16;16)(p13.1;q22); CBFB-MYH11* Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITDlow* Biallelic mutated *CEBPA*
Intermediate	Mutated *NPM1* and *FLT3*-ITDhigh* Wild-type NPM1 without *FLT3*-ITD or with *FLT3*-ITDlow* (without adverse-risk genetic lesion) *t(9;11)(p21.3;q23.3); MLLT3-KMT2A* Cytogenetic abnormalities not classified as favourable or adverse
Adverse	*t(6;9)(p23;q34.1); DEK-NUP214* *t(v;11q23.3); KMT2A* rearranged *t(9;22)(q34.1;q11.2); BCR-ABL1* *inv(3)(q21.3q26.2)* or *t(3;3)(q21.3;q26.2); GATA2,MECOM(EVI1)* *–5* or *del(5q); –7; –17/abn(17p)* Complex karyotype**, monosomal karyotype*** Wild-type *NPM1* and *FLT3*-ITDhigh Mutated *RUNX1* Mutated *ASXL1* Mutated *TP53*

Fig. 1.10

*Low, low allelic ratio (<0.5), high, high allelic ratio (≥0.5)
**Three or more unrelated chromosome abnormalities in the absence of WHO-designated recurring translocations
***Defined by the presence of 1 single monosomy (excluding loss of X or Y) in association with at least 1 additional monosomy or structural chromosome abnormality
ELN, European LeukemiaNet; ITD, internal tandem duplication; WHO, World Health Organization.

Proposed new AML classification scheme discriminates 13 subgroups

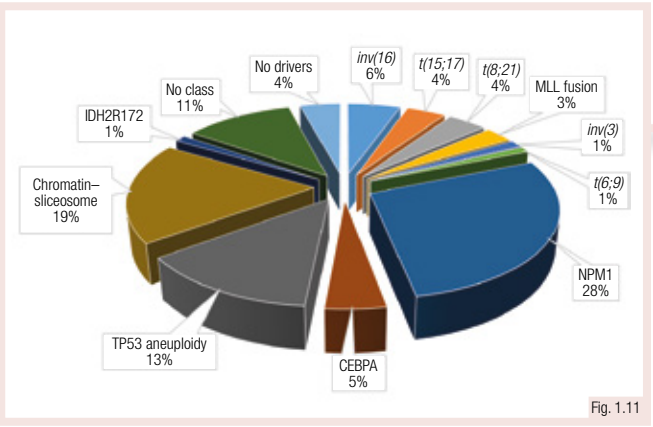


Fig. 1.11

AML, Acute myeloid leukaemia.

A new classification scheme was proposed, including karyotype and somatic mutations, and defines 13 AML subgroups (Papaemmanuil et al. 2016).

Specific chromosomal aberrations such as *t(8;21)*, *inv(16)*, *t(15;17)* are disease-defining, irrespective of the quantified blast count.

In the future, diagnosis of AML might rely solely on genetic findings.

Typical peripheral blood (A) and bone marrow (B) smear of CML patient, with hypercellularity and left shift. (C) FISH detects the *t(9;22)* translocation

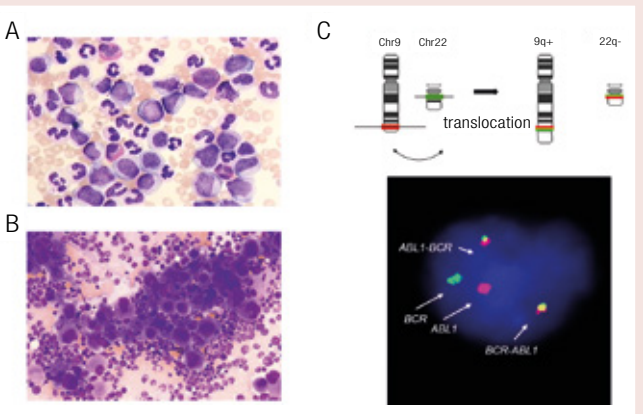


Fig. 1.12

CML, Chronic myeloid leukaemia; FISH, fluorescent *in situ* hybridisation.

CML is characterised by leukocytosis with myeloid progenitors in the peripheral blood termed 'left shift'. The disease is driven by the Philadelphia chromosome *t(9;22)*, which produces the constitutive active fusion protein BCR-ABL1.

CML is classified into chronic phase, accelerated phase and blast phase, according to the blast cell count.

Therapy monitoring is performed using highly sensitive real-time PCR to detect BCR-ABL1.

REVISION QUESTIONS

1. What is the basis for the WHO 2016 AML classification?
2. Which aberrations and mutations are diagnostic for AML without a need for ≥20% blasts?
3. What is the genetic basis of CML?

Classification of ALL and MDS

The FAB classification for ALL is no longer in use. The European Group for the Immunological Characterization of Leukaemias (EGIL) classification is based on the immunophenotype according to maturation markers.

The EGIL subgroups are informative about prognosis and guide treatment, e.g. early allogeneic transplantation.

The WHO 2016 classification defines genetic ALL subtypes. There is a special focus on *BCR-ABL1*-positive and Philadelphia-like ALL, which require targeted treatment.

Immunophenotype as basis for EGIL classification: ALL subtypes include B and T cell lineages and different maturation stages

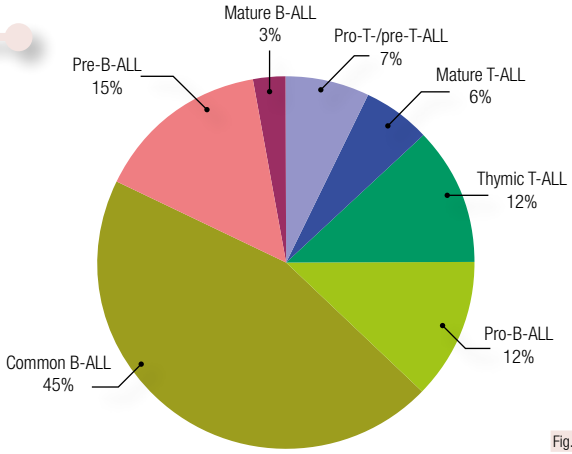


Fig. 1.13

ALL, Acute lymphoblastic leukaemia; EGIL, European Group for the Immunological Characterization of Leukaemias.

Clonal haematopoiesis and evolution to overt AML: There is a mutational continuum from pre-MDS to MDS and full-blown AML

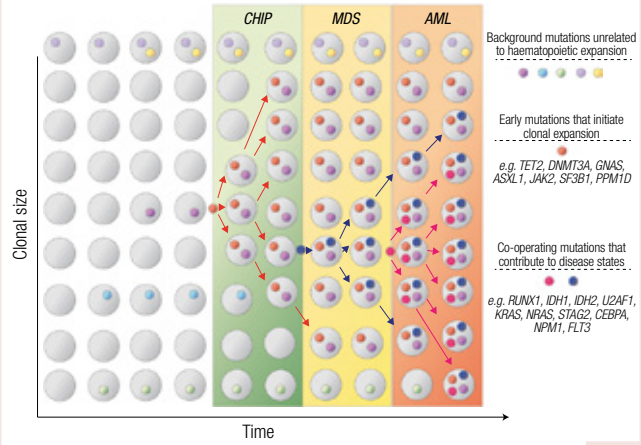


Fig. 1.14

AML, acute myeloid leukaemia; CHIP, clonal haematopoiesis of indeterminate potential; MDS, myelodysplastic syndrome.

MDS is a heterogeneous disease characterised by cytopaenia and single- or multilineage dysplasia.

Cytomorphologic diagnosis on bone marrow smears is gold standard. Certain genetic abnormalities such as *5q* deletion are associated with good prognosis and respond to targeted treatment.

Analysis of somatic mutations revealed the continuum from healthy individuals to MDS and AML in the pathogenesis of disease (Steensma et al. 2015).

Patients with cytopaenia and certain somatic mutations can be diagnosed with CCUS – clonal cytopaenia of undetermined significance.

Spliceosome mutations or co-mutations with *ASXL1*, *TET2* and *DNMT3A* in a patient with unexplained cytopaenia are highly predictive of a haematological malignancy.

The Revised International Prognostic Scoring System (IPSS-R) score is used for risk stratification: it defines risk groups according to karyotype, haemoglobin level and percentage of blast cells, platelet and neutrophil counts (Greenberg et al. 2012).

The IPSS-R score uses diagnostic parameters at initial presentation to define the patient's risk for progression and death

Subgroup	0	0.5	1	1.5	2	3	4
Cytogenetics	Very good	–	Good	–	Intermediate	Poor	Very poor
BM blast, %	≤2	–	>2–<5	–	5–10	>10	
Haemoglobin	≥10	–	8–<10	<8	–	–	–
Platelets	≥100	50–100	<50	–	–	–	–
Neutrophils	≥0.8	<0.8	–	–	–	–	–

Risk category: very low ≤1.5, low >1.5–3, intermediate >3–4.5, high >4.5–6, very high >6
BM, Bone marrow; IPSS-R, Revised International Prognostic Scoring System.

Fig. 1.15

REVISION QUESTIONS

1. What is the basis for the EGIL ALL classification?
2. What is the role of somatic mutations in a patient with cytopaenia?
3. Which parameters are needed for risk stratification of MDS?

Summary: Diagnosis and classification of leukaemias

- The diagnostic material for AML, ALL, CML and MDS is peripheral blood, bone marrow aspirate and histology
- Cytomorphology and cytochemistry are cheap and fast and can accurately diagnose leukaemias and MDS
- Flow cytometry is used to differentiate AML from ALL and defines ALL subgroups
- A LAIP can be used for MRD monitoring
- Cytogenetic evaluation by karyotyping and FISH is a diagnostic tool that also yields prognostic information
- The WHO 2016 classification of haematological neoplasms recognises the importance of genetic aberrations and somatic mutations
- The Philadelphia chromosome *t(9;22)* generates the fusion protein BCR-ABL1, which drives CML
- *BCR-ABL1*+ or Ph+ ALL is a specific ALL subgroup that needs specific targeted treatment
- Somatic mutations define clonal haematopoiesis. In a patient with cytopaenia, this results in the diagnosis of CCUS
- Specific mutations (spliceosome) or mutational patterns (co-mutations with *ASXL1*, *TET2*, *DNMT3A*) might become disease-defining or diagnostic in the future

Further Reading

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2 Acute myeloid leukaemia

Diagnosis and clinical presentation

Acute myeloid leukaemia (AML) diagnosis is based on patient history, physical examination, blood and marrow cytomorphology, multiparameter flow cytometry, and cytogenetic and molecular analyses.

A marrow and/or blood blast count of ≥20% is required to diagnose AML except for rare cases with disease-defining genetic alterations, such as *t(8;21)/RUNX1-RUNX1T1*.

On flow cytometry, blasts in AML typically express CD34, CD117, CD33, CD13, and human leukocyte antigen DR (HLA-DR), or may express monocytic markers. Aberrant lymphatic coexpression may be observed.

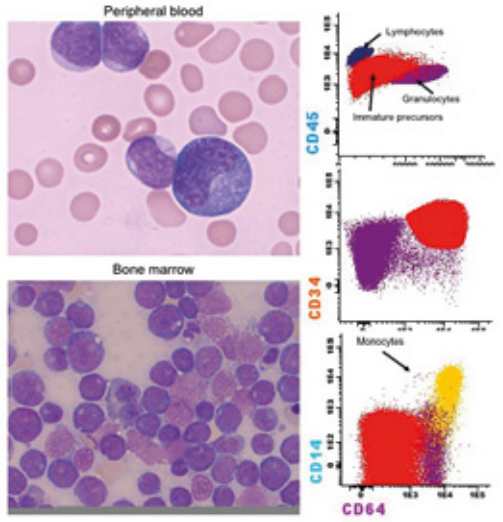


Fig. 2.1

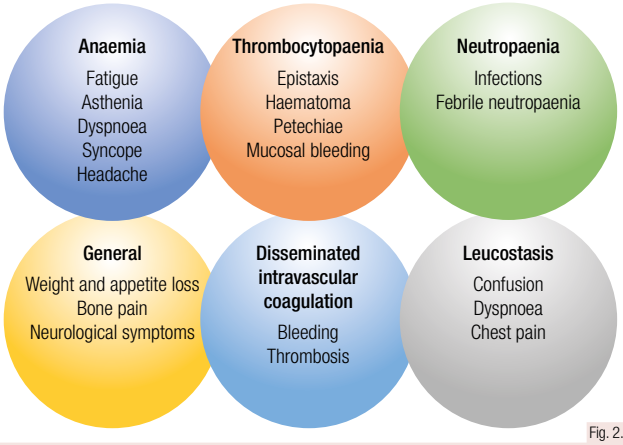


Fig. 2.2

AML symptoms are mostly non-specific and related to cytopaenias (e.g. infections due to neutropaenia), accompanying coagulation disorders or paraneoplastic syndromes.

Disseminated intravascular coagulation (DIC) may occur at diagnosis, thus screening for this complication is mandatory.

AML may show extramedullary manifestations (e.g. gingival hyperplasia or cutaneous infiltrations), or may present as solid tumours (chloroma) or meningeosis leukaemica.

AML at diagnosis is predominantly a disease of elderly patients. Median age at diagnosis is around 70 years. Younger patients are defined as <60 years in most studies.

The incidence of AML in younger patients is 2–3/100 000, whereas it increases to 13–15/100 000 in elderly patients.

In younger patients (A), survival has continuously improved in the last decades. In the elderly (B), complete response (CR) and overall survival (OS) after intensive chemotherapy (ChT) recently showed some improvement.

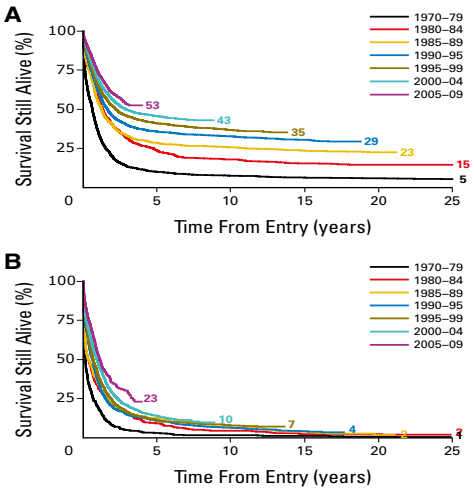


Fig. 2.3

REVISION QUESTIONS

1. On which analyses is initial diagnosis mainly based?
2. Which symptoms may be seen in AML patients?
3. What is the main age category for AML patients?

Disease classification and risk stratification

Substantial progress has been made using integrated genomic approaches, with a rapidly increasing number of genetically defined sub-entities (World Health Organization [WHO] classification).

The most frequent WHO categories are AML with recurrent genetic abnormalities, therapy-related myeloid neoplasms and AML with myelodysplasia-related changes.

In 2016, the WHO added new provisional subtypes (AML with *BCR-ABL1*; AML with mutated *RUNX1*) and a heterogeneous group of myeloid neoplasia with germline mutations.

Acute myeloid leukaemia (AML) and related neoplasms
AML with recurrent genetic abnormalities
AML with *t(8;21)(q22;q22.1);RUNX1-RUNX1T1*
AML with *inv(16)(p13.1q22)* or *t(16;16)(p13.1;q22);CBFB-MYH11*
APL with *PML-RARA*
AML with *t(9;11)(p21.3;q23.3);MLLT3-KMT2A*
AML with *t(6;9)(p23;q34.1);DEK-NUP214*
AML with *inv(3)(q21.3q26.2)* or *t(3;3)(q21.3;q26.2);GATA2, MECOM*
AML (megakaryoblastic) with *t(1;22)(p13.3;q13.3);RBM15-MKL1*
Provisional entity: AML with BCR-ABL1
AML with mutated *NPM1*
AML with biallelic mutations of *CEBPA*
Provisional entity: AML with mutated RUNX1
AML with myelodysplasia-related changes
Therapy-related myeloid neoplasms
AML, NOS
AML with minimal differentiation
AML without maturation
AML with maturation
Acute myelomonocytic leukaemia
Acute monoblastic/monocytic leukaemia
Pure erythroid leukaemia
Acute megakaryoblastic leukaemia
Acute basophilic leukaemia
Acute panmyelosis with myelofibrosis
Myeloid sarcoma

APL, Acute promyelocytic leukaemia; NOS, not otherwise specified. Fig. 2.4

Genetic and molecular analysis are highly relevant for risk stratification. Karyotype (KT) is the single most important prognostic factor in AML patients.

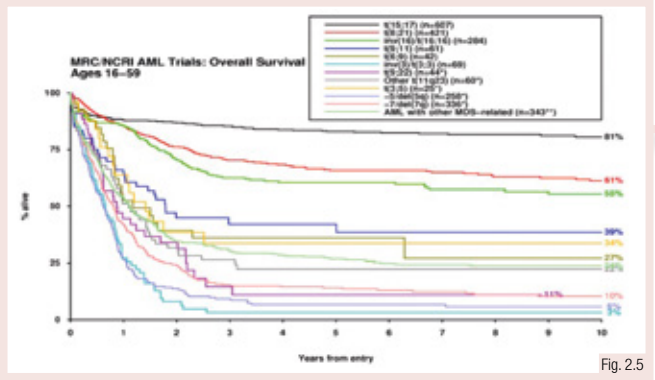


Fig. 2.5

AML, Acute myeloid leukaemia; MRC, Medical Research Council; NCRI, National Cancer Research Institute.

10-year survival ranges from >80% to <10% depending on the KT. Patients with a normal KT are prognostically subclassified by molecular analysis (e.g. *NPM1* mutations, *FLT3* ITD [internal tandem duplications]).

The European LeukemiaNet (ELN) distinguishes 3 risk groups (favourable, intermediate, adverse) by cytogenetic and molecular profiles; these determine the consolidation strategy.

Favourable risk AML patients are treated with consolidation ChT or autologous stem cell transplantation (ASCT), while patients with intermediate and adverse risk are candidates for allogeneic SCT (alloSCT).

Minimal residual disease (MRD) assessment by molecular techniques and flow cytometry after induction and alloSCT are becoming increasingly relevant for therapy decisions.

Examples of molecular MRD markers are *NPM1* mutations or reciprocal rearrangements such as *CBFB-MYH11* in AML with *inv(16)* or *PML-RARA* in acute promyelocytic leukaemia (APL).

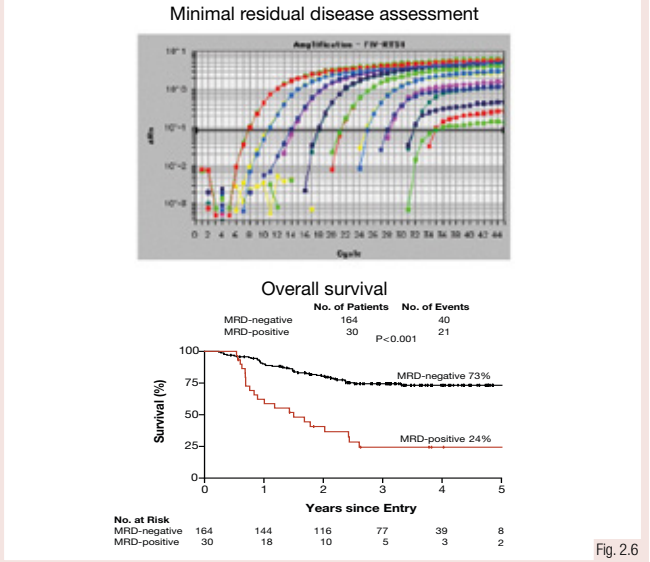


Fig. 2.6

MRD, Minimal residual disease.

REVISION QUESTIONS

1. What are the most frequent AML categories in the 2016 WHO classification?
2. Which are the most important tools for risk assessment in AML patients?
3. How can risk assessment affect treatment decisions in AML patients?

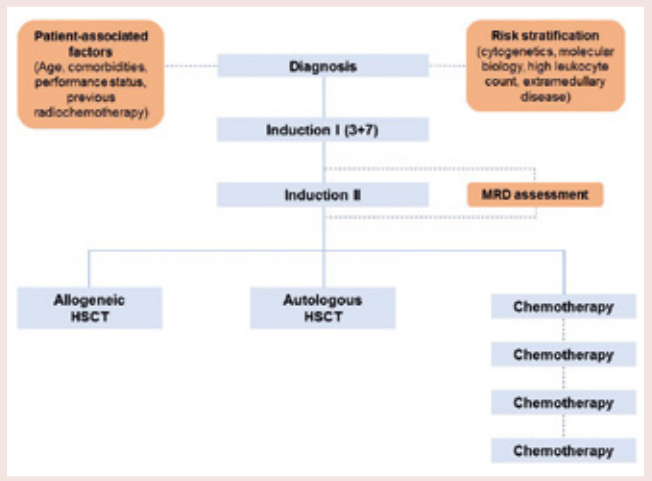
First-line treatment

Most induction schemes present 1–2 induction cycles followed by consolidation with 1 or several ChT cycles, ASCT or alloSCT.

The standard induction regimen is referred to as the '3+7' scheme: a continuous 7-day cytarabine infusion combined with 3 days of anthracyclines.

Standard doses of cytarabine are 100–200 mg/m^2. Daunorubicin should be administered at no less than 60 mg/m^2, corresponding to idarubicin 10–12 mg/m^2.

Patients with a favourable ELN risk profile often receive standard post-remission/consolidation therapies with 2-4 cycles of intermediate- or high-dose cytarabine (HD-Ara-C).



HSCT, Haematopoietic stem cell transplantation; MRD, minimal residual disease. Fig. 2.7

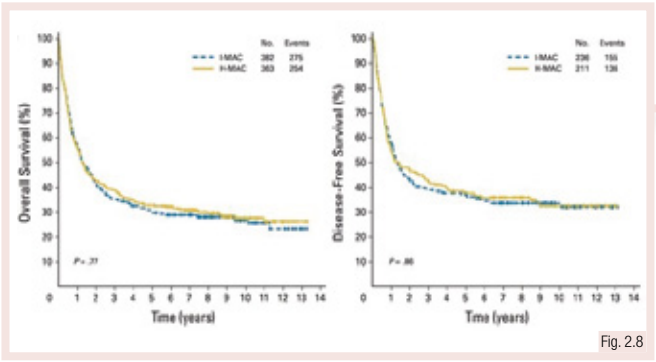


Fig. 2.8

H-MAC, High-dose myeloablative conditioning; I-MAC, intermediate-dose myeloablative conditioning.

There is growing evidence that intermediate-dose cytarabine (ID-Ara-C) has a sufficient anti-leukaemic effect. The ideal number of post-remission cycles is unknown.

ASCT with BuCy (busulfan and cyclophosphamide) conditioning appears to be superior to conventional consolidation therapy in favourable and intermediate ELN risk groups, especially if MRD-negative.

APL shows excellent outcomes. All-trans retinoic acid (ATRA) combined with arsenic trioxide (ATO) is a frequently used curative approach.

ATRA combined with ATO is non-inferior to ATRA plus cytotoxic ChT, and less toxic in low- and intermediate-risk APL patients.

Key prognostic factors in APL are rapid diagnosis and start of ATRA (to prevent early mortality/bleeding), and early treatment of ATRA-associated differentiation syndrome.

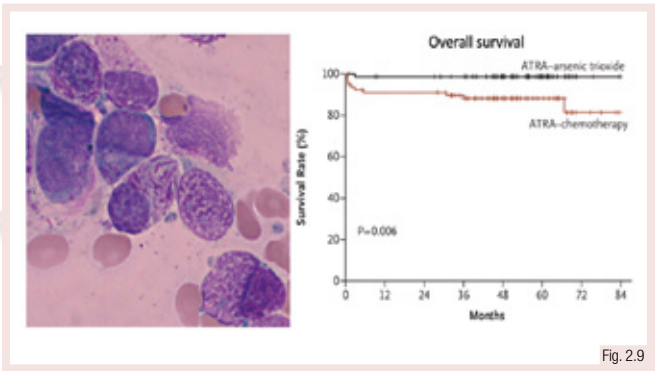


Fig. 2.9

ATRA, All-trans retinoic acid.

REVISION QUESTIONS

1. What is the most commonly used induction scheme?
2. Is ID-Ara-C (as monotherapy) sufficient for AML treatment?
3. What is the currently applied ChT-free regimen for patients with APL?

Haematopoietic stem cell transplantation and treatment of relapsed AML

AlloSCT is the strongest anti-leukaemic therapy in AML, due to the cytoreductive effect of conditioning and the immunological graft-versus-leukaemia (GvL) effect.

The anti-leukaemic effect is often outweighed by increased transplant-related mortality (TRM), which depends on factors such as age, HLA compatibility and comorbidities.

AlloSCT is indicated in intermediate and adverse risk patients, but remains an individual decision based on disease-, patient-, and donor-related risk factors.

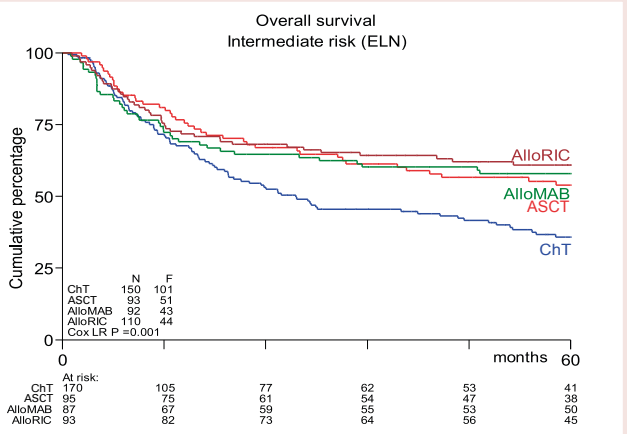
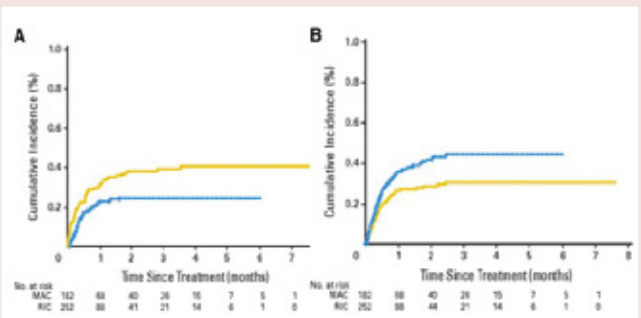


Fig. 2.10

AlloMAB, Myeloablative allogeneic haematopoietic stem cell transplantation; AlloRIC, reduced intensity conditioning allogeneic haematopoietic stem cell transplantation; ASCT, autologous stem cell transplantation; ChT, chemotherapy; ELN, European LeukemiaNet; LR, logistic regression.



(A) Cumulative incidence of non-relapse mortality in patients ≥50 years of age receiving RIC (blue line) or MAC (gold line). Patients at risk treated with MAC or RIC at the different time intervals are given.

(B) Cumulative incidence of relapse (RIC –blue line; MAC – gold line).

Fig. 2.11

MAC, Myeloablative conditioning; RIC, reduced intensity conditioning.

Myeloablative conditioning (MAC) reduces relapse, but increases toxicity. Reduced intensity conditioning (RIC) results in higher relapse risk, but lower toxicity.

Increasing donor registries, alternative donor sources and the advent of RIC have substantially increased the number of alloSCTs performed in AML.

AML is the most common indication for alloSCT, usually from HLA-matched unrelated or related donors. Alternative options are haplo-identical HSCT or cord blood transplantation.

The prognosis for patients with relapsed AML remains poor. AlloSCT is curative for a minority, but many patients fail to achieve a second CR after reinduction.

No standard rescue scheme exists. Applied regimens are often combinations of HD-Ara-C, anthracyclines and purine analogues, e.g. FLAG-Ida (FLudarabine, cytArabine, G-CSF-IDArubicin), CLAG-Ida (CLAdribine, G-CSF-IDArubicin) or HAM (High-dose cytosine Arabinoside and Mitoxantrone).

Relapse after alloSCT is prognostically adverse. A second HSCT, demethylating agents and/or donor lymphocyte infusion (DLI) are options. Duration of first CR is a prognostic factor for a second HSCT.

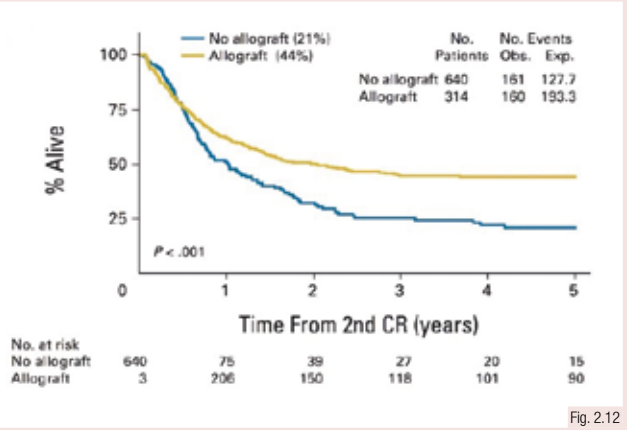


Fig. 2.12

CR, Complete response.

REVISION QUESTIONS

1. What are the main anti-leukaemic effects of alloSCT?
2. Which are the potential alternative donors/stem cell sources for patients in need of an alloSCT without suitable HLA-matched unrelated or related donor?
3. What is the main scope of therapy in relapsed AML patients?

Treatment of elderly patients and experimental AML therapies

Intensive chemotherapy (IChT) is considered the best option for fit elderly patients. It prolongs OS and reduces hospitalisation duration.

AlloSCT can be evaluated in fit elderly patients, especially with adverse prognostic factors. These patients will mostly undergo RIC protocols.

Selection of treatment options in fit elderly AML patients is challenging and should be based on comorbidities, geriatric scores and disease-specific factors.

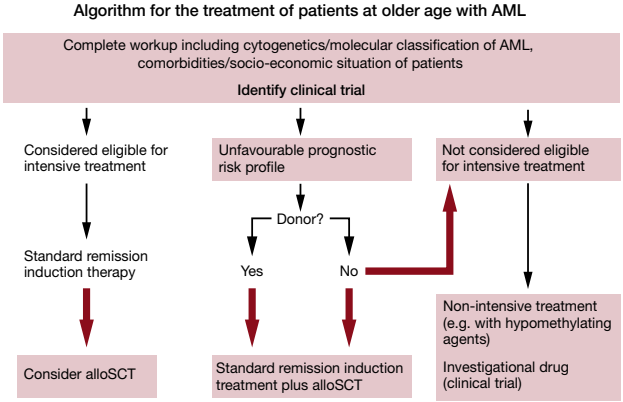


Fig. 2.13

AlloSCT, Allogeneic stem cell transplantation; AML, acute myeloid leukaemia.

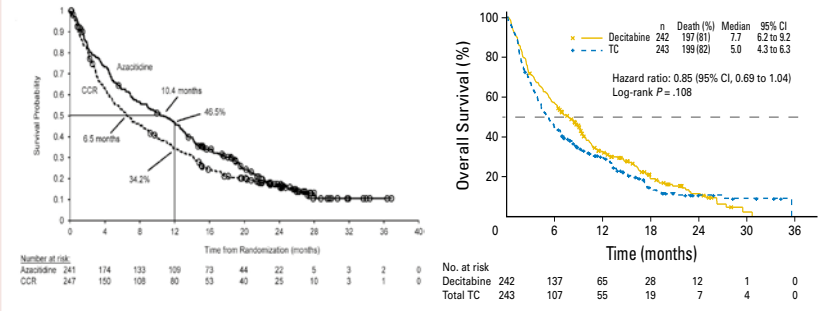


Fig. 2.14

CI, Confidence interval; CCR, conventional care regimen; TC, treatment of choice.

Although IChT is considered the best treatment option, many elderly AML patients are too frail for this strategy and are alternatively treated with low intensity regimens.

Widely applied options for unfit elderly patients are demethylating agents (azacitidine, decitabine) or low-dose cytarabine (LD-Ara-C). So far, there is no standard treatment for this patient group.

Supportive therapy procedures (e.g. immediate anti-infective therapy in the case of febrile neutropaenia) are crucial in the treatment of all AML patients.

Drugs tested in studies may either interfere with signalling pathways (e.g. tyrosine kinase inhibitors [TKIs]) or be epigenetic modifiers or cell-cycle or nuclear export inhibitors. Isocitrate dehydrogenase (IDH) inhibitors are under investigation.

Addition of FLT3 inhibitors (e.g. midostaurin) to induction, consolidation and maintenance therapy in *FLT3*-mutated AML has recently shown promising results.

Antibody therapies in AML target surface proteins such as CD33 or CD123. Bispecific antibodies and also chimeric antigen receptor (CAR)-T cells are currently being evaluated in clinical trials.

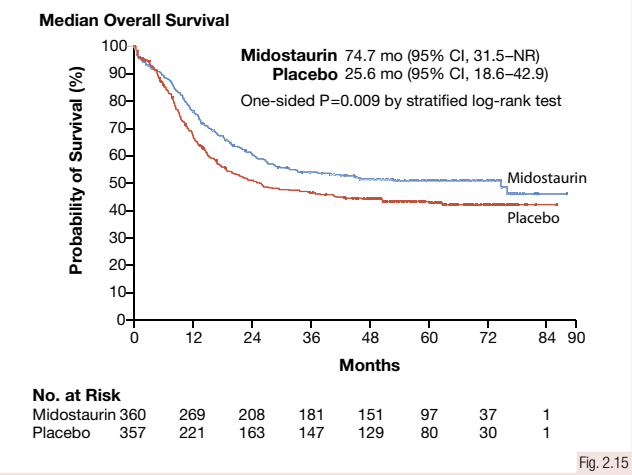


Fig. 2.15

CI, Confidence interval; NR, not reached.

REVISION QUESTIONS

1. What is the standard therapy for fit elderly patients?
2. What are the most widely applied treatment schemes in unfit elderly patients?
3. What are the promising new therapeutic developments?

Summary: Acute myeloid leukaemia

- Risk stratification according to the ELN criteria, including cytogenetics and molecular mutation profiles, should be assessed in all patients as it guides the optimal choice of post-remission therapy modalities
- Measurement of MRD load is becoming increasingly important for therapeutic decision making during follow-up
- The standard AML induction treatment consists of 7 days of cytarabine and 3 days of anthracyclines ('3+7')
- The most frequent post-remission therapies are additional cycles of ChT, ASCT or alloSCT, depending on the risk assessment
- AlloSCT provides the strongest anti-leukaemic effect, but is associated with a substantial risk of TRM often outweighing its benefit
- The increasing availability of volunteer donors, alternative donor sources including haploidentical transplantation and RIC have substantially increased the access to alloSCT
- AML may occur at any age but is typically a disease of elderly patients
- OS in younger patients has substantially improved during the last decades
- IChT is considered the best treatment for fit, elderly patients with AML; however, selecting appropriate treatment in elderly patients is very challenging
- In unfit, elderly patients, the most frequently used palliative treatment options are demethylating agents (azacitidine, decitabine) and LD-Ara-C
- Supportive therapy is of utmost importance for AML patients of all age groups
- Outcomes of patients with APL are excellent in case of early treatment with ATRA

Further Reading

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3 Acute lymphoblastic leukaemia

Definition and diagnosis

Acute lymphoblastic leukaemia (ALL) is a malignant disease of precursor cells of the lymphatic system. It is defined by more than 25% infiltration of the bone marrow with lymphatic blast cells. ALL can involve other lymphatic tissues and non-lymphatic organs.

Physiological B and T cell lymphopoiesis is disrupted by the malignant event, and immature blasts accumulate.

ALL is characterised by small- to medium-sized leukaemic blasts. The cytoplasmic rim tends to be basophilic.

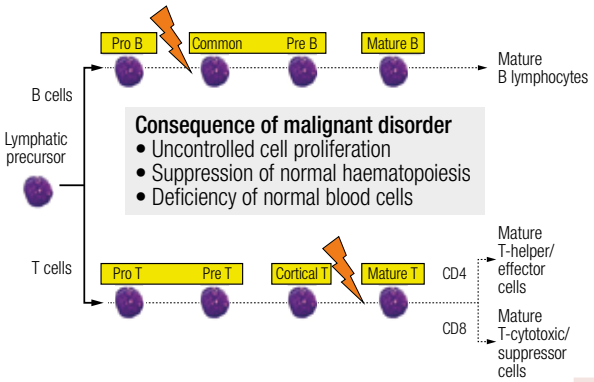

Fig. 3.1

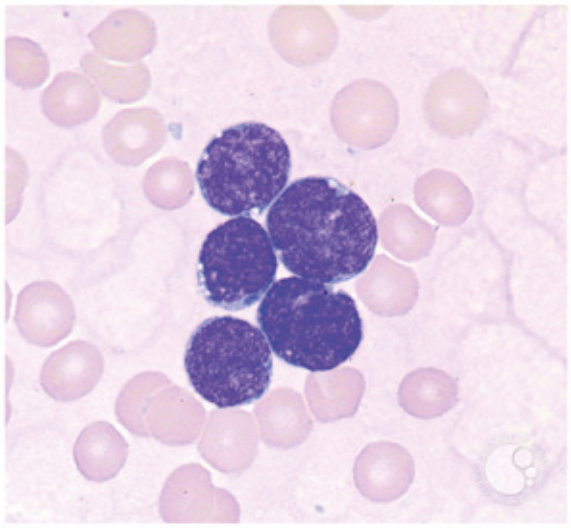
Fig. 3.2

Essential diagnostic procedures in ALL

Confirmation of diagnosis:

- Cytomorphology, immunophenotyping

Identification of risk factors:

- Cytogenetics / molecular genetics

Identification of therapy targets:

- CD19, CD20, CD22, CD33, CD52
- *BCR-ABL*
- Establishment of MRD (minimal residual disease) assay
- Biobanking

Immunophenotype is subdivided into T and B cells. Seventy-five percent of cases are B-precursor ALL. Each phenotype is associated with distinct cytogenetic and molecular aberrations and clinical features.

The most frequent cytogenetic aberration is the translocation *t(9;22)* with the corresponding fusion gene *BCR-ABL*, which occurs in B-precursor ALL only, with an overall incidence of 25%–50%, depending on age.

Cytology	Immunophenotype		Frequency	Cytogenetics	Molecular genetics
L1/2	T-lineage	TdT+, cyCD3+, CD7+	24%	*t(10;14)*	*HOX11-TCRa/d* *LMO1/2-TCRa/d* *TAL1-TCRa/d*
	Early	CD2-, sCD3-, CD1a-	6%	*t(11;14)*	
	Thymic	sCD3±, CD1a+	12%	*t(1;14)*	
	Mature	sCD3+, CD1a-	6%	p15,16 ab.	
L1/2	B-lineage	HLA-DR+,TdT+,CD19+	76%		
	Pro	CD10-	11%	*t(4;11)*	*ALL1(MLL)-AF4*
	Common	CD10+	49%	*t(9;22)*	*BCR-ABL*
	Pre	CD10±, cylgM+	12%	*t(9;22), t(1;19)*	*BCR-ABL,E2A-PBX1*
L3	Mature	TdT±, CD10±, slgM+	4%	*t(8;14)*	*cMYC-IgH*

HLA-DR+, Human leukocyte antigen-DR-positive.

Fig. 3.3

The World Health Organization (WHO) 2016 classification groups lymphoblastic lymphoma together with lymphoblastic leukaemia; they are treated similarly.

REVISION QUESTIONS

1. What is the most frequent genetic aberration in ALL?
2. Which method is required to confirm morphological diagnosis?
3. Beyond confirmation of diagnosis, what is the goal of diagnostic characterisation?

Prognostic factors

ALL is not a uniform disease but shows differences in outcome, defined by prognostic factors ranging from 30%–40% for high-risk B-precursor and T cell ALL (T-ALL) to 60%–70% for standard-risk B cell ALL (B-ALL) and T-ALL, and 70%–80% for mature B-ALL. The relevance of prognostic factors depends on the treatment protocol.

Clinical and genetic prognostic factors can be identified at diagnosis, and potential criteria are different for B- and T-precursor ALL.

Age is a highly relevant prognostic factor in all subgroups of ALL. With increasing age, the incidence of poor prognostic factors increases and therapy is less well tolerated. Patients are at increasing risk of early mortality, mortality in remission and relapse.

	All	B-Precursor	T-ALL
High WBC count		**>30 000/µL** (20-50)	>100 000/µL
Subtype		**Pro B**	**Early T** **Mature T** ETP phenotype
Cyto/mol genetics	Complex karyotype Low hypodiploid Near tetraploid *TP53* mutations	***t(9;22)/BCR-ABL*** ***t(4;11)/ALL1-AF4*** *t(1;19)/E2A-PBX* *IZKF1*-deletion *BCR-ABL*-like	*Notch1* wildtype *N/K-RAS* mutated *PTEN* mutated

Fig. 3.4

ETP, Early T cell precursor; *PTEN*, phosphatase and tensin homologue; T-ALL, T cell acute lymphoblastic leukaemia; WBC, white blood cell.

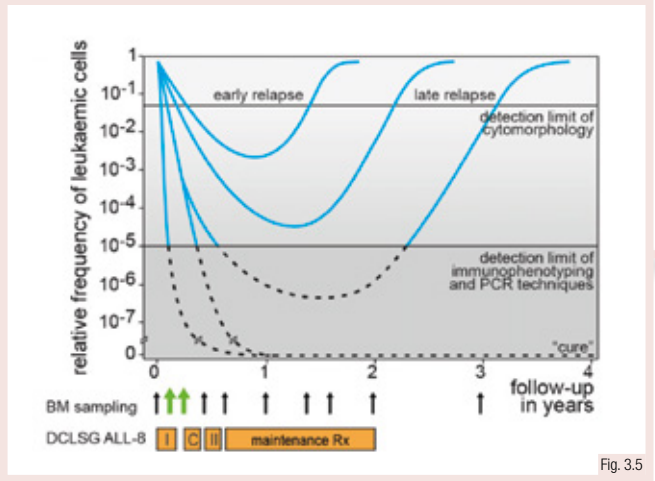

Fig. 3.5

BM, Bone marrow; DCLSG, Dutch Childhood Leukemia Study Group; PCR, polymerase chain reaction; Rx, treatment.

Response to treatment is essential for prognosis. Prognosis is poor in patients without complete response (CR) after induction and/or with persistent MRD.

MRD is defined as persistence of leukaemic blasts below the detection level of microscopy (5%).

Definition of CR in bone marrow
- Complete haematological remission: <5% blasts
- MRD: 1%-0.01% blasts
- Complete molecular remission: <0.01% blasts

Patients who do not achieve a negative MRD status (MRD failure) or show newly detected MRD during treatment (MRD relapse) have a high risk for relapse despite continued treatment.

Prognostic factors relevant for treatment decisions:
- Age-adapted therapy
- Intensified therapy with stem cell transplantation (SCT)
- Utilisation of targeted and experimental drugs

Probability of continuous complete remission in GMALL trials (including SCT)

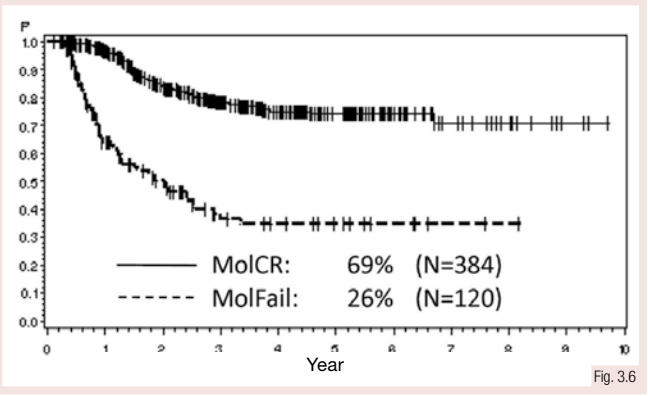

Fig. 3.6

GMALL, German Multicenter Study Group for Adult Acute Lymphoblastic Leukemia; MolCR, molecular complete remission; MolFail, molecular failure; SCT, stem cell transplantation.

REVISION QUESTIONS

1. What is the definition of MRD?
2. Which level of white blood cell count at diagnosis is associated with a poor prognosis?
3. For which treatment decisions are prognostic factors relevant?

Clinical presentation and supportive care

ALL is often associated with a rapid deterioration of general condition. Symptoms are usually unspecific: fatigue due to anaemia, bleeding due to thrombocytopaenia, infections due to granulocytopaenia. Bone pain may also occur. Additional symptoms may occur, due to infiltration of organs.

T-ALL patients frequently show mediastinal tumours, whereas patients with mature B-ALL show other organ involvement.

Mediastinal tumours can lead to emergency situations with dyspnoea and upper venous compression.

	T-Lineage	B-Precursor	Mature B
Bleeding	28%	28%	30%
Infections	22%	29%	37%
Enlarged lymph nodes	77%	40%	61%
Hepatomegaly	45%	41%	56%
Splenomegaly	55%	43%	47%
Mediastinal tumour	62%	1%	5%
CNS involvement	8%	3%	13%
Other organ involvement	15%	4%	32%

CNS, Central nervous system.

Fig. 3.7

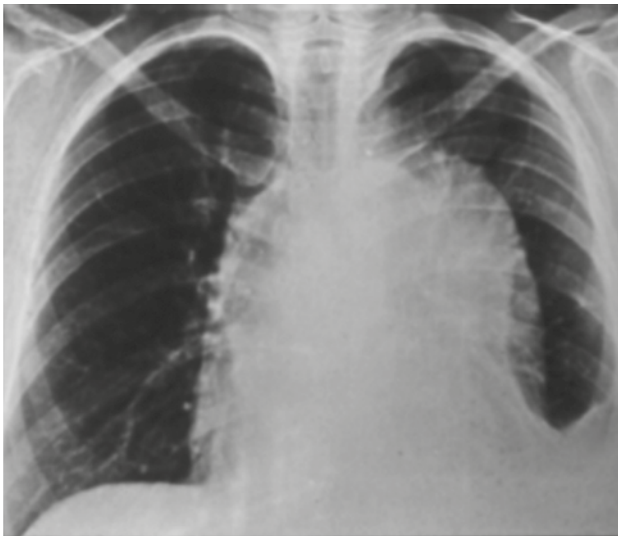

Fig. 3.8

Most ALL patients show cytopaenias of different lineages and immature lymphatic blasts in the peripheral blood. Absence of blast cells and normal blood counts do not exclude ALL.

Supportive therapy should be started at first diagnosis, including hydration, tumour lysis prophylaxis and infection prophylaxis.

Initial workup in ALL includes: clinical assessment and anamnesis, comorbidity scoring, laboratory analysis including CSF examination, microbial assessments, imaging procedures for extramedullary involvement, cardiac function testing, HLA (human leukocyte antigen) typing for potential bone marrow donors.

To diagnose ALL, a bone marrow aspirate is necessary. Sufficient material for different diagnostic procedures should be obtained.

Analysis of cerebrospinal fluid (CSF) is an essential part of the initial workup. In ALL, it should be associated with a first intrathecal prophylaxis, usually consisting of methotrexate (MTX) or a combination of MTX, cytarabine and steroids.

Advice for fertility preservation should be offered in all applicable cases.

		Patients (%)
White blood cell count (× 10^6/L)	<5000	27
	5000–10 000	14
	10 000–50 000	31
	50 000–100 000	12
	>100 000	16
Blasts in peripheral blood	Present	92
	Not present	8
Blasts in bone marrow	<50%	3
	51–90%	51
	>90%	46
Neutrophils (× 10^6/L)	<500	23
	500–1000	14
	1000–1500	9
	>1500	54
Platelets (× 10^6/L)	<25 000	30
	25 000–50 000	22
	50 000–150 000	33
	>150 000	15
Haemoglobin (g/dL)	<6	8
	6–8	20
	8–10	27
	10–12	24
	>12	21

Fig. 3.9

REVISION QUESTIONS

1. What is the incidence of subtotal bone marrow infiltration in ALL?
2. What is a typical clinical presentation of T-ALL?
3. What is the essential diagnostic procedure in ALL?

Treatment of newly diagnosed ALL

Most successful treatment protocols are based on paediatric treatment strategies. Protocols are adapted for adult patients in order to improve tolerability. Mature B-ALL is treated like Burkitt's lymphoma.

ALL outcome is most favourable in children and young adults. In older patients, the incidence of early mortality increases significantly.

Essential drugs for ALL treatment are steroids, vincristine, asparaginase, high-dose MTX and a low-dose continuation therapy with mercaptopurine and MTX.

	Number of trials	Number of patients	CR	ED	OS/LFS
Children	>20	>10 000	>95%	<3%	>80%
AYAs 18–40 years	6	513	>90%	<5%	72% (2y)
Adults 18–55/65 years	15	7262	84%	7%	35%-60%
Older adults >55–65 years	5	187	58%	16%	22%-50%
Relapsed patients	4	1494	~40%		6%-22%

AYA, Adolescent and young adult; CR, complete response; ED, early death; LFS, leukaemia-free survival; OS, overall survival.

Fig. 3.10

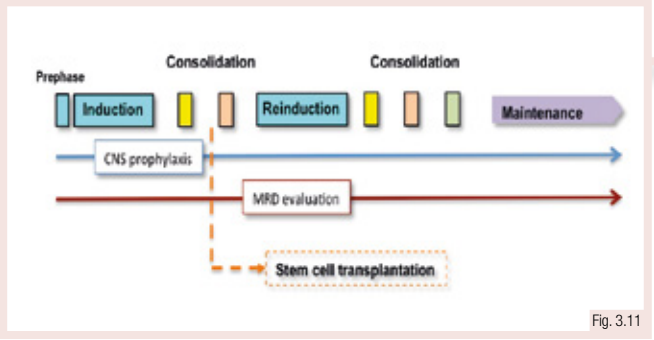

Fig. 3.11

CNS, Central nervous system; MRD, minimal residual disease.

ALL treatment consists of several cycles of combination therapies accompanied by intrathecal therapy for central nervous system (CNS) relapse prophylaxis.

Treatment compliance is important and prognostically relevant in ALL therapy. Long treatment-free intervals should be avoided, but patients need to regenerate peripheral blood counts before the next cycle.

CNS relapse prophylaxis is essential in ALL. It consists of intrathecal therapy, systemic high-dose therapy (MTX, cytarabine) and, in several protocols, CNS irradiation.

Targeted therapies are added to chemotherapy (ChT) if possible. The most important approaches are: imatinib in *BCR-ABL*-positive ALL and rituximab in CD20-positive ALL.

SCT is an essential part of ALL management. Outcomes are similar for matched sibling and matched unrelated donors. Mortality increases with age.

Most study groups establish a risk-based indication for SCT: high-risk prognostic factors, persistent MRD and any situation after relapse.

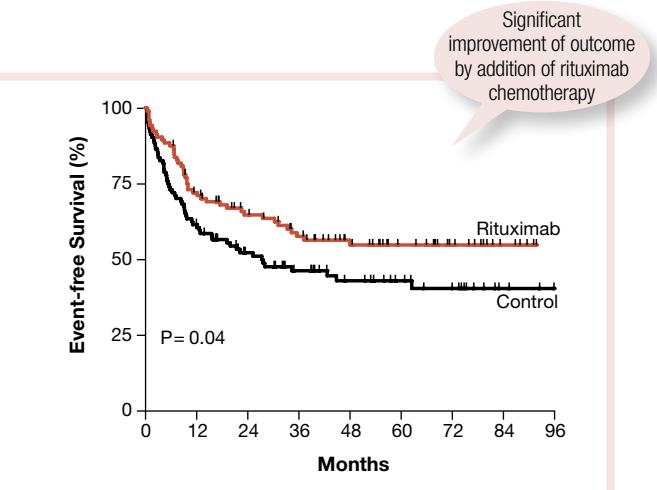

Fig. 3.12

REVISION QUESTIONS

1. Which essential elements are part of ALL ChT?
2. What is the survival trend in young adults with ALL?
3. Name an indication for SCT in ALL.

Treatment of relapse and aftercare

Relapse in ALL is an emergency. For optimal management, extramedullary involvement, subtype, potential target structures, previous remission duration and prior treatment must be considered.

ALL at relapse has a poor prognosis with remission rates of only 40% for first salvage and a median survival of 6 months.

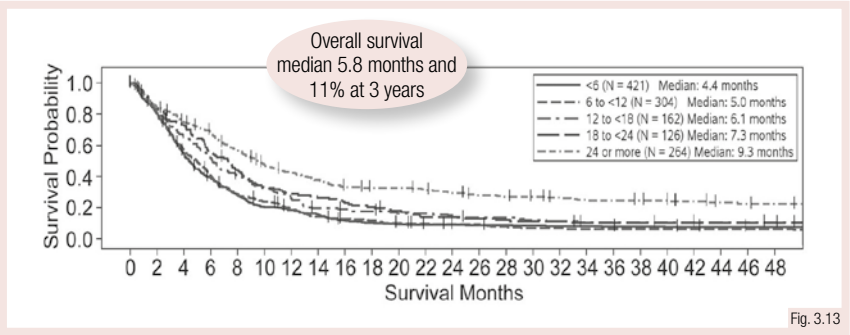

Fig. 3.13

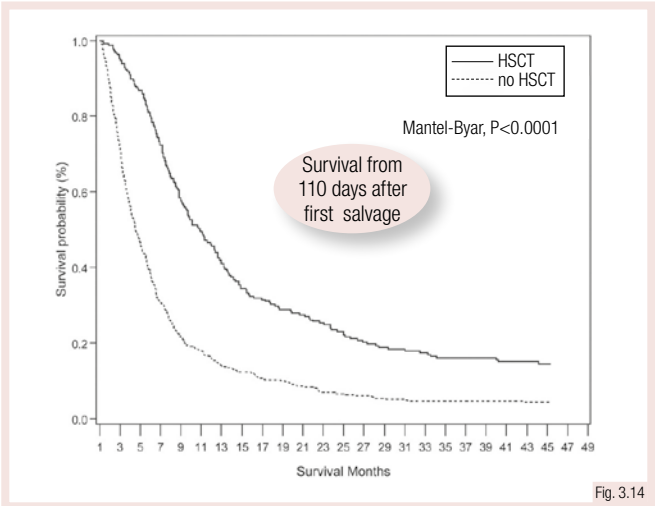

Fig. 3.14

HSCT, Haematopoietic stem cell transplantation.

The goal of relapse therapy is to achieve a CR including MRD response, and to offer an SCT. Continuous MRD assessment gives the opportunity to detect upcoming relapse and treat earlier.

The incidence of SCT in CR after first salvage was 28% in one international trial. SCT in CR offers a chance of cure in relapsed ALL.

Early relapses during ongoing treatment and refractory relapses show profound ChT resistance. Alternative, targeted therapies should be considered.

Due to low incidence of molecular targets in ALL, immunotherapies are the most important new compounds under development for ALL.

In randomised trials, conjugated antibodies to CD22 such as inotuzumab or bispecific antibodies to CD19 such as blinatumomab showed superior CR rates and survival compared with standard of care.

Immunotherapies in ALL include antibodies and genetically modified chimeric antigen receptor T cells (CAR-T cells). CD19 and CD22 are the preferred surface target.

Increasing cure rates raise the focus on patient aftercare. Patients should be screened for long-term effects such as immune dysfunction, neuropsychological disorders, endocrine disorders or aseptic bone necrosis.

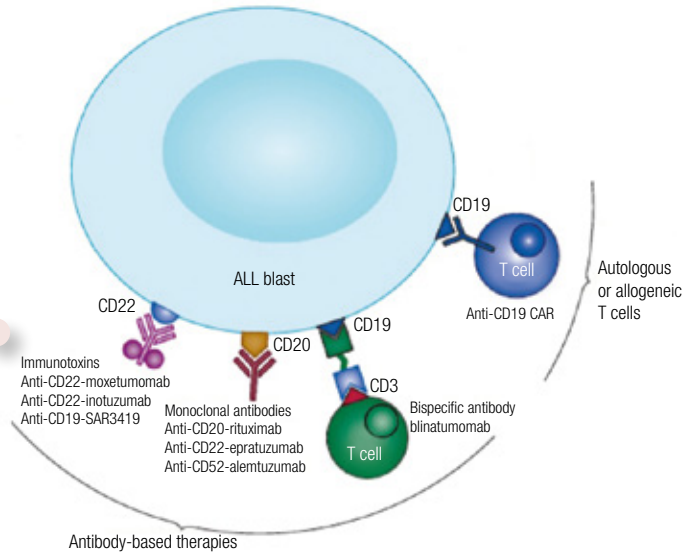

Fig. 3.15

ALL, Acute lymphoblastic leukaemia; CAR, chimeric antigen receptor.

REVISION QUESTIONS

1. What response rate can be expected in relapsed ALL?
2. Which group of compounds is most promising for relapsed ALL?
3. Which long-term effect in ALL patients may lead to an artificial hip?

Summary: Acute lymphoblastic leukaemia

- Diagnosis of ALL is based on morphology, immunophenotyping, cyto- and molecular genetics
- Intensified ChT based on paediatric protocols is possible in adults and leads to improved survival
- Treatment compliance is essential; the most important drugs are steroids, vincristine, asparaginase, high-dose MTX and maintenance therapy with mercaptopurine/MTX
- MRD assessment should be performed in all patients since MRD persistence or recurrence is the most relevant poor prognostic factor
- Targeted treatment with tyrosine kinase inhibitors in *BCR-ABL*-positive ALL or rituximab in CD20-positive ALL has improved prognosis
- Patients with high-risk features are candidates for an SCT, depending on protocol
- Relapsed patients have a poor prognosis, but new immunotherapies yield superior response and survival rates compared with standard ChT
- ALL should be treated in specialised centres
- With improving outcomes, patients should be screened for long-term effects of treatment

Further Reading

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4 Chronic myeloid leukaemia

Epidemiology and pathology

In Europe, the raw and age-standardised incidence of chronic myeloid leukaemia (CML) is around 1/100 000 persons/year, and this number is stable. The incidence of CML increases with age.

Due to treatment-based survival improvement and the increasing life expectancy in the general population, the prevalence of CML will almost double in the next 30 years.

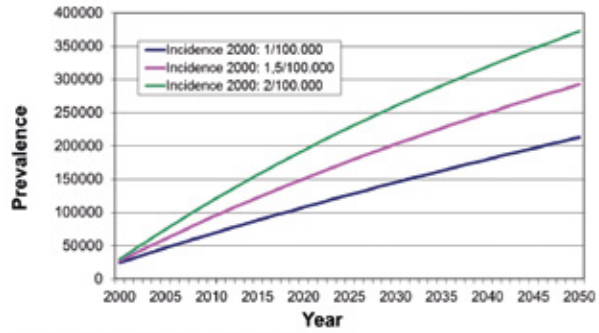

Fig. 4.1

CML is more common in males than in females, with a male-to-female ratio varying between 1.2:1 and 1.7:1. The median age at diagnosis is around 60 years.

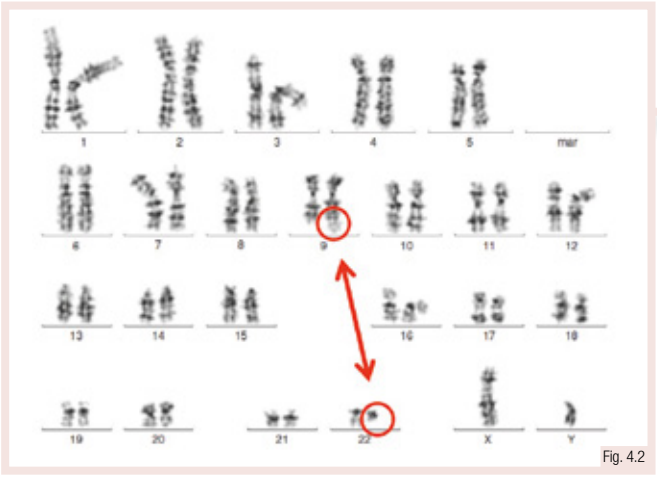
Fig. 4.2

CML is characterised by a translocation between the long arms of chromosomes 9 and 22 *t(9;22)(q34;q11)*, the derivative chromosome 22 being the Philadelphia (Ph) chromosome.

The reciprocal translocation *t(9;22)* leads to a fusion of the tyrosine kinase gene *ABL1* (Abelson) on chromosome 9 with the *BCR* (breakpoint cluster) gene on chromosome 22.

Additional major [+8, +der(22)*t(9;22)*, i(17), +19] or minor (–Y, +21, +17, –7, and –17) route cytogenetic aberrations (ACAs [additional chromosomal abnormalities]) can occur, the former with a worse prognostic significance.

The variable breakpoints of the *BCR* (intron 13 or 14) gene fused to the 140 kb region of the *ABL1* genome result in two different BCR-ABL1 transcripts (e13a2 or e14a2).

Both transcripts lead to the expression of a 210 kDa BCR-ABL1 protein, which has a pathogenic constitutive kinase activity, an important target for selective inhibition.

The BCR-ABL1 protein gives rise to aberrant activation of cell signalling pathways (e.g. JAK/STAT, PI3K/AKT, RAS/MEK) and a cellular environment that supports leukaemia.

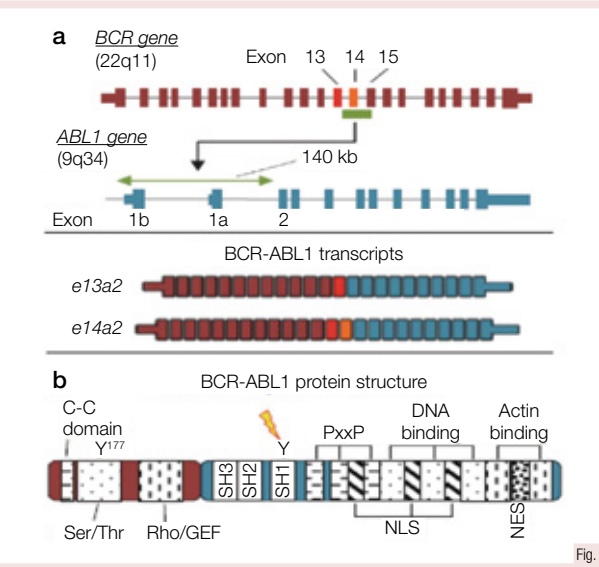

Fig. 4.3

REVISION QUESTIONS

1. What is the prevalence of CML?
2. What is the characteristic genetic background of CML?
3. What is the role of the pathogenetic BCR-ABL1 oncoprotein?

Clinical presentation, phases of CML and prognostic scores at diagnosis

The main symptoms and signs at presentation are fatigue, anaemia, splenomegaly and abdominal discomfort.

Approximately 50% of patients, however, are asymptomatic, being diagnosed after unrelated medical examination.

CML has to be suspected upon leukocytosis with precursors (promyelocytes, metamyelocytes, myelocytes), eosinophilia and basophilia in the peripheral blood.

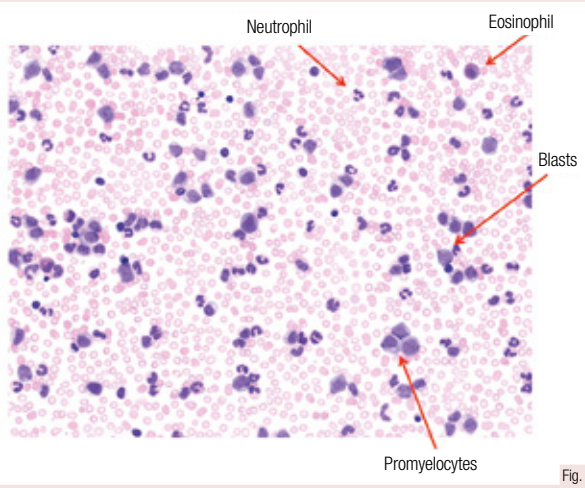

Fig. 4.4

Phases of CML		
Chronic phase approx. 90%	Advanced phases approx. 10%	
	Accelerated phase	Blast crisis
Median survival without treatment 5–6 years	Median survival without treatment 6–9 months	Median survival without treatment 3–6 months

Fig. 4.5

CML, Chronic myeloid leukaemia.

There are 3 phases of CML: a chronic (CP) and accelerated phase (AP) as well as blast crisis (BC). CML is usually diagnosed in CP.

Survival clearly decreases with progression of the disease in AP.

Criteria for the definition of AP and BC according to World Health Organization (WHO) or European LeukemiaNet (ELN) depend on the number of blast cells, basophils, platelets, ACAs in Ph+ cells and extramedullary involvement.

The Sokal, Hasford, EUTOS (European Treatment and Outcome Study) and EUTOS long-term survival (ELTS) prognostic scores are based on patient characteristics (age, spleen size, platelet and blast count, eosinophils, basophils) at diagnosis.

The scores define a low-, intermediate- or high-risk situation for treatment outcome, and have been developed based on cohorts of patients with CML in CP receiving the standard care of treatment during the given time period.

The ELTS score was introduced to take into account the reduced risk of death due to CML with targeted therapies.

CML prognostic scores				
Score	Sokal	EURO Hasford	EUTOS	ELTS Pfirrmann
Year	1984	1998	2011	2016
Parameters used	Age Spleen size Blasts Platelets	Age Spleen size Blasts Platelets Eosinophils Basophils	Age Basophils	Age Spleen size Blasts Platelets
Study treatment	Chemotherapy	Interferon-α	Imatinib	Imatinib
End point	Survival	Survival	CCyR	Survival (CML-dependent death)

Fig. 4.6

CCyR, Complete cytogenetic response; CML, chronic myeloid leukaemia; ELTS, EUTOS long-term survival; EUTOS, European Treatment and Outcome Study.

REVISION QUESTIONS

1. What symptoms and signs lead to the suspicion of CML?
2. What are the typical findings in the blood smear of a patient with CML?
3. Which factors define the prognosis of CML?

First-line treatment, monitoring of CML patients with tyrosine kinase inhibitors and treatment-free remission

The introduction of the orally available BCR-ABL1 tyrosine kinase inhibitor (TKI) therapy with imatinib in 2000 significantly improved the survival and quality of life of patients with CML.

Three BCR-ABL1 TKIs are registered and available in most European countries as first-line therapy for CML in CP: imatinib 400 mg/day, nilotinib 2 × 300 mg/day, dasatinib 100 mg/day.

The second-generation TKIs nilotinib and dasatinib reveal faster cytogenetic and molecular responses compared with imatinib; the 5-year overall survival is, however, not statistically significantly different.

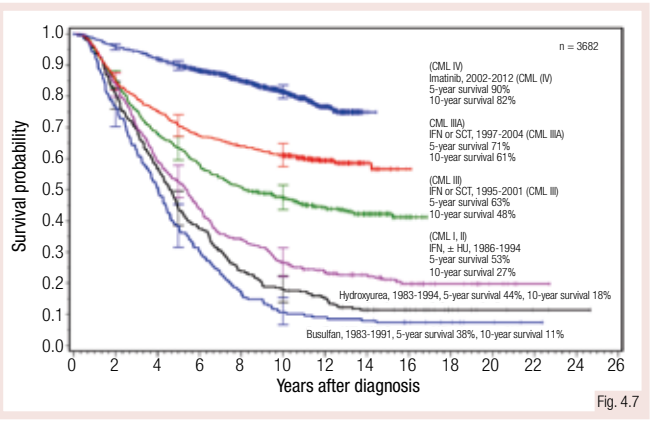

Fig. 4.7

CML, Chronic myeloid leukaemia; HU, hydroxyurea; IFN, interferon; SCT, stem cell transplantation.

Milestones for patients treated with TKI first line*, 1-2

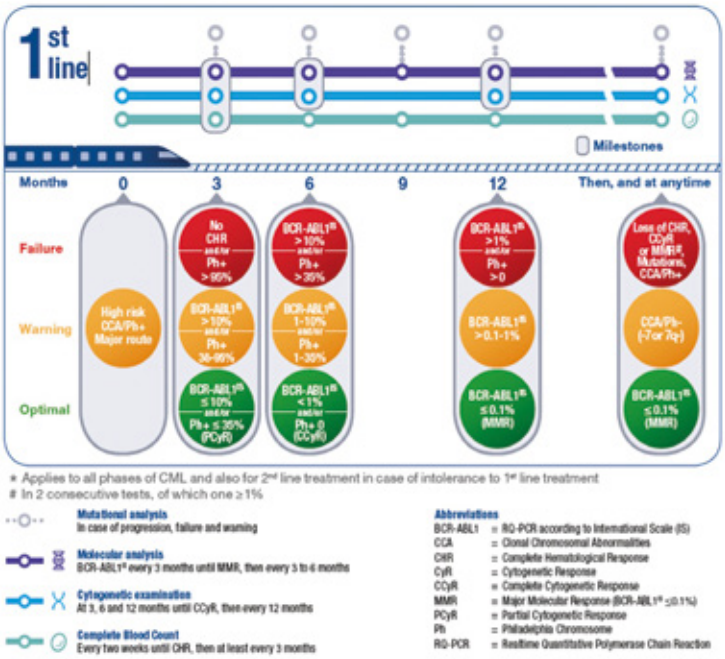

Fig. 4.8

CML, Chronic myeloid leukaemia; TKI, tyrosine kinase inhibitor.

CML experts on behalf of the ELN and the National Comprehensive Cancer Network established milestones to be achieved during CML treatment with TKIs.

Monitoring of CML patients is based on regular haematological, conventional cytogenetic and reverse transcription quantitative polymerase chain reaction (RTqPCR)-based standardised molecular (International Scale [IS]) assessments.

'Optimal' predicts an excellent outcome: continue treatment. 'Failure' means the patient is at risk of progression: change treatment. 'Warning' means careful 'watch and wait'.

In the European Stop Kinase Inhibitor (Euro-SKI) trial where patients had a TKI for >3 years and an MR4 (molecular response 4) for >1 year, around 50% of the patients achieved a treatment-free remission (TFR).

The ultimate goal in CML therapy is to achieve a sustained deep molecular response (<MR4), to gain the option of stopping TKI therapy (for now only recommended in clinical studies).

Longer duration of TKI treatment, deeper molecular response and low Sokal risk are predictive of a TFR.

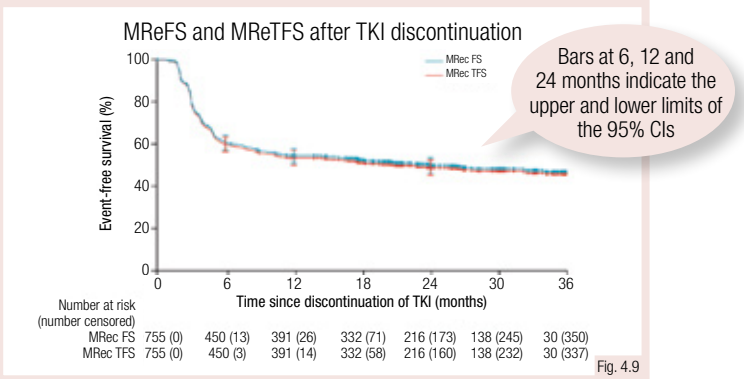

Fig. 4.9

CI, Confidence interval; MReFS, molecular relapse-free survival; MReTFS, molecular relapse-free and treatment-free survival; TKI, tyrosine kinase inhibitor.

REVISION QUESTIONS

1. What are the first-line treatment options for CML in CP?
2. Which laboratory parameters are important to monitor a patient with CML?
3. What are the optimal milestones a patient with CML should achieve in the first 12 months and long-term?

Intolerance and resistance

Although generally well tolerated, TKIs can be associated with a wide range of adverse events. Most are mild to moderate and cease either spontaneously or upon symptomatic treatment.

Whenever treatment interruptions are necessary due to intolerance, the same TKI may be reintroduced at the prior or a lower dose as long as efficacy is maintained, otherwise a change to an alternative TKI will need to be considered.

Importantly, all TKIs are CYP3A4 substrates and inhibitors and present relevant drug interactions.

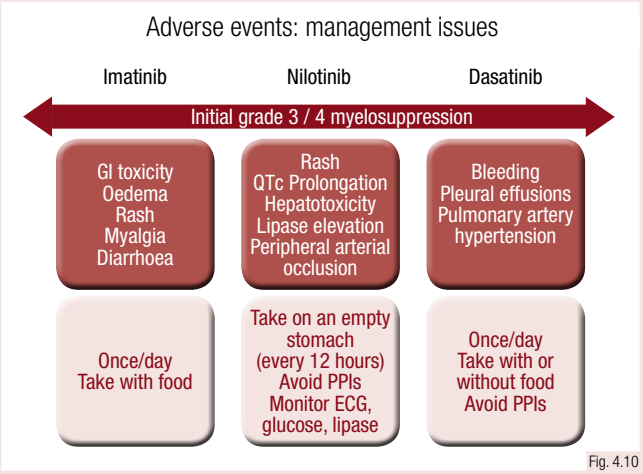

Fig. 4.10

GI, Gastrointestinal; ECG, electrocardiogram; PPI, proton pump inhibitor.

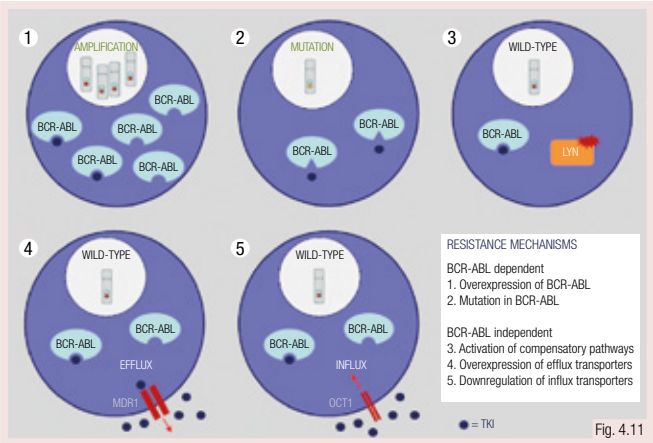

Fig. 4.11

TKI, Tyrosine kinase inhibitor.

Several *BCR-ABL1*-dependent or -independent mechanisms of resistance to TKI treatment can occur.

If a patient fails the optimal treatment milestones: evaluate drug compliance, co-medications, insufficient plasma drug level, clonal evolution, gene amplification, polymorphisms.

An important mechanism of resistance is the evolution of a mutation or mutations with TKI treatment.

At diagnosis, a mutational analysis is only recommended for advanced phases of CML, but for all phases of CML if there is resistance to treatment.

The type and combinations of mutations determine the grade of resistance to the TKI and can guide the choice of further therapy.

Ponatinib is the only drug suitable for a T315I mutation.

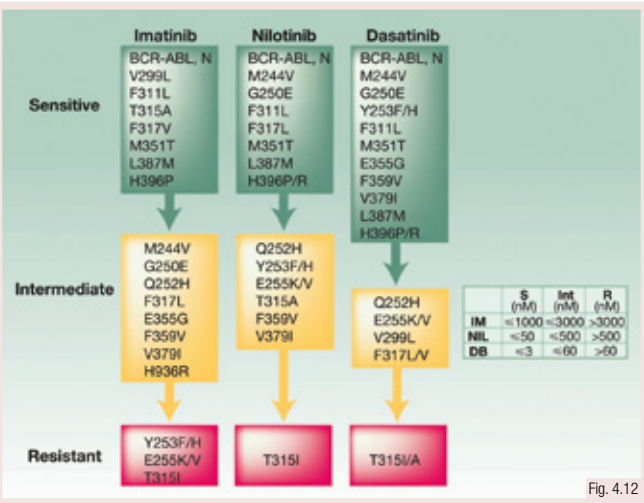

Fig. 4.12

DB, Dasatinib; IM, imatinib; NIL, nilotinib.

REVISION QUESTIONS

1. What main types of adverse events can occur with TKI treatment?
2. Which mechanisms of therapy resistance can occur?
3. When should a mutational analysis be considered and what consequence does a mutation(s) imply?

Treatment options after first-line treatment, HSCT, TKIs in pregnancy

Failure of, or intolerance to, treatment with a TKI warrants a switch to another TKI or to consider allogeneic stem cell transplantation (alloSCT).

Five TKIs are currently options after first-line therapy (check country-specific regulations).

Patients who fail two or more TKIs should definitely be referred to a specialised centre.

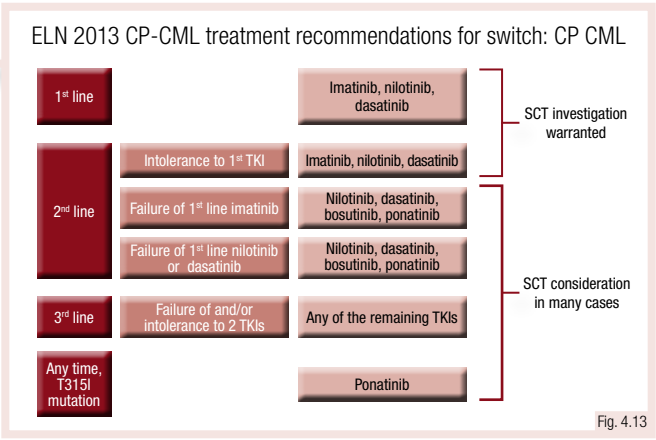

Fig. 4.13

CML, Chronic myeloid leukaemia; CP, chronic phase; ELN, European LeukemiaNet; SCT, stem cell transplantation; TKI, tyrosine kinase inhibitor.

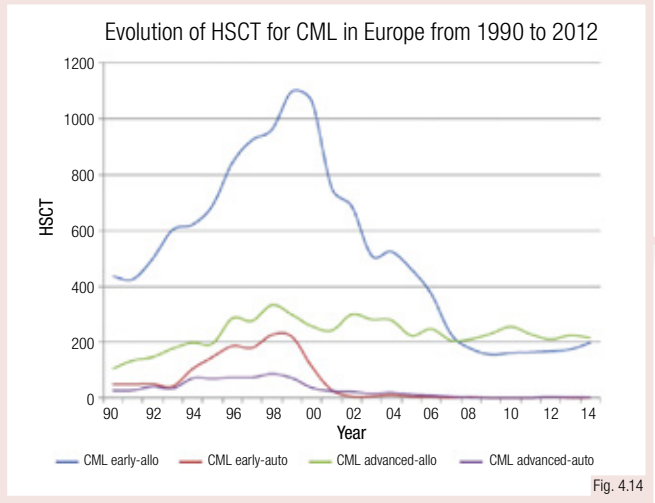

Fig. 4.14

CML, Chronic myeloid leukaemia; HSCT, haematopoietic stem cell transplantation.

With the introduction of TKIs as targeted therapy, the number of alloSCTs has decreased.

AlloSCT is, however, still an important therapy option for patients in CML BC and for patients in CML CP and AP who do not achieve an optimal response on TKIs.

An evaluation for a potential alloSCT should be integrated at diagnosis by assessing family history, human leukocyte antigen (HLA) typing, rating of the likelihood of finding a donor and transplant risk assessment.

Fertility preservation should be initiated and completed prior to any cancer therapy that may impact on gonadal function. All TKIs should be avoided during pregnancy.

Women of childbearing potential should be advised to practise effective contraception and avoid becoming pregnant while on TKI therapy. In case of pregnancy, consider the treatment options on the right.

Women with CML who want to become pregnant or are pregnant should be referred to a specialised centre for multidisciplinary management during pregnancy.

Treatment options during pregnancy			
First trimester	Second trimester	Third trimester	Breastfeeding
Leukapheresis (keep leukocyte count <100 G/L and platelet count <500 G/L)	Leukapheresis	Leukapheresis	
Aspirin +/- LMWH if platelets >500 G/L	Aspirin +/- LMWH if platelets >500 G/L	Aspirin +/- LMWH if platelets >500 G/L	
Avoid INFα, hydroxycarbamide, TKI during period of organogenesis	Avoid INFα, hydroxycarbamide, TKI (particularly 2nd-generation TKI)	Avoid INFα, hydroxycarbamide, TKI (particularly 2nd-generation TKI)	TKI and hydroxy-carbamide are contraindicated due to potential secretion into breast milk
	INFα may be considered	INFα may be considered	INFα not recommended
Pegylated INFα is contraindicated	Pegylated INFα is contraindicated	Pegylated INFα is contraindicated	

Fig. 4.15

INFα, Interferon alpha; LMWH, low molecular weight heparin; TKI, tyrosine kinase inhibitor.

REVISION QUESTIONS

1. What are the treatment options after failure or intolerance of first-line treatment or after second-line treatment?
2. What is the role of alloSCT in patients with CML?
3. Is TKI treatment recommended during pregnancy?

Summary: Chronic myeloid leukaemia

- CML should be suspected in patients with fatigue, anaemia, splenomegaly, abdominal discomfort and leukocytosis with precursor cells, eosinophilia and basophilia
- CML is diagnosed by molecular analysis of BCR-ABL1 transcripts in the peripheral blood
- Cytogenetic analysis confirms a translocation between the long arms of chromosomes 9 and 22
- The resulting oncogenic BCR-ABL1 protein can be targeted by specific TKIs, being the first choice of CML treatment in CP and AP
- Determining the phase of CML (CP, AP or BC), a relevant parameter for the prognosis and the treatment strategy, requires a bone marrow aspirate and biopsy
- Several prognostic scores (Sokal, Hasford, EUTOS, ELTS) have been established based on age, spleen size and platelet, blast, eosinophil and basophil counts
- Monitoring patients with CML treated with TKIs consists of response evaluation at least every 3 months (optimal, failure or warning) based on the achievement at certain milestones
- The milestones are defined by quantitative measurements of BCR-ABL1 transcripts in the peripheral blood, differential blood counts as well as cytogenetic assessments in the bone marrow at 3 months and every 3 months until a complete cytogenetic response has been achieved
- Careful attention should be paid to symptoms and signs of intolerance and resistance to TKIs, which should trigger re-evaluation of the treatment strategy
- Patients with CML who fail two or more TKIs or women with CML who want to become pregnant or are pregnant should be referred to a specialist centre

Further Reading

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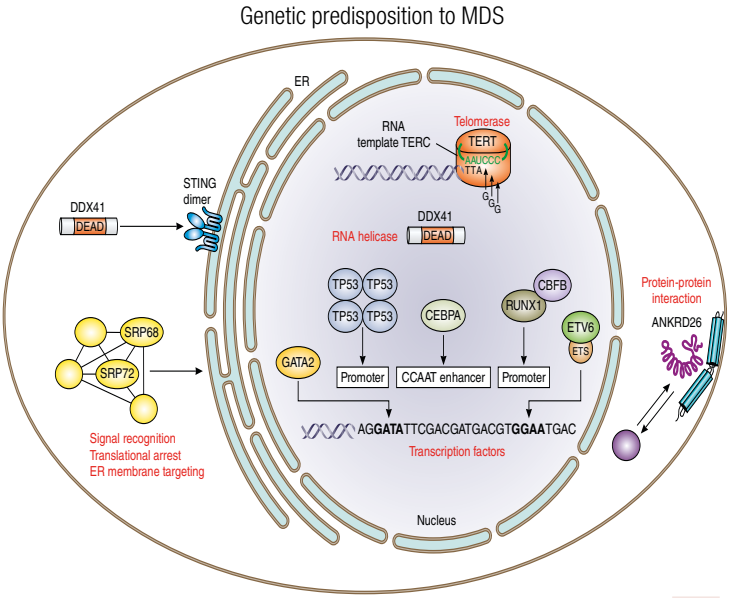
5 Myelodysplastic syndromes

Epidemiology and pathogenesis

Myelodysplastic syndromes (MDS) are a heterogeneous group of haematological malignancies of the elderly (median age 70 years) with a slight male predominance.

The risk of MDS is increased by anti-cancer treatment and occupational exposure, including ionising radiation, alkylating agents and benzene.

Some germline mutations (*GATA2, RUNX1, TERT* genes, etc.) predispose to MDS, and must be suspected in MDS diagnosed at <40 years, or if familial history of MDS or acute myeloid leukaemia (AML).



ER, Endoplasmic reticulum; MDS, myelodysplastic syndromes. Fig. 5.1

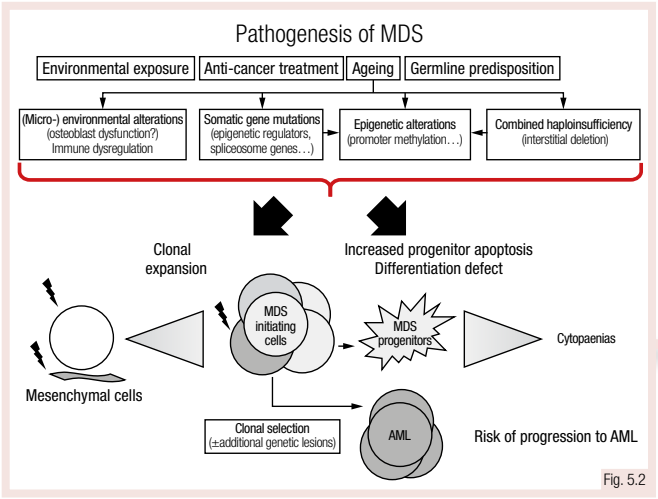


Fig. 5.2

AML, Acute myeloid leukaemia; MDS, myelodysplastic syndrome.

Somatic genetic variants accumulate in haematopoietic stem cells, leading to clonal expansion of dysplastic myeloid progenitors and precursors.

Cytopaenias arise as a result of ineffective progenitor differentiation or apoptosis of myeloid precursors such as erythroblasts.

The disease can progress with an excess of blasts in bone marrow (BM) and/or peripheral blood, and later transform into AML.

Complete blood count and BM cytomorphology based on aspirate and/or biopsy and cytogenetics are key to a correct diagnosis of MDS.

Three diagnostic criteria must be met: persistent cytopaenia(s), BM dysplasia/blast excess/cytogenetic anomaly and exclusion of differential diagnoses.

The World Health Organization (WHO) criteria distinguish several groups of MDS based on marrow blast percentage, number of dysplastic lineages, presence of ring sideroblasts and cytogenetic alterations.

WHO 2016 classification of MDS

Feature	MDS-SLD	MDS-MLD	MDS-RS	MDS with isolated *del(5q)*	MDS-EB	MDS-U
Dysplastic lineages	1	2-3	1-3	1-3	0-3	0-3
Cytopaenias	1-2	1-3	1-3	1-2	1-3	1-3
Ringed sideroblasts*	<15%	<15%	≥15%	Any	Any	<15%
PB blasts	<1%	<1%	<1%	<5%	MDS-EB-1: 2-4% MDS-EB-2: 5-19%	<1%
BM blasts	<5%	<5%	<5%	<5%	MDS-EB-1: 5-9% MDS-EB-2: 10-19%**	<5%
Cytogenetics	Any non *del(5q)*	Any non *del(5q)*	Any non *del(5q)*	*del(5q)****	Any	Any non *del(5q)*

Fig. 5.3

BM, Bone marrow; MDS, myelodysplastic syndromes; MDS-EB, MDS with excess of blasts; MDS-MLD, MDS with multilineage dysplasia; MDS-RS, MDS with ringed sideroblasts; MDS-SLD, MDS with single lineage dysplasia; MDS-U, MDS unclassified; PB, peripheral blood; WHO, World Health Organization. *as percent of erythroid cells (threshold 5% if SF3B1 mutation);**or Auer rods;***isolated or +1 abnormality except -7/*del(7q)*.

REVISION QUESTIONS

1. Which aetiology should be investigated in younger adults diagnosed with MDS?
2. What are the mechanisms of cytopaenias in MDS?
3. Are BM cytogenetics mandatory for a diagnosis of MDS?

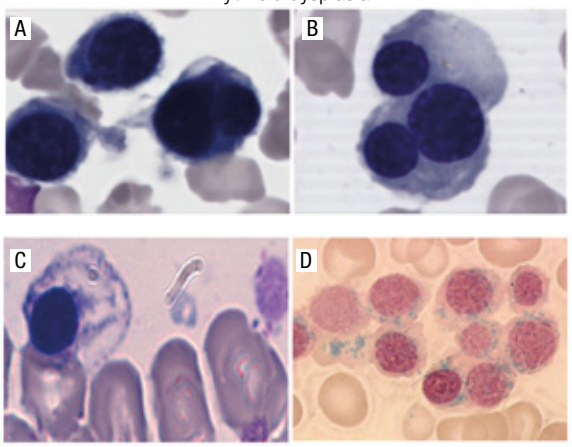
Cytomorphology

Macrocytic anaemia is present in most MDS patients. Isolated neutropaenia or thrombocytopaenia are less frequent.

In MDS patients, BM is often hypercellular, but may also be normo- or hypocellular.

Dysplastic features can be seen in the blood but BM morphology is often more informative.

Erythroid dysplasia



A. Nuclear budding, **B.** Binucleated erythroblast, **C.** Laminated cytoplasm, **D.** Ring sideroblasts (Perls' staining).

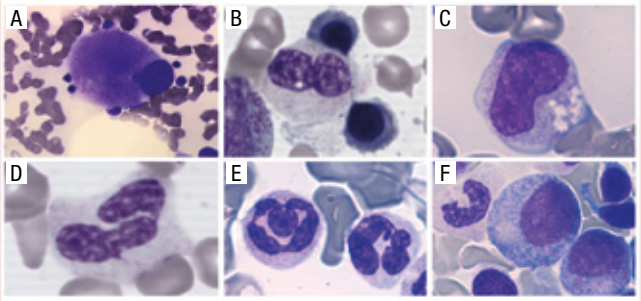
Fig. 5.4

Dyserythropoiesis includes nuclear (e.g. budding) and cytoplasmic (e.g. vacuolisation) anomalies.

The most frequent signs of dysgranulopoiesis include nuclear hypolobation (pseudo-Pelger-Huët) and hypogranularity.

The most frequent dysplastic features in the megakaryocytic lineage include micromegakaryocytes, hypolobulated nuclei and multi-nucleation.

Other dysplasias and blasts



A. Megakaryocyte with monolobated nucleus, **B.** Internuclear bridge, **C.** Abnormal metamyelocyte granulation, **D.** Neutrophil with bilobed nucleus and hypogranular cytoplasm, **E.** Neutrophil with abnormal ring nucleus, **F.** Agranular promyelocyte.

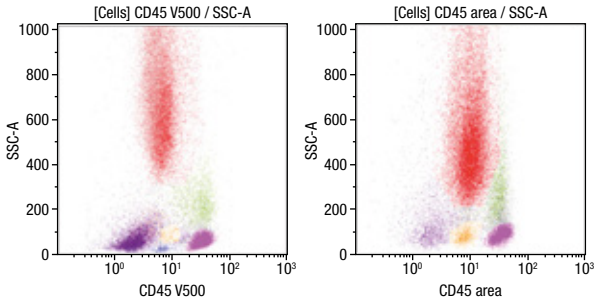
Fig. 5.5

Iron staining in BM can identify ringed sideroblasts, which help classify MDS in the absence of blast excess.

The presence of ringed sideroblasts is associated with somatic mutations in the spliceosome gene *SF3B1*.

Flow cytometry can also document the diagnosis and prognosis of MDS, but consensus tools have yet to emerge in routine practice for this technique.

Flow cytometry in MDS



CD45 versus Side Scatter (SSC) scattergram in a normal control and a MDS patient. The MDS patient's flow profile shows:
- hypogranulation (low SSC) of granulocytes (red),
- increase in CD34+ myeloblasts (orange),
- lack of CD34+ B cell progenitors (blue),
- decrease of erythroblasts (purple).

Fig. 5.6

MDS, Myelodysplastic syndromes.

REVISION QUESTIONS

1. What is the most frequent cytopaenia in MDS?
2. What type of BM cellularity is seen in MDS?
3. Does the presence of micromegakaryocytes exclude the diagnosis of MDS?

Cytogenetics and molecular biology

Cytogenetic alterations by conventional karyotyping are found in 50% of MDS. Alterations are mostly imbalanced, total or interstitial chromosome gains or losses.

Interstitial deletion of chromosome 5q *(del[5q31-q33])* is the most frequent alteration found in MDS and defines the '*5q-* syndrome'.

Fluorescent *in situ* hybridisation (FISH) can complement conventional karyotyping to identify gains/losses of chromosome arms. Single nucleotide polymorphism (SNP) and comparative genomic hybridisation (CGH) arrays can also find copy number alterations in normal karyotypes.

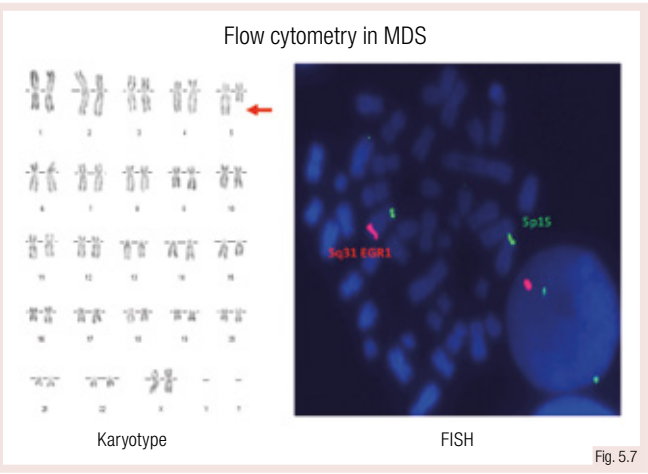


Fig. 5.7

FISH, Fluorescent *in situ* hybridisation; MDS, myelodysplastic syndromes.

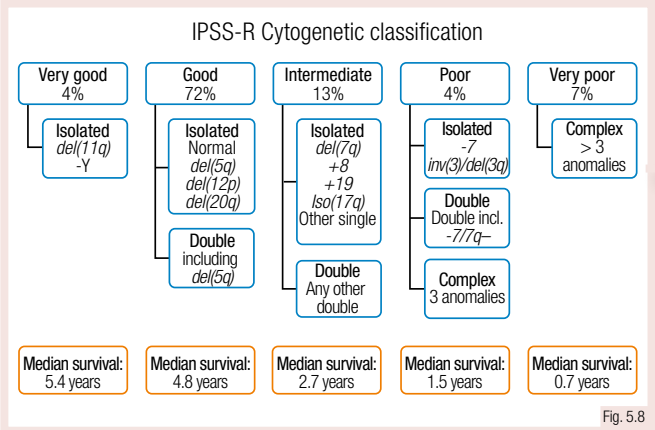


Fig. 5.8

IPSS-R, Revised International Prognostic Scoring System.

A detailed prognostic classification of cytogenetic alterations stratifies the majority of patients.

Frequent alterations associated with good prognosis include -Y, *del(20q)* and non-complex *del(5q)*, in addition to normal karyotype.

Frequent alterations associated with poor prognosis include chromosome 7 deletions and complex karyotypes.

Recurrent somatic mutations can be found in 80% of MDS patients by targeted sequencing of 20-30 genes.

Mutations in genes involved in splicing (*SF3B1, SRSF2, U2AF1, ZRSR2*) are among the most frequent and are relatively specific to MDS and AML post-MDS.

Except for *SF3B1*, somatic mutations have a limited impact on clinical presentation and their prognostic role has yet to be integrated into validated prognostic models.

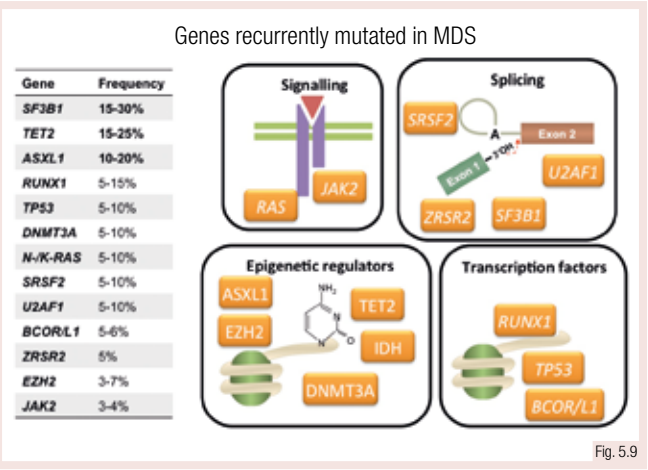


Fig. 5.9

MDS, Myelodysplastic syndromes.

REVISION QUESTIONS

1. What is the proportion of MDS with normal karyotype identified by conventional cytogenetics?
2. What is the prognostic value of isolated *del(5q)* in MDS?
3. Which family of genes is specifically mutated in MDS and secondary AML?

Prognostic factors and treatment stratification

The International Prognostic Scoring System (IPSS) has long been used to stratify patients in MDS.

Treatment of higher-risk MDS (IPSS intermediate-2 or high) aims to alter the natural history of the disease and delay progression to AML.

Treatment in lower-risk MDS (IPSS low or intermediate-1) aims to correct cytopaenias, notably anaemia. Prognosis in this group is heterogeneous.

IPSS and classical dichotomy of MDS

	Score value				
Prognostic variable	0	0.5	1.0	1.5	2.0
Blasts, %	<5	5–10		11–20	21–30
Karyotype*	Good	Intermediate	Poor		
Cytopaenias	0–1	2–3			

*Good: normal, -Y, *del(5q)*, *del(20q)*. Poor: complex (≥3 abnormalities), -7/*del(7q)*. Intermediate: all other.

Score	Risk groups		Endpoint	Treatment aim
0	Low	Lower-risk	Quality of life	Coping with cytopaenias
0.5–1.0	Intermediate-1			
1.5–2.0	Intermediate-2	Higher-risk	Survival	Delaying progression
≥2.5	High			

IPSS, International Prognostic Scoring System; MDS, myelodysplastic syndromes. Fig. 5.10

Revised IPSS (IPSS-R)

Points	0	0.5	1	1.5	2	3	4
Cytogenetics	Very Good		Good		Int	Poor	Very poor
BM blast, %	≤ 2%		>2%- < 5%		5%-10%	> 10%	
Hb (g/dL)	≥ 10		8- < 10	< 8			
Plt (10^9/L)	≥ 100	50-< 100	< 50				
ANC (10^9/L)	≥ 0.8	< 0.8					

Risk category	Risk score	Median OS (y)	Median AML25% (y)
Very low	≤ 1.5	8.8	NR
Low	> 1.5-3	5.3	10.8
Intermediate	> 3-4.5	3.0	3.2
High	> 4.5-6	1.6	1.4
Very high	> 6	0.8	0.73

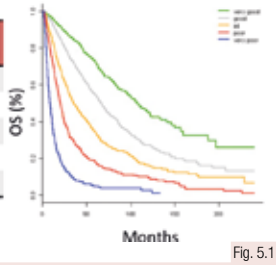


Fig. 5.11

AML, Acute myeloid leukaemia; ANC, absolute neutrophil count; BM, bone marrow; Hb, haemoglobin; IPSS, International Prognostic Scoring System; OS, overall survival; NR, not reached; Plt, platelet.

The revised IPSS (IPSS-R) better stratifies patients and, notably, better discriminates between patients with good and intermediate prognosis.

IPSS-R uses refined cut-offs for marrow blasts and blood cytopaenias, and incorporates a more sophisticated cytogenetic classification (see Fig. 5.8).

IPSS-R has yet to be integrated into therapeutic decisions in MDS, where the labelling of drugs still mostly relies on standard IPSS.

Additional prognostic factors in MDS include host-related factors such as age and comorbidities.

Additional disease-related factors include somatic mutations, flow cytometry and gene expression profiles.

Mutations in *SF3B1* are favourable and mutations of *TP53* unfavourable. Mutations in other genes can be unfavourable but have yet to be incorporated into prognostic scoring systems.

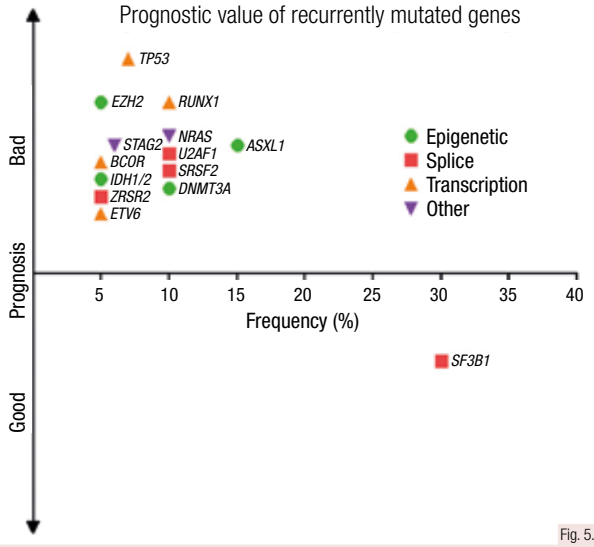


Fig. 5.12

REVISION QUESTIONS

1. Is prognosis of lower-risk MDS homogeneous?
2. Does IPSS-R require additional investigations compared with standard IPSS?
3. Can host-related factors influence prognosis in MDS?

Treatment

Allogeneic stem cell transplantation (alloSCT) is the only curative option in MDS.

AlloSCT should be considered in all patients with higher-risk MDS (IPSS intermediate-2/high, IPSS-R high/very high) or otherwise delayed, except perhaps in some IPSS-R intermediate patients.

Older patients should receive reduced intensity conditioning. Lowering the blast count below 10% is preferable prior to transplant.

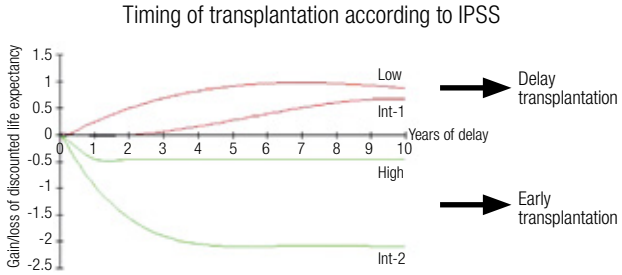


Fig. 5.13

IPSS, International Prognostic Scoring System.

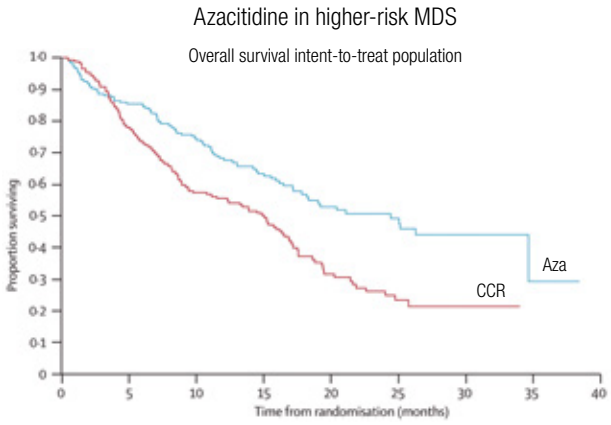


Fig. 5.14

Aza, Azacitidine; CCR, conventional care regimens (supportive care, low-dose cytarabine, intensive chemotherapy); MDS, myelodysplastic syndromes.

Hypomethylating agents are active in higher-risk MDS. Azacitidine improves overall survival over conventional care in patients not eligible for transplant.

Response to hypomethylating agents is best evaluated after 6 cycles. Treatment should be continued in responding patients until progression.

Outcome after failure of hypomethylating agents is poor, with a median survival of 6 months and no approved second-line therapy.

High-dose erythropoiesis-stimulating agents (ESAs) are the first-line treatment of symptomatic anaemia in lower-risk MDS.

Lenalidomide provides a high rate of durable response in lower risk patients with *del(5q)* with anaemia after failure of ESAs.

Treatment of other cytopaenias is less well codified and may rely on thrombopoietin (TPO) agonists, granulocyte colony-stimulating factor (G-CSF) and immunosuppressive therapy in selected patients.

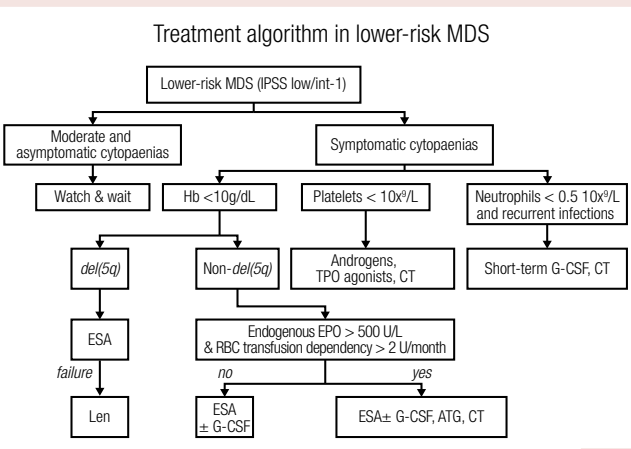


Fig. 5.15

ATG, Anti-thymocyte globulin; CT, clinical trial; EPO, erythropoietin; ESA, erythropoiesis-stimulating agent; G-CSF, granulocyte colony-stimulating factor; Hb, haemoglobin; IPSS, International Prognostic Scoring System; Len, lenalidomide; MDS, myelodysplastic syndromes; RBC, red blood cell; TPO, thrombopoietin.

REVISION QUESTIONS

1. Should a patient with lower-risk MDS and an available donor be transplanted upfront?
2. How should a higher-risk MDS patient with stable disease after two cycles of azacitidine be managed?
3. How should a lower-risk MDS patient with *del(5q)* failing ESAs be managed?

Summary: Myelodysplastic syndromes

- MDS are a heterogeneous group of clonal malignancies of the elderly, characterised by ineffective haematopoiesis resulting in chronic cytopaenias and a variable risk of progression to AML
- BM is typically hypercellular, with dysplasia in one or several myeloid lineages, including ringed sideroblasts in some subgroups and a possible excess of blasts
- Cytogenetics are normal in half of patients
- Isolated *del(5q)* defines a subset of patients with good prognosis and persistent anaemia responding to lenalidomide
- Recurrent somatic mutations in genes involved in splicing, such as *SF3B1*, are very suggestive of MDS among other myeloid neoplasms
- The classical IPSS, based on cytopaenias, marrow blast percent and cytogenetics, is currently used to manage patients
- A revised IPSS (IPSS-R) based on the same criteria allows better prognostic stratification but has yet to be incorporated into treatment algorithms
- AlloSCT is the only curative treatment in MDS and should be performed upfront in eligible higher-risk patients with a suitable donor
- The hypomethylating agent azacitidine is approved in Europe for the front-line treatment of higher-risk MDS patients not eligible for transplant
- High-dose ESAs are the mainstay of treatment of anaemia in lower-risk MDS without *del(5q)*

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6 Classification, diagnosis and response assessment of myeloma

Classification

Monoclonal gammopathy of undetermined significance (MGUS) is one of the most common pre-malignant disorders and affects 3.5% of the Caucasian population >50 years of age, and double this in the Afro-descendent population.

Multiple myeloma (MM) is always preceded by MGUS, but only 1% of individuals with MGUS per year progress to myeloma.

Smouldering (asymptomatic) multiple myeloma (SMM) is a precursor state with a higher tumour burden and a higher risk of progression compared with MGUS (around 10% per year).

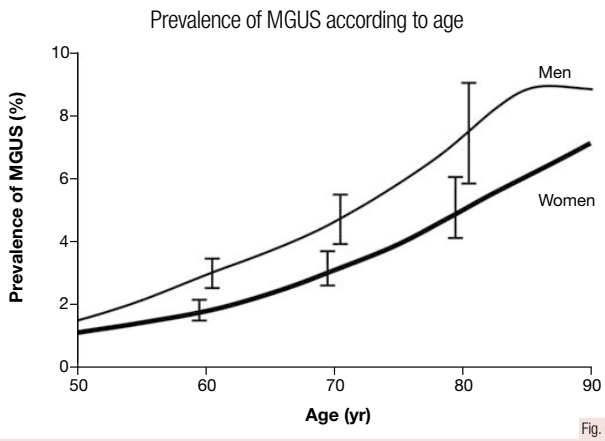

Fig. 6.1

MGUS, Monoclonal gammopathy of undetermined significance.

	MGUS	SMM	MM
Serum or urine M protein level	<30 g/L AND	IgG or IgA ≥30 g/L or urinary M protein ≥500 mg per 24 h AND/OR	
Bone marrow plasma cells	<10% AND	≥10% and <60% AND	≥10% OR biopsy proven plasmacytoma AND
CRAB criteria and/or biomarkers of malignancy	Absence	Absence	≥1 criteria

Fig. 6.2

CRAB, HyperCalcaemia, Renal insufficiency, Anaemia and Bone lesions; IgA, immunoglobulin A; IgG, immunoglobulin G; M, monoclonal; MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma; SMM, smouldering multiple myeloma.

MGUS is defined by monoclonal (M) protein <30 g/L and <10% bone marrow plasma cells (BMPCs) and the absence of any signs or symptoms related to myeloma or myeloma-defining biomarkers.

SMM is defined as M protein >30 g/L (or urinary ≥500 mg/24 h) and/or ≥10% to <60% BMPCs in the absence of any signs or symptoms.

MM is defined by the presence of at least 10% BMPCs, and evidence of at least one end organ damage or one biomarker of malignancy (see Diagnosis section).

Risk factors for malignant transformation are:
M protein ≥15 g/L or evolving (i.e. gradually increasing), non-immunoglobulin (Ig) G subtype, abnormal serum free light chain (sFLC) ratio, ≥95% aberrant BMPCs.

There is no reduction in risk of progression for MGUS, even after several decades of follow-up.

It is recommended to follow MGUS subjects at 6 months and annually thereafter. Low-risk subjects can be followed less frequently, every 2–3 years.

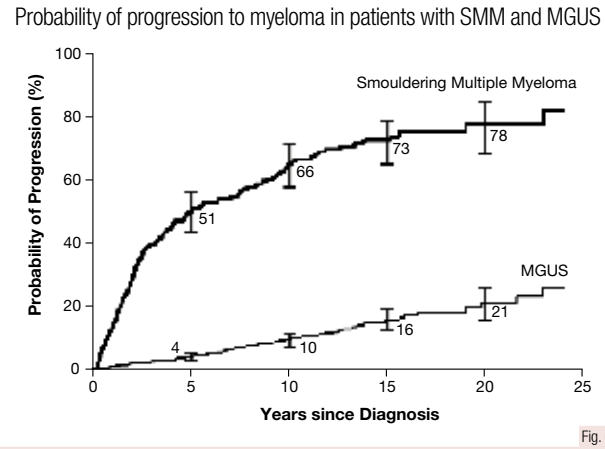

Fig. 6.3

MGUS, Monoclonal gammopathy of undetermined significance; SMM, smouldering multiple myeloma.

REVISION QUESTIONS

1. How is MGUS defined?
2. What is the proportion of MGUS subjects progressing to myeloma each year?
3. How is SMM defined?

Diagnosis

MM accounts for 13% of haematological cancers and 1% of all cancers; it occurs mainly in the elderly population (median age at diagnosis of 65–70 years).

MM is characterised by the accumulation of tumour plasma cells within the bone marrow compartment, and the production of an M protein in serum and/or urine.

Intact Ig MM (~80%, including 52% IgG and 21% IgA) and light chain MM (~15%–20%) are distinguished. The most common light chain is Kappa (~2/3κ, 1/3λ).

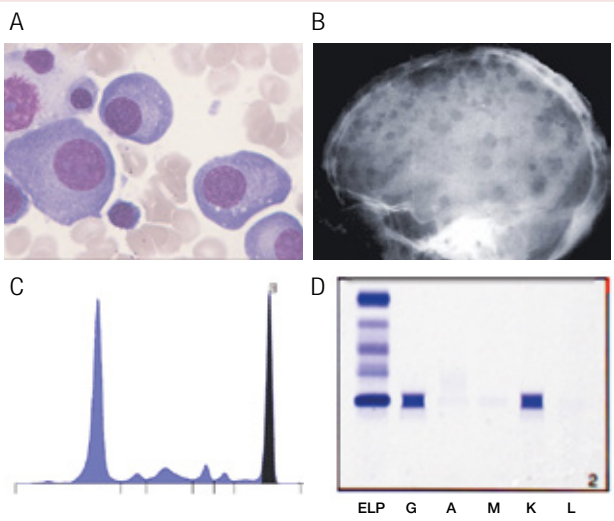

Fig. 6.4

A. Bone marrow plasma cells, B. Bone lesions, C. Serum electrophoresis, D. Serum immunofixation.

Clinical/laboratory features	Proportion of patients with abnormality (%)
Anaemia	72
Bone lesions	80
Renal failure	19
Hypercalcaemia	13
M protein on serum electrophoresis	82
M protein on serum immunofixation	93
M protein on serum plus urine immunofixation (or sFLC assay)	97
≥10% clonal BMPCs	96

BMPC, Bone marrow plasma cell; M, monoclonal; sFLC, serum free light chain. Fig. 6.5

Apart from MGUS follow-up, usual circumstances leading to the diagnosis of myeloma include bone pain and fractures, anaemia and renal dysfunction.

M protein must be evaluated in the serum (electrophoresis, immunofixation, sFLC assay) and in the urine (Bence Jones protein electrophoresis and immunofixation).

Non- or oligo-secretory myeloma represents <5% of cases.

The keystone diagnostic test is bone marrow aspirate or biopsy, showing at least 10% clonal BMPCs.

Diagnostic evaluation also includes blood cell count, serum calcium, serum creatinine and creatinine clearance measurements, and imaging studies (X-ray, positron emission tomography [PET]–computed tomography [CT], magnetic resonance imaging [MRI]).

MM is defined by the presence of at least one of the CRAB criteria (hyperCalcaemia, Renal insufficiency, Anaemia and Bone lesions) or any of the 3 biomarkers of malignancy.

Definition of multiple myeloma	
Clonal BMPCs ≥10% AND one or more of the following myeloma-defining events:	
CRAB criteria	HyperCalcaemia
	Renal insufficiency
	Anaemia
	Bone lesions
OR	
Biomarkers of malignancy	Clonal BMPCs ≥60%
	sFLC ratio ≥100
	>1 focal lesion on MRI

BMPC, Bone marrow plasma cell; MRI, magnetic resonance imaging; sFLC, serum free light chain. Fig. 6.6

REVISION QUESTIONS

1. What are the usual circumstances of myeloma diagnosis?
2. What are the biological and imaging analyses required to define myeloma?
3. Is there a monoclonal spike detectable on serum electrophoresis in all cases of myeloma?

Prognostic evaluation

MM is characterised by a wide heterogeneity of outcome (rapid fatal evolution in few months, long-term progression-free survival [PFS] 10 years after diagnosis or even cure).

Many prognostic factors have been described in MM, including factors related to the patient and to the tumour.

As in every cancer, age is prognostic because of comorbidities but also because of different treatment approaches (younger patients are treated with high-dose therapies).

Prognostic factors (non-exhaustive)	
Related to patient	Age
	Comorbidities
Related to tumour burden	Anaemia
	Thrombopaenia
	β2-microglobulin serum level
Intrinsic cellular	Genetic
	Proliferation index
Mixed	Hypoalbuminaemia
	Renal insufficiency
	Response to treatment

Fig. 6.7

Cytogenetic abnormality	Frequency	Prognosis
Trisomy 3	35%	Good
Trisomy 5	37%	Good
Translocation *t(4;14)*	15%	Poor
Translocation *t(14;16)*	3%	Poor
1q gain	8%	Poor
Deletion *1p32*	8%	Poor
Trisomy 21	23%	Poor
Deletion *17p*	8%	Poor

Fig. 6.8

Cytogenetic abnormalities have a dramatic impact on prognosis and must be systematically determined at diagnosis and relapse.

In clinical routine these abnormalities can be detected by interphase FISH (fluorescent *in situ* hybridisation) or SNP (single nucleotide polymorphism) array on sorted BMPCs.

Some poor-prognosis abnormalities such as *del(17p)* may appear during disease evolution.

The ISS (International Staging System) is a very simple prognostic classification based on serum β2-microglobulin and albumin levels.

The revised ISS (R-ISS) includes, in addition to ISS, the serum LDH (lactate dehydrogenase) level and some high risk cytogenetic abnormalities, and allows identification of very high risk patients.

The prognostic evaluation is a necessary step of myeloma management, in particular with the objective of personalised medicine.

Prognostic factor		Criteria	OS at 5 years	PFS at 5 years
ISS stage	I	β2-microglobulin <3.5 mg/dL and albumin ≥3.5 g/dL	77%	49%
	II	No ISS stage I or III	62%	36%
	III	β2-microglobulin ≥5.5 mg/dL	47%	30%
CA by iFISH	Standard risk	No high-risk CA	69%	45%
	High risk	Presence of *del(17p)* and/or translocation *t(4;14)* and/or translocation *t(14;16)*	50%	24%
LDH	Normal	LDH < upper limit of normal	68%	42%
	High	LDH > upper limit of normal	47%	31%
R-ISS stage	I	ISS stage I and standard risk CA and normal LDH	82%	55%
	II	No R-ISS stage I or III	62%	36%
	III	ISS stage III and either high-risk CA or high LDH	40%	24%

Fig. 6.9

CA, Chromosomal abnormalities; iFISH, interphase fluorescent *in situ* hybridisation; ISS, International Staging System; LDH, lactate dehydrogenase; OS, overall survival; PFS, progression-free survival; R-ISS, Revised International Staging System.

REVISION QUESTIONS

1. What are the required biological tests to determine the ISS stage of a newly diagnosed patient?
2. How should cytological analysis be routinely performed in myeloma?
3. What is the prognosis associated with presence of *del(17p)* in BMPCs?

Assessment of treatment response

Evaluation of response is based on the measurement of the M protein in the serum and the urine, plus bone marrow assessment.

A measurable disease is defined by the presence of >10 g/L of M protein in serum, or >200 mg/24 h of Bence Jones protein for light chain myeloma.

sFLC values are useful for the assessment of oligo-secretory myeloma. A measurable disease is defined by an involved FLC level ≥100 mg/L.

Measurable disease definition	
Serum M protein	≥10 g/L
Urine M protein	≥200 mg/24 h
Serum FLC assay	Involved FLC level ≥100 mg/L provided serum FLC ratio is abnormal

FLC, Free light chain; M, monoclonal.

Fig. 6.10

In order to allow uniform reporting within and outside clinical trials, the International Myeloma Working Group (IMWG) has defined several response subcategories.

Response subcategory	Response criteria
Stringent complete response (sCR)	Complete response plus normal FLC ratio and absence of clonal cells in bone marrow
Complete response (CR)	Negative immunofixation on the serum and urine and <5% plasma cells in bone marrow
Very good partial response (VGPR)	Serum and urine M protein detectable by immunofixation but not on electrophoresis, or ≥90% reduction in serum M protein plus urine M protein level <100 mg per 24 h
Partial response (PR)	≥50% reduction of serum M protein plus reduction in 24 h urinary M protein by ≥90% or to <200 mg per 24 h; if the serum and urine M protein are unmeasurable, a ≥50% decrease in the difference between involved and uninvolved FLC levels is required
Stable disease (SD)	Not meeting criteria for CR, VGPR, PR or PD
Progressive disease (PD)	- Increase of 25% from lowest value in serum M component (absolute increase must be ≥0.5 g/dL) and/or urine M component (absolute increase must be ≥200 mg/24 h); if the serum and urine M protein are unmeasurable, a ≥25% increase in the difference between involved and uninvolved FLC levels is required and/or - Development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas and/or - Development of hypercalcaemia

Fig. 6.11

FLC, Free light chain; M, monoclonal.

Stringent complete response (sCR) is associated with both longer PFS and overall survival.

Defining a progressive disease is necessary to measure time to progression and PFS.

Any evaluation requires two consecutive assessments.

Response to treatment is a major prognostic factor in myeloma, whatever the age of the patient.

However, most patients in complete remission relapse, reflecting a persistent disease undetected by conventional methods.

Laboratory testing for follow-up of myeloma patients			
	Every treatment cycle	At suspected complete response	At suspected progression
Serum protein electrophoresis	Yes	Yes	Yes
Serum immunofixation	Only if not measurable at electrophoresis	Yes	Yes
Urine protein electrophoresis	Yes	Yes	Yes
Urine immunofixation	Only if not measurable at electrophoresis	Yes	No
Serum free light chain	Only if not measurable at electrophoresis	Yes	Yes
Bone marrow aspirate/biopsy	No	Yes	Yes
Haemoglobin, serum creatinine, calcium	Yes	Yes	Yes

Fig. 6.12

REVISION QUESTIONS

1. How is measurable disease defined?
2. What is the definition of a complete response to treatment?
3. Which laboratory tests are required to follow myeloma patients during treatment?

Minimal residual disease

Complete response (CR) rates have dramatically improved in the last decades. Up to a large majority of myeloma patients in some clinical trials can now achieve CR.

Consequently, tools enabling the quantification of minimal residual disease (MRD) have been developed and enable the identification of the residual tumour cells.

Cell-based (MFC, multiparameter flow cytometry), molecular-based (NGS, next generation sequencing) and imaging-based (MRI and PET-CT) techniques are available for MRD assessment.

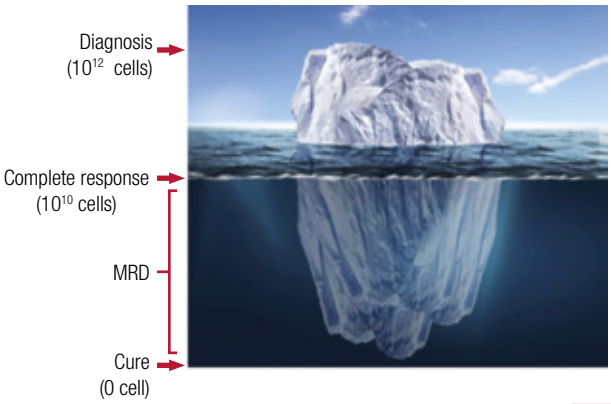

Fig. 6.13

MRD, Minimal residual disease.

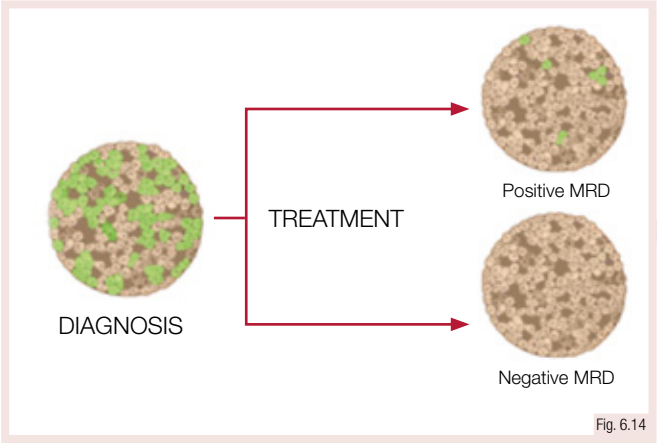

Fig. 6.14

MRD, Minimal residual disease.

Using fluorescent specific antibodies targeting membrane or intracellular proteins, the MFC technique allows the recognition of malignant BMPCs with high specificity and sensitivity.

Malignant plasma cells are characterised by unique clonal rearrangements of their immunoglobulin genes. The NGS technique allows sequencing of these rearrangements at diagnosis and specific follow-up in remission.

Imaging is a necessary complement of assessment which evaluates extramedullary disease and prevents false negative results of biological MRD (patchy infiltration, haemodiluted sample).

The IMWG has included MRD negativity by MFC or NGS and imaging techniques as new response categories.

Correlation between MRD negativity and survival in patients achieving CR is established, especially when a sensitivity of 10^{-6} is reached.

MRD negativity may be part of the definition of cure in myeloma and become a surrogate marker for survival.

MRD criteria	
Flow MRD-negative	Absence of phenotypically aberrant clonal plasma cells by NGF on bone marrow aspirates with a minimum sensitivity of 1 in 10^5 cells (EuroFlow procedure or validated equivalent method)
Sequencing MRD-negative	Absence of clonal plasma cells by NGS on bone marrow aspirate with a minimum sensitivity of 1 in 10^5 cells (LymphoSIGHT platform or validated equivalent method)
Imaging plus MRD-negative	MRD negativity by NGF or NGS plus disappearance of every area of increased tracer uptake found at baseline or a preceding PET/CT or decrease to less mediastinal blood pool SUV or decrease to less than that of surrounding normal tissue

Fig. 6.15

CT, Computed tomography; MRD, minimal residual disease; NGF, next generation flow; NGS, next generation sequencing; PET, positron emission tomography; SUV, standardised uptake value.

REVISION QUESTIONS

1. What are the available laboratory techniques to assess MRD in myeloma?
2. What is the necessary complement to biological MRD assessment?
3. Why target MRD negativity in myeloma treatment?

Summary: Classification, diagnosis and response assessment of myeloma

- Myeloma is always preceded by MGUS, but only 1% per year of MGUS progresses to myeloma
- Myeloma is a malignancy that accounts for 13% of haematological cancers and occurs mainly in the elderly population
- Symptomatic myeloma is defined as ≥10% BMPCs and ≥1 CRAB criteria or biomarker of malignancy
- Circumstances leading to the diagnosis include MGUS follow-up, bone pain and fractures, anaemia and renal dysfunction
- M protein is evaluated in serum and urine (electrophoresis, immunofixation, sFLC assay)
- Myeloma is characterised by a wide heterogeneity of clinical outcomes
- Cytogenetic abnormalities have a dramatic impact on prognosis and can be detected by FISH or SNP array
- A CR is defined by negative immunofixation in serum and urine and <5% BMPCs
- MRD can be assessed by MFC or NGS techniques on a bone marrow sample, but also by imaging (MRI, PET-CT)
- MRD negativity defined by very highly sensitive methods correlates with both PFS and OS

Further Reading

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7 Newly diagnosed myeloma, transplant-eligible patients

Patient selection criteria and procedures of autotransplantation

Multiple myeloma (MM) is a disease of the elderly, the median age at the time of diagnosis being 70–74 years.

Approximately 30%–40% of patients are diagnosed with MM before the age of 66 years and are operatively identified as younger patients.

Younger MM patients represent the ideal candidates to be offered high-dose therapy (HDT) requiring reinfusion of autologous haematopoietic stem cells (HSCs).

Myeloma: 2012-2014. Average number of new cases per year and age-specific incidence rates per 100 000 population, UK

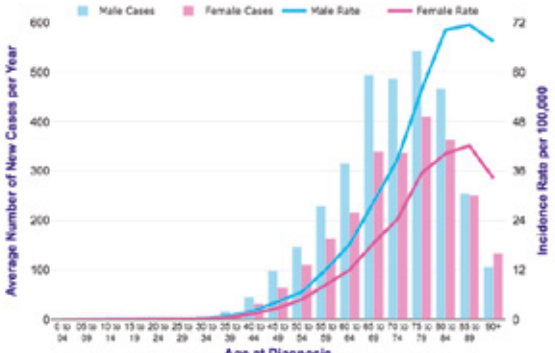

Fig. 7.1

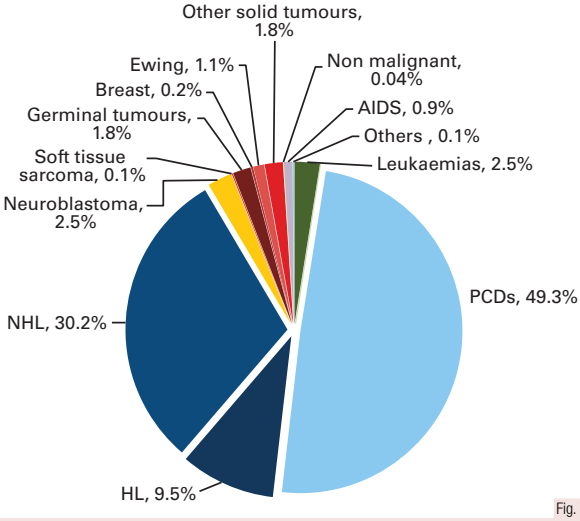

Fig. 7.2

AIDS, Acquired immune deficiency syndrome; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma; PCD, plasma cell disorder.

In addition to chronological age, performance status and comorbidities are major criteria to determine if a patient is eligible to receive autologous stem cell transplantation (ASCT) or not.

The 65-year age cut-off is arbitrary and does not exclude older patients from ASCT (up to 70–75 years old), if they are fit and without major comorbidities.

In 2013, plasma cell disorders (PCDs) were the most frequent indication to provide ASCT in European countries, with an increase of 6.1% compared with the previous year.

The ASCT process includes harvest of the patient's HSCs, which are subsequently cryopreserved and then reinfused into the bloodstream of the same patient 1–2 days after HDT has been administered.

CD34⁺ autologous HSCs mobilised from bone marrow into peripheral blood stem cells (PBSCs) and collected by one or more leukapheresis are the preferred source of stem cells to reconstitute haematopoiesis after HDT.

Granulocyte colony-stimulating factor (G-CSF), possibly with added plerixafor, or cyclophosphamide plus G-CSF, are typically used to mobilise and harvest PBSCs.

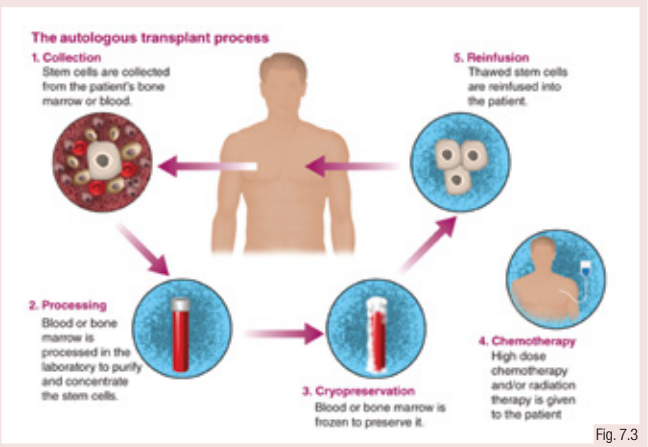

Fig. 7.3

REVISION QUESTIONS

1. Is age >65 years a contraindication to receive ASCT?
2. What are the main procedures in the ASCT process?
3. Which is the preferred source of autologous HSCs to support bone marrow recovery after HDT?

Sequential treatment phases of ASCT

Newly diagnosed MM patients who are fit for ASCT receive treatment in sequential phases.

Induction therapy aims to reduce tumour cell mass and bone marrow plasma cell infiltration before PBSC harvest and subsequent ASCT. Intravenous high-dose melphalan (HDM) at a dose of 200 mg/m^2 is the standard HDT used in MM.

Consolidation and maintenance therapy are given to further increase the rate and depth of response after ASCT (consolidation) and to sustain response over time (maintenance).

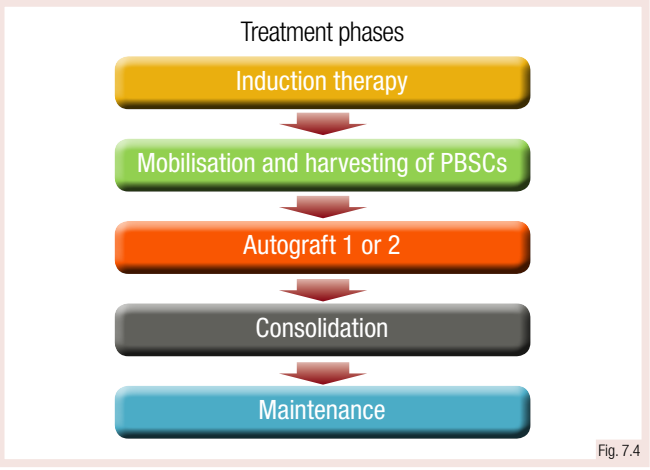

Fig. 7.4

PBSC, Peripheral blood stem cell.

Study	Randomisation	No.	CR (%)	EFS	OS
IFM 90	ChT vs ASCT	200	5 vs 22*	10% vs 28%* at 5 years	12% vs 52%* at 5 years
MRC VII	ChT vs ASCT	401	8 vs 44*	19 vs 31 months*, median (PFS)	42 vs 54 months*, median
IFM 94	Single vs double ASCT	399	42 vs 50 (VGPR)	25 vs 30 months*, median	48 vs 58 months*, median
Bologna 96	Single vs double ASCT	321	33 vs 47* nCR	23 vs 35 months*, median	67 vs 71 months, median

Fig. 7.5

* Statistically significant difference.
ASCT, Autologous stem cell transplantation; ChT, chemotherapy; CR, complete response; EFS, event-free survival; nCR, near complete response; OS, overall survival; PFS, progression-free survival; VGPR, very good partial response.

In the past, ASCT has traditionally been used to overcome resistance to conventional chemotherapy (ChT) and to increase the complete response (CR) rate.

For almost 15 years, upfront ASCT has been considered the standard of care for younger MM patients, as it was associated with improved outcomes when compared in randomised studies with conventional ChT given at standard doses.

In several studies, double ASCT (e.g. timely administration, 3–6 months apart, of two sequential courses of HDT requiring autologous HSC support) was more effective than a single ASCT.

In the past, the CR rate yielded after induction with conventional ChT regimens was below 10%.

Over the past 10–15 years, highly active non-genotoxic agents have been successfully integrated into induction therapy.

Newer induction regimens, incorporating one of the immunomodulatory drugs (IMiDs) thalidomide or lenalidomide combined with the first-in-class proteasome inhibitor (PI) bortezomib or the second-generation PI carfilzomib, have increased CR rates up to 30%–35%.

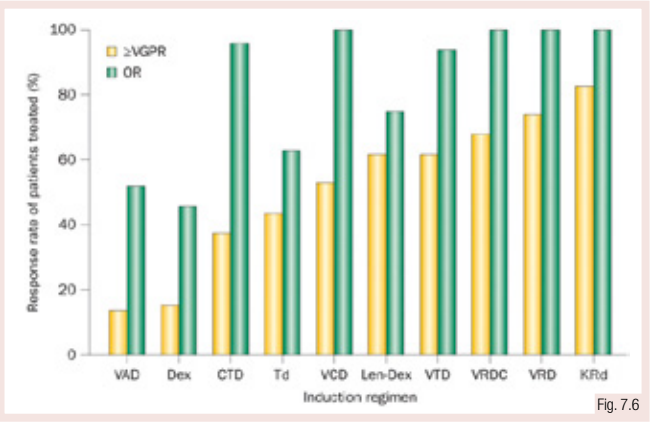

Fig. 7.6

CTD, Cyclophosphamide/thalidomide/dexamethasone; Dex, dexamethasone; KRd, carfilzomib/lenalidomide/dexamethasone; Len-Dex, lenalidomide/dexamethasone; OR, overall response; Td, thalidomide/dexamethasone; VAD, vincristine/doxorubicin/dexamethasone; VCD, bortezomib/cyclophosphamide/dexamethasone; VGPR, very good partial response; VRD, bortezomib/lenalidomide/dexamethasone; VRDC, bortezomib/lenalidomide/dexamethasone/cyclophosphamide; VTD, bortezomib/thalidomide/dexamethasone.

REVISION QUESTIONS

1. Why is ASCT considered the standard of care for younger MM patients?
2. What is the goal of induction therapy?
3. What is the maximum CR rate achieved now with novel agent-based induction regimens?

The role of ASCT in the era of novel agents

Achievement of at least 90% reduction in monoclonal (M) protein concentration after bortezomib-based induction therapy was an early and independent predictor of favourable outcomes following ASCT.

Bortezomib plus dexamethasone (Vd) and Vd combined with thalidomide (VTD) have been approved by the European Medicines Agency (EMA) as induction therapy (for 4 to 6 cycles) in newly diagnosed, ASCT-eligible MM patients.

In addition to VTD, alternative Vd-based triplets incorporate either doxorubicin (PAD), cyclophosphamide (VCD) or lenalidomide (VRD).

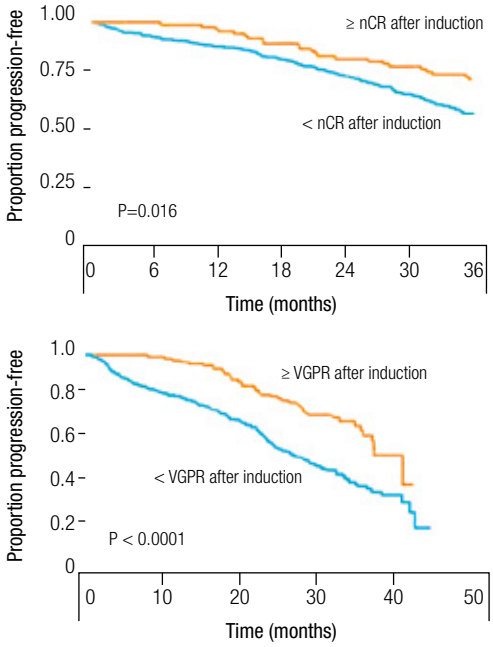

Fig. 7.7

nCR, Near complete response; VGPR, very good partial response.

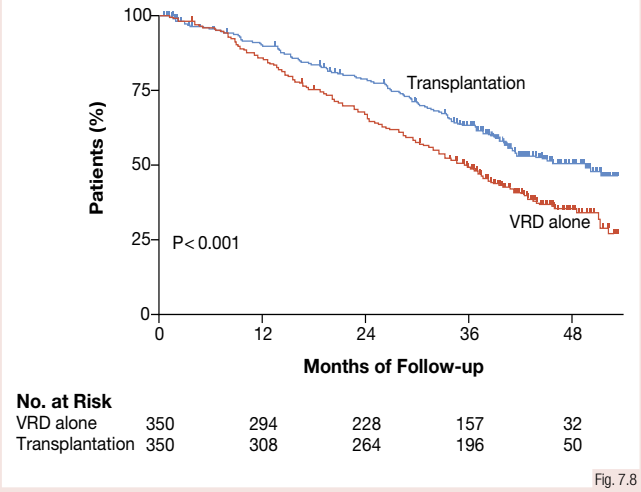

Fig. 7.8

VRD, Bortezomib/lenalidomide/dexamethasone.

The role of upfront ASCT in the treatment paradigm of newly diagnosed MM patients has been questioned in the era of novel agents.

HDM is complementary with PI- and/or IMiD-based induction regimens and further enhances the rate and depth of CR.

A recent study compared VRD as induction and consolidation therapy versus VRD induction followed by upfront ASCT. The latter was associated with superior CR rate and progression-free survival (PFS).

The superiority of ASCT over standard-dose, bortezomib-based therapy was confirmed in an additional large, multicentre, phase III study.

REVISION QUESTIONS

1. Which novel agent-based induction regimens have been approved by the EMA?
2. Does the achievement of high-quality responses to induction therapy predict post-ASCT outcomes?
3. Is there a role for ASCT in the era of novel agents?

The role of double ASCT, consolidation and maintenance therapy

Another important question in the era of novel agents is the role of single versus double ASCT.

In a retrospective analysis comparing single versus double ASCT, the latter was associated with prolonged PFS and overall survival (OS) in patients with high-risk cytogenetic abnormalities (including *del[17p]* and/or *t[4;14]*) who had failed to achieve CR to bortezomib-based induction therapy.

Preliminary results of a European study designed to prospectively randomise patients to a single or double ASCT confirmed the superior outcomes afforded by double over single ASCT in patients with high-risk cytogenetics.

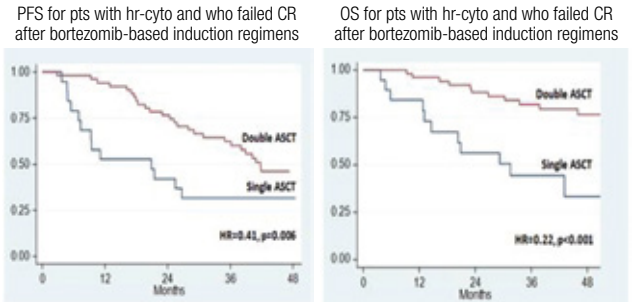

Fig. 7.9

ASCT, Autologous stem cell transplantation; CR, complete response; HR, hazard ratio; hr-cyto, high-risk cytogenetic abnormalities; OS, overall survival; PFS, progression-free survival.

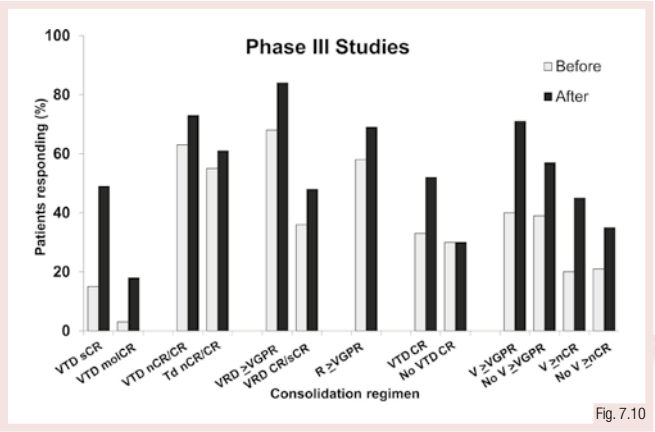

Fig. 7.10

CR, Complete response; molCR, molecular complete response; nCR, near complete response; R, lenalidomide; sCR, stringent complete response; Td, thalidomide/dexamethasone; V, bortezomib; VGPR, very good partial response; VRD, bortezomib/lenalidomide/dexamethasone; VTD, bortezomib/thalidomide/dexamethasone

Although median time to relapse is shorter in patients who fail to achieve CR compared with those in CR, relapse occurs in most of these latter patients.

Consolidation therapy is typically short term and aims to further increase the rate and depth of response after HDM to improve clinical outcomes.

Though novel agents as consolidation therapy have successfully enhanced the rate and depth of response after ASCT, their use cannot be recommended yet outside clinical trials.

Maintenance therapy aims to prolong the duration of response and to prevent or delay disease progression.

An ideal maintenance therapy should prolong OS without inducing the selection of tumour-resistant clones and be well tolerated without adversely affecting the patient's quality of life.

A meta-analysis of three randomised trials comparing lenalidomide maintenance versus placebo or observation after ASCT showed that lenalidomide reduced death risk by 26%.

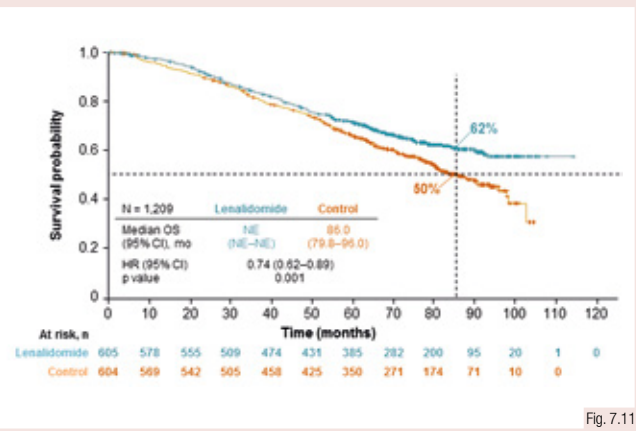

Fig. 7.11

CI, Confidence interval; HR, hazard ratio; NE, not estimable; OS, overall survival.

REVISION QUESTIONS

1. Which subgroups of patients are more likely to benefit from double ASCT?
2. What is the goal of consolidation therapy?
3. Which are the requirements for an ideal maintenance therapy?

The changing landscape of therapy for ASCT-eligible patients

Integration of novel agents into induction therapy before ASCT, and then as part of consolidation and maintenance therapy after ASCT, has transformed the treatment paradigm for younger MM patients.

These sequential blocks of treatment incorporate new drugs with different mechanisms of action and synergistic effects. These agents are administered either in combination or sequentially, aiming to progressively maximise the rate and depth of response.

Recent knowledge that 'the deeper the response, the better the outcome' supports the delivery of sequential blocks of therapy aimed at (possibly) eliminating all clonal cells or eventually at keeping residual tumour cells under control.

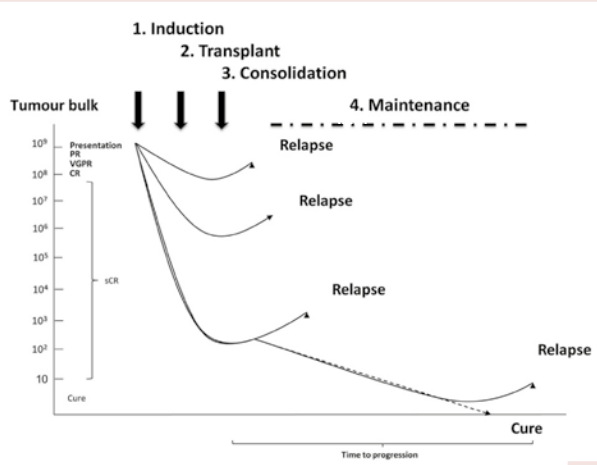

Fig. 7.12

CR, Complete response; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.

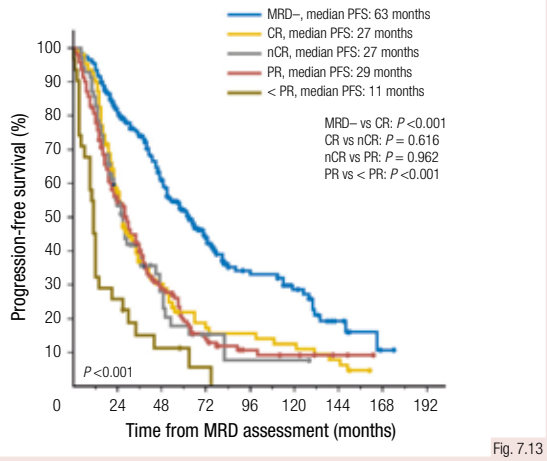

Fig. 7.13

CR, Complete response; MRD, minimal residual disease; nCR, near complete response; PFS, progression-free survival; PR, partial response.

Minimal residual disease (MRD) negativity is a better predictor of favourable outcomes in comparison with conventionally defined CR or lower quality responses.

Among currently available tools for assessment of MRD, multiparametric flow cytometry and next generation sequencing of variable, diversity and joining (VDJ) gene sequences can detect 1 tumour cell in 100 000–1 000 000 normal cells in the bone marrow.

MRD negativity represents the primary endpoint of modern treatment strategies, since it correlates with long-term outcomes.

According to the 2017 European Society for Medical Oncology (ESMO) guidelines, a 3-drug regimen including bortezomib is the preferred induction therapy to be used in preparation for subsequent ASCT.

Upfront ASCT is still the reference treatment for patients who can tolerate HDT. Double ASCT might improve the poor prognosis of patients with unfavourable cytogenetics.

Lenalidomide, the first novel agent approved by the EMA as maintenance therapy after ASCT, is now the preferred treatment in this setting. The optimal duration of maintenance therapy is still debated.

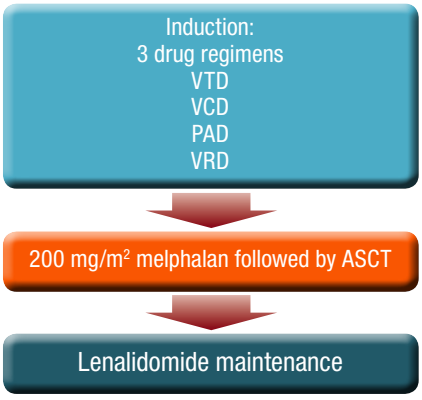

Fig. 7.14

ASCT, Autologous stem cell transplantation; PAD, bortezomib/doxorubicin/dexamethasone; VCD, bortezomib/cyclophosphamide/dexamethasone; VRD, bortezomib/lenalidomide/dexamethasone; VTD, bortezomib/thalidomide/dexamethasone.

The changing landscape of therapy for ASCT-eligible patients (continued)

The current and future treatment algorithm for ASCT-eligible patients

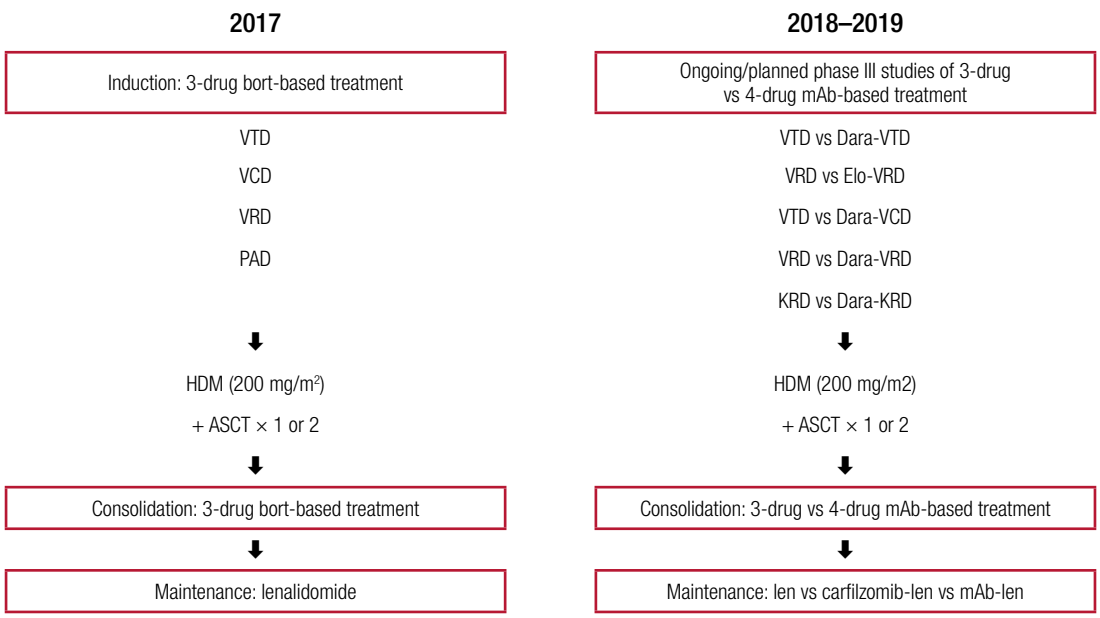

Fig. 7.15

ASCT, Autologous stem cell transplantation; bort, bortezomib; Dara, daratumumab; Elo, elotuzumab; HDM, high-dose melphalan; KRD, carfilzomib/lenalidomide/dexamethasone; len, lenalidomide; mAb, monoclonal antibody; PAD, bortezomib/doxorubicin/dexamethasone; VCD, bortezomib/cyclophosphamide/dexamethasone; VRD, bortezomib/lenalidomide/dexamethasone; VTD, bortezomib/thalidomide/dexamethasone.

Approved novel drugs for the management of MM have extended the median OS from 3 to 8–10 years. Monoclonal antibodies (mAbs) will further improve outcomes.

Ongoing phase III trials are currently investigating 3- versus 4-drug regimens incorporating a mAb combined with a first- or second-generation PI and an IMiD as the backbone of future sequential blocks of therapy for ASCT-eligible MM patients.

In the maintenance phase, 2- or even 3-drug combinations given for different time periods are also being explored in both low-risk and high-risk subgroups of patients.

REVISION QUESTIONS

1. Which endpoint of modern treatments for MM is nowadays considered as a surrogate marker of improved outcomes?
2. What are the ESMO practice recommendations for newly diagnosed ASCT-eligible MM patients?
3. How might the treatment landscape in the ASCT setting change in the next years?

Summary: Newly diagnosed myeloma, transplant-eligible patients

- 30%–40% of patients are diagnosed with MM before the age of 66 years and are operatively defined as younger patients
- Chronological age, performance status and comorbidities represent the criteria to identify patients who can tolerate HDT requiring ASCT
- The ASCT process includes harvest of patient's peripheral blood $CD34^+$ HSCs, which are reinfused into the bloodstream of the same patient to quickly reconstitute haematopoiesis one or two days after HDT
- Induction therapy comprising a bortezomib-based regimen (preferentially a 3-drug) is usually given for 4–6 cycles to reduce tumour load before ASCT and yields up to 30%–35% of conventionally defined CR, which is an early predictor of favourable post-ASCT outcomes
- ASCT after HDM at 200 mg/m^2 remains the standard of care for younger MM patients even in the era of novel agents, due to its ability to further enhance the rate and depth of response and to extend PFS. Double ASCT might improve the poor prognosis of patients with unfavourable cytogenetic abnormalities
- Treatment phases delivered after ASCT include consolidation and maintenance. Consolidation is aimed at (possibly) eliminating all tumour clones, up to the level of MRD negativity
- The goal of maintenance therapy is to sustain the duration of response by preventing or delaying disease progression. Lenalidomide has recently been granted approval by the EMA for use as maintenance therapy and is now the standard treatment in daily clinical practice
- Integration of novel agents into sequential blocks of therapy delivered both before and after ASCT has transformed the treatment paradigm for younger MM patients, ultimately leading to a 3- to 4-fold prolongation of their OS
- MRD negativity represents the primary endpoint of modern treatment strategies since it correlates with long-term outcomes
- 4-drug regimens incorporating a mAb combined with a proteasome inhibitor are likely to be the backbone of future induction and consolidation therapies, while 2- or even 3-drug combinations might be offered as maintenance therapy to special subgroups of patients

Further Reading

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Newly diagnosed myeloma, transplant-ineligible patients

Epidemiology and prognosis

Multiple myeloma (MM) accounts for 13% of all haematological malignancies and 20% of all haematological malignancy-related deaths.

MM is a disease of the elderly: the median age at diagnosis is approximately 70 years.

35%–40% of patients are older than 75 years, with approximately 20% of patients over 80 years old.

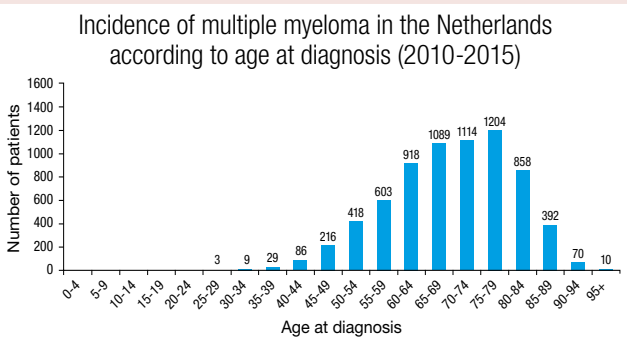

Fig. 8.1

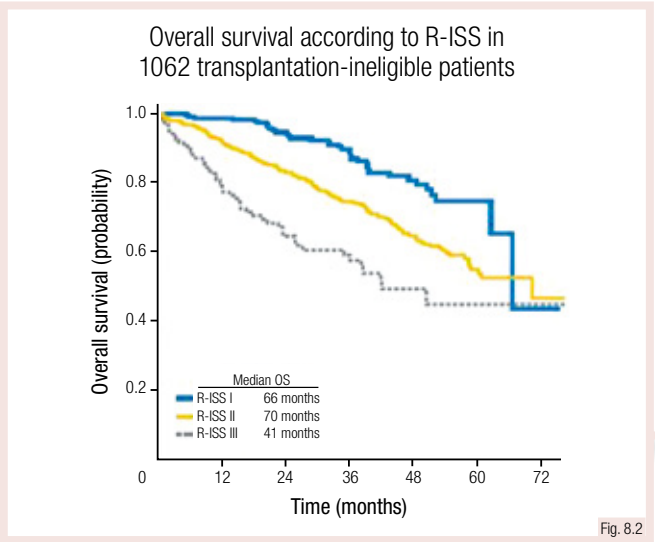

Fig. 8.2

OS, Overall survival; R-ISS, Revised International Staging System.

The prognosis of elderly MM patients not eligible for stem cell transplantation depends on disease characteristics, patient characteristics and treatment.

The two most important disease characteristics are the International Staging System (ISS) (based on the assessment of ß2-microglobulin and albumin) and cytogenetic abnormalities. Cytogenetic high-risk disease is defined by *del(17p)*, *t(4;14)* and *t(14;16)*, and there is no evidence of a higher incidence in the elderly.

The revised ISS (R-ISS), based on the combination of lactate dehydrogenase (LDH), ISS and cytogenetics, is associated with prognosis, even in transplant-ineligible patients.

The introduction of immunomodulatory drugs (IMiDs: thalidomide, lenalidomide [Len] and pomalidomide) and proteasome inhibitors (PIs: bortezomib [Btz], carfilzomib and ixazomib), improved median overall survival (OS) to approximately 5 years.

Patients ≥75 years benefit from new standards of care: either Btz, melphalan and prednisone (VMP) or Len and dexamethasone (Rd); however, the benefit is less than it is for younger transplant-ineligible patients.

Population-based registries show similar results: patients over 65 years who received Len and/or Btz also approach a median OS of 5 years.

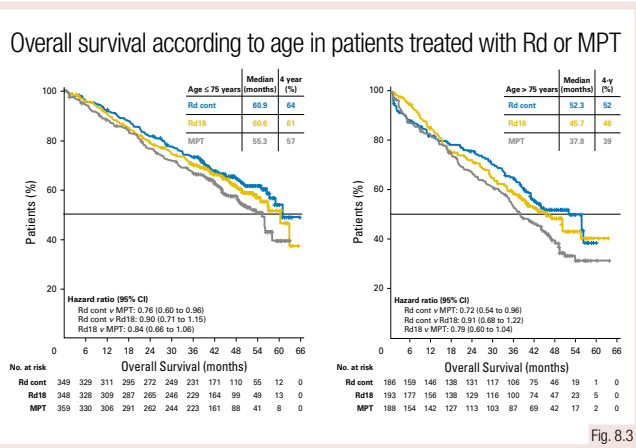

Fig. 8.3

CI, Confidence interval; MPT, melphalan/prednisone/thalidomide; Rd, lenalidomide/dexamethasone; Rd18, same as Rd, for 18 cycles.

REVISION QUESTIONS

1. What is the median age at diagnosis of MM?
2. Which parameters define the R-ISS, and what is its prognostic value?
3. What is the median OS for transplant-ineligible patients with the use of novel agents such as IMiDs and PIs?

Treatment options in transplant-ineligible patients

In fit patients >65 years, an autologous stem cell transplantation (ASCT) should be considered, as stem cell transplantation (SCT) has been shown to improve survival in patients ≤65 years as well as in patients aged 65–75 years.

However, in patients ≥70 years, toxicity-related death after ASCT was higher than in patients aged 65–69: approximately 19% versus 5%.

Therefore, in patients <70 years, SCT should be considered. In non-fit patients and patients ≥70 years, the standard of care in Europe is either VMP or Rd.

Discontinuation for adverse events or death related to adverse events in all patients according to age

	All patients (n=102)	Patients age <70 (n=76)	Patients age ≥70 (n=26)
Discontinuation for adverse events or death related to adverse events	30 (29%)	20 (26%)	10 (38%)
Adverse events	22 (22%)	17 (22%)	5 (19%)
Death related to adverse events	8 (8%)	3 (5%)*	5 (19%)*

Fig. 8.4

*P value (Fisher exact test) 0.024.

Overall survival in patients treated with VMP or MP after a median follow-up of 5 years

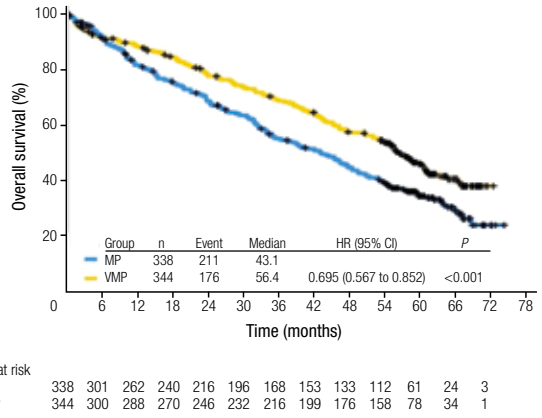

Fig. 8.5

CI, Confidence interval; HR, hazard ratio; MP, melphalan/prednisone; VMP, bortezomib/melphalan/prednisone.

In the VISTA trial, treatment with 9 cycles of VMP resulted in a progression-free survival (PFS) of 20 months and an OS of 56 months.

Btz was found to benefit patients irrespective of age ≥75 years old, cytogenetic risk profile and renal impairment.

In patients with renal impairment, Btz is preferred over Len. Also in cytogenetic high-risk patients, treatment with Btz instead of Len should be considered.

In the VISTA trial, toxicity of VMP consisted mainly of peripheral neuropathy (PNP, grade 2: 17%, grade 3–4: 14%), gastrointestinal (GI) symptoms (grade 3–4: 19%) and herpes zoster (13%).

Thirty-four percent of patients had to discontinue therapy because of toxicity, of which 19% discontinued Btz only. Six cycles of VMP with Btz once-weekly followed by maintenance therapy with Btz for 2–3 years resulted in lower rates of PNP (grade 3–4: 7%) and a PFS of 30.5 months.

Feasibility of VMP was improved by Btz subcutaneous versus intravenous, decreasing the incidence of PNP.

Incidence of peripheral neuropathy with subcutaneous and intravenous bortezomib

	SC bortezomib (n=147)	IV bortezomib (n=74)
Any peripheral neuropathy adverse event	56 (38%)†	39 (53%)
Grade ≥2	35 (24%)‡	30 (41%)
Grade ≥3	9 (6%)∫	12 (16%)
Time to onset of peripheral neuropathy (safety population; months [95% CI])	NE (4.7–NE)	4.4 (2.8–NE)
Cumulative dose at 1st onset of peripheral neuropathy (safety population; mg/m^2 [95% CI])	41.0 (31.2–NE)	25.1 (18.2–39.4)

Fig. 8.6

CI, Confidence interval; IV, intravenous; NE, not estimable; SC, subcutaneous.

For comparison between intravenous and subcutaneous groups, two-sided Fisher's exact test: †p=0.044; ‡p=0.012; ∫p=0.026.

REVISION QUESTIONS

1. Until what age would you consider performing an ASCT in MM patients?
2. What is the efficacy and toxicity profile of VMP?
3. How can the outcome of VMP be improved?

Treatment options in transplant-ineligible patients (continued)

In the FIRST trial, Rd continuously (Rd) was compared with Rd for 18 cycles (Rd18) and melphalan + prednisone (MP)/thalidomide (MPT).
Treatment with Rd until progression resulted in a superior median PFS of 26 months.

The median OS of Rd and Rd18 were similar: 59.1 and 62.3 months, respectively; both superior to MPT (49.1 months).

Rd and Rd18 were not found to be superior to MPT in patients with renal impairment or with high-risk cytogenetics.

Overall survival in patients treated with Rd continuously, Rd 18 cycles or MPT after a median follow-up of 67 months

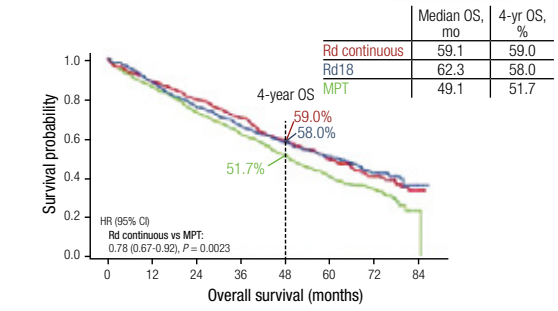

Fig. 8.7

CI, Confidence interval; HR, hazard ratio; MPT, melphalan/prednisone/thalidomide; OS, overall survival; Rd, lenalidomide/dexamethasone; Rd18, same as Rd, for 18 cycles.

Lenalidomide and dexamethasone in transplant-ineligible patients with myeloma

Grade 3 or 4 adverse events			
Event	Continuous Len-Dex (N=532)	Len-Dex for 18 cycles (N=540)	MPT (N=541)
Any grade 3 or 4 adverse event	453 (85%)	433 (80%)	480 (89%)
Haematological adverse events			
Neutropaenia	148 (28%)	143 (26%)	243 (45%)
Anaemia	97 (18%)	85 (16%)	102 (19%)
Thrombocytopaenia	44 (8%)	43 (8%)	60 (11%)
Non-haematological adverse events			
Infection	154 (29%)	118 (22%)	93 (17%)
Deep vein thrombosis, pulmonary embolism or both	42 (8%)	30 (6%)	29 (5%)
Cardiac disorder	63 (12%)	39 (7%)	46 (9%)
Dyspnoea	30 (6%)	22 (4%)	18 (3%)
Fatigue	39 (7%)	46 (9%)	31 (6%)
Rash	33 (6%)	28 (5%)	28 (5%)
Peripheral sensory neuropathy	6 (1%)	2 (<1%)	51 (9%)

Dex, Dexamethasone; Len, lenalidomide; MPT, melphalan/prednisolone/thalidomide.

Fig. 8.8

*The grade 3 or 4 adverse events listed here were those reported by the investigator in at least 5% of any study group in the safety population, which was defined as all patients who underwent randomisation and received at least one dose of the study treatment (lenalidomide, dexamethasone, melphalan, prednisone or thalidomide)

Rd and Rd18 are thus the standard of care in transplant-ineligible patients without renal impairment or cytogenetic high-risk profile. In these two situations VMP is preferred.

Grade 3 and 4 toxicities of Rd consisted of infections (29%), neutropaenia (28%), anaemia (18%) and cardiac disorders (12%). Discontinuation rate due to toxicity was 12%.

Long-term therapy with Len may, after a long asymptomatic period, induce diarrhoea, due to bile salt malabsorption syndrome. Colesevelam or cholestyramine lead to rapid improvement.

The outcome of transplant-ineligible patients can be improved by combination of a PI and an IMiD or the addition of another drug to either VMP or Rd.

8 cycles of VRd (Rd plus Btz) followed by Rd until progression resulted in a median OS of 43 months, versus 30 months with Rd alone until progression.

Addition of daratumumab to VMP and subsequent maintenance therapy resulted in a superior PFS of not reached (NR) versus 18.1 months (hazard ratio [HR] 0.50; 95% confidence interval [CI] 0.38–0.65).

Progression-free survival in patients treated with VMP or daratumumab/VMP

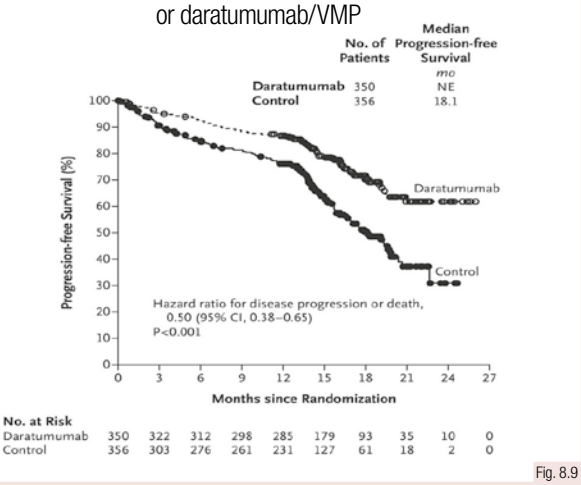

Fig. 8.9

CI, Confidence interval; NE, not estimable; VMP, bortezomib/melphalan/prednisone.

REVISION QUESTIONS

1. What is the efficacy and toxicity profile of Rd?
2. How is lenalidomide-induced bile salt malabsorption syndrome treated?
3. Which treatment can improve the outcome of transplant-ineligible patients?

How to define fitness of MM patients

There are two prognostic scoring systems based on patient-related characteristics: the International Myeloma Working Group (IMWG) Frailty Index and the Revised-Myeloma Comorbidity Index (R-MCI).

The IMWG Frailty Index is based on age, Charlson Comorbidity Index (CCI) and (Instrumental) Activities of Daily Living ([I]ADL). Definitions are as follows: fit score 0, unfit/intermediate fit score 1 and frail score 2 or higher.

In a multivariate analysis, frailty, ISS stage III and high-risk cytogenetics equally predicted PFS, whereas for OS, the HR increased most with frailty, as compared with ISS stage III and high-risk cytogenetics.

Multivariate analysis (final Cox regression model)			
	HR for OS (95% CI)	P	Score
Age, years			
≤75	1	–	0
76–80	1.13 (0.76–1.69)	0.549	1
>80	2.40 (1.56–3.71)	<0.001	2
ADL			
>4	1	–	0
≤4	1.67 (1.08–2.56)	0.020	1
IADL			
>5	1	–	0
≤5	1.43 (0.96–2.14)	0.078	1
CCI			
≤1	1	–	0
≥2	1.37 (0.92–2.05)	0.125	1

ADL, Activities of Daily Living; CCI, Charlson Comorbidity Index; CI, confidence interval; HR, hazard ratio; IADL, Instrumental Activities of Daily Living; OS, overall survival. Fig. 8.10

Among frail patients, 47% were >80 years, and 19% were found to be frail due to age >80 only.

Overall survival (a) and discontinuation rate (b) in fit, unfit and frail patients.

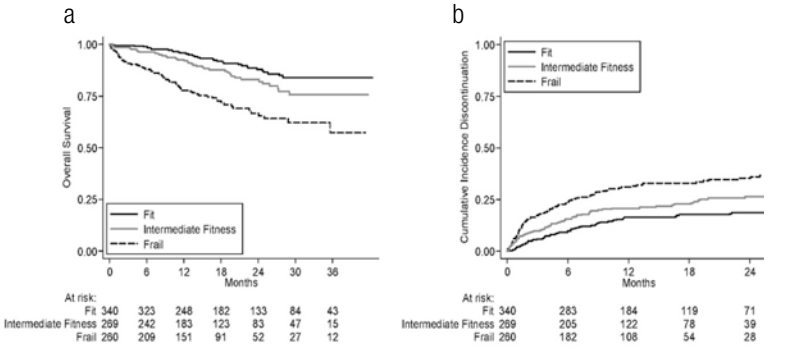

Fig. 8.11

The 3-year OS was 84% in fit, 76% in unfit and 57% in frail patients. The IMWG Frailty Index was validated in a large cohort of patients, showing a 3-year OS of 91%, 77% and 47%, respectively.

Frail patients (score ≥2) experienced more non-haematological side effects than fit patients. Moreover, frail patients had a 2.2 times higher discontinuation rate as compared with fit patients (score 0).

The R-MCI, being validated in roughly 800 MM patients, includes parameters such as renal and pulmonary function, Karnofsky Performance Status, frailty, age and cytogenetic abnormalities.

These parameters were combined in the weighted R-MCI, allowing identification of fit (R-MCI 1–3 [30.8%]), intermediate-fit (R-MCI 4–6 [55.7%]) and frail patients (R-MCI 7–9 [13.5%]).

The median OS for fit, unfit and frail patients was 10.1, 4.4 and 1.2 years, respectively. The R-MCI was also associated with OS in patients not receiving an SCT.

Overall survival according to R-MCI based frailty assessment in patients who did not receive an SCT

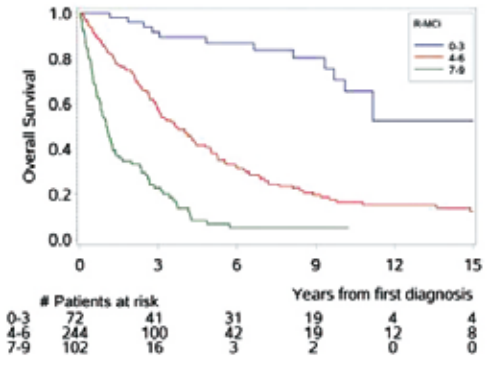

Fig. 8.12

R-MCI, Revised-Myeloma Comorbidity Index; SCT, stem cell transplantation.

REVISION QUESTIONS

1. How can frailty be defined?
2. Which parameters are of importance?
3. What is the impact of frailty on OS and discontinuation rate?

How to adapt therapy in unfit and frail patients?

There are no randomised clinical trials comparing different treatment regimens in unfit and frail patients.

High-dose dexamethasone (Dex) (480 mg per month) is associated with more adverse events than low-dose Dex (160 mg per month) or prednisone, with infections, diabetes, GI and psychiatric complications, and early mortality.

In the FIRST trial, patients >75 years old received 20 mg Dex weekly instead of 40 mg. With this dose modification, grade 3–4 infections were comparable with patients ≤75 years: approximately 30% in patients treated with Rd continuously and 20% for patients treated with Rd18.

Overall survival of patients receiving lenalidomide with either high-dose or low-dose dexamethasone, approximately 50% of patients being over ≥65 years

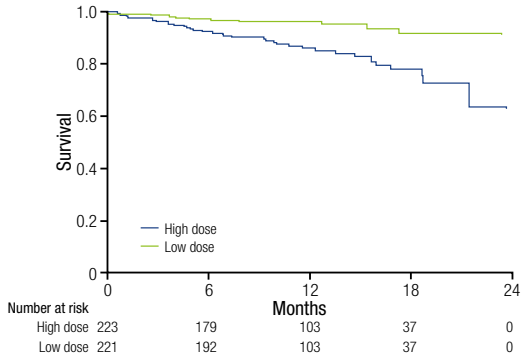

Fig. 8.13

Example of dose modification based on age and comorbidities, or on IMWG frailty index or the R-MCI				
RISK FACTOR				
IMWG Frailty index[1]	0	1	1 + occurrence of grade 3–4 haematological adverse event	≥2
R-MCI[2]	1–3	4–6	7–9	
DOSE LEVEL	0	-1	-2	-2

Treatment doses	LEVEL 0	LEVEL -1	LEVEL -2
Prednisone	2 mg/kg d1-4 of q4-6w 60 mg/m² d1-4 of q6w	1 mg/kg d1–4 of q4–6w 30 mg/m² d1–4 of q6w	0.3 mg/kg d1–4 of q4–6w 10–15 mg/m² d1–4 of q6w
Dexamethasone	40 mg d1, 8, 15, 22 of q28d	20 mg d1, 8, 15, 22 of q28d	10 mg d1, 8, 15, 22 of q28d
Melphalan	0.25 mg/kg d1–4 of q4–6w 9 mg/m² d1–4 of q6w	0.18 mg/kg d1–4 of q4–6w 7.5 mg/m² d1–4 of q6w	0.13 mg/kg d1–4 of q4–6w 5 mg/m² d1–4 of q6w
Thalidomide	100 (–200) mg/day	50 (–100) mg/day	50 mg qod (–50 mg/day
Lenalidomide	25 mg d1–21 of q28d	15 mg d1–21 of q28d	10 mg d1–21 of q28d
Bortezomib	1.3 mg/m² twice weekly d1, 4, 8, 11 of q3w	1.3 mg/m² once weekly d1, 8, 15, 22 of q5w	1.0 mg/m² once weekly d1, 8, 15, 22 of q5w

d, Day; IMWG, International Myeloma Working Group; R-MCI, Revised-Myeloma Comorbidity Index; qod, every other day; qXd, every X days; qXw, every X weeks.

Fig. 8.14

1. http://www.myelomafrailtyscorecalculator.net/
2. http://www.myelomacomorbidityindex.org/en_about.html (31 January 2019, date last accessed)

Once-weekly administration of Btz instead of twice-weekly resulted in a decrease in grade 3–4 PNP from 14% to 7%.

Without randomised clinical trials investigating optimal frailty-based treatment regimens, expert opinion-based dose modification schemes for first-line treatment of transplant-ineligible patients are based on age and comorbidities.

Besides dose modification schemes such as VMP-light, 2-drug instead of 3-drug regimens can be used in elderly non-fit and frail patients.

Regimens such as Btz/Dex instead of VMP in elderly patients have demonstrated lower response rates, but also lower toxicity and related early discontinuation, finally resulting in similar outcomes.

New drugs with different toxicity or mechanisms of action might be of added value in elderly and unfit/frail patients. Oral PIs, with much less PNP, and monoclonal antibodies, with only limited infusion-related side effects, such as anti-CD38 and anti-SLAMF7, are of particular interest.

REVISION QUESTIONS

1. How can treatment be adapted in the eldest, unfit and frail MM patients?
2. What are the main limiting toxicities?
3. Which new drugs are of interest for less fit patients?

Summary: Newly diagnosed myeloma, transplant-ineligible patients

- MM is a disease of the elderly with a median age at diagnosis of approximately 70 years
- The introduction of IMiDs and PIs improved median OS of transplant-ineligible MM patients to approximately 5 years
- First-line therapy for transplant-ineligible MM patients is either VMP or Rd. An ASCT should be considered in fit MM patients <70 years
- A bortezomib-based regimen was found to benefit patients irrespective of cytogenetic high-risk profile and renal impairment, and is preferred above lenalidomide in these patients
- Further improvement in outcome can be reached by a combination of an IMiD and a PI – either VRd or a combination of 9 cycles of VMP and 9 cycles of Rd, or the addition of another drug to VMP or Rd (being currently shown for daratumumab-VMP)
- Two prognostic scoring systems can define the fitness of MM patients: the IMWG Frailty Index and the R-MCI
- Frail patients have a shorter median OS, experience more non-haematological side effects, and have a higher discontinuation rate as compared with fit patients; therefore therapy must be adjusted
- However, there are no randomised clinical trials comparing different treatment regimens in unfit and frail patients
- Expert opinion-based dose modification schemes and 2-drug regimens instead of 3-drug regimens are recommended for transplant-ineligible patients, based on age and comorbidities
- New drugs, such as monoclonal antibody-based regimens, with different mechanisms of action and a favourable toxicity profile, might be of added value in elderly and unfit/frail patients

Further Reading

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Relapsed and refractory multiple myeloma

General considerations

Prompt treatment initiation should be considered for multiple myeloma (MM) patients with rapid, symptomatic relapse, while patients with slow, asymptomatic relapse can be followed closely.

The treatment strategy is driven by factors related to the patient (performance status, comorbidities), prior treatment regimens (transplant or not, toxicity from previous regimens) and disease (cytogenetic profile).

Primary refractoriness, treatment-free interval <1 year and treatment-free interval <2 years after achieving a complete response (CR) should be considered as adverse prognostic factors.

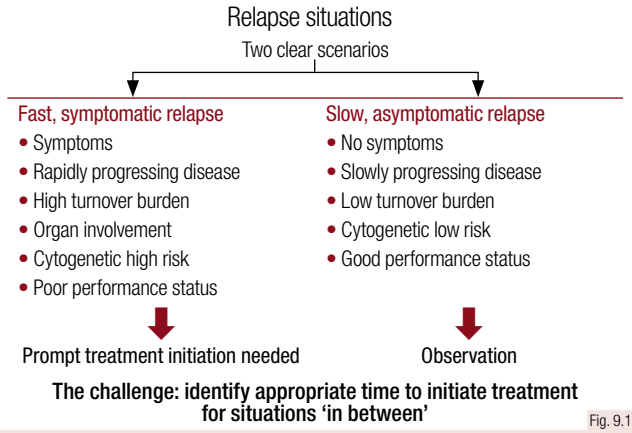
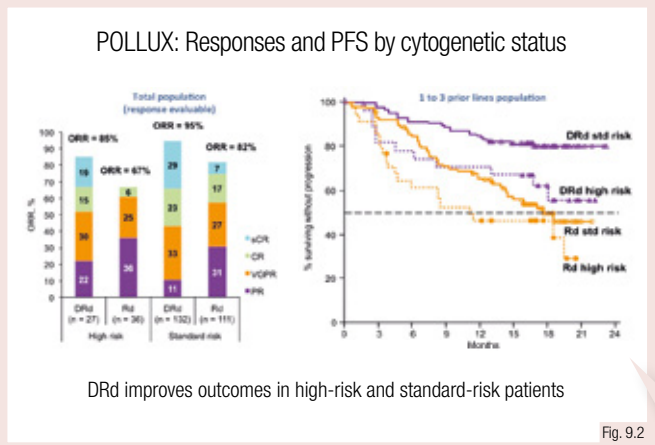


Fig. 9.1



DRd improves outcomes in high-risk and standard-risk patients

Fig. 9.2

CR, Complete response; DRd, daratumumab/lenalidomide/dexamethasone; ORR, overall response rate; PFS, progression-free survival; PR, partial response; Rd, lenalidomide/dexamethasone; sCR, stringent complete response; VGPR, very good partial response.

Further adverse prognostic factors are aggressive relapse, the presence of adverse cytogenetic abnormalities (especially deletion *17p*), advanced age, extramedullary disease and comorbidities.

Historically, patients with relapse were treated with bortezomib or lenalidomide, either as single agents or in combination with other drugs. More recently, other classes of drugs are increasingly included in the treatment strategy for relapse.

All the drug combinations appear to achieve better results in younger patients.

Even the most active treatments cannot compensate for adverse prognostic factors

If patients relapse after a previous ASCT, a second ASCT induces a longer remission compared with oral cyclophosphamide

For transplantation-eligible patients relapsing after a primary therapy NOT including an autologous stem cell transplantation (ASCT), high-dose therapy (HDT) with ASCT should be considered.

HDT and ASCT may also be considered an appropriate treatment for selected patients relapsing after primary therapy that included an ASCT if the initial remission duration was >18 months.

For some selected patients, HDT and ASCT can be used as a bridging strategy to allogeneic stem cell transplantation (alloSCT).

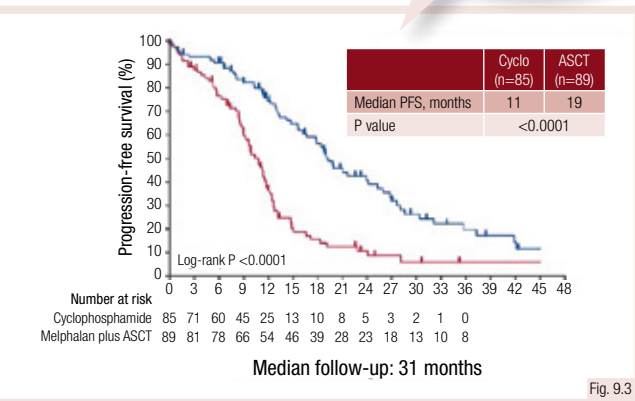


Fig. 9.3

ASCT, Autologous stem cell transplantation; Cyclo, cyclophosphamide; PFS, progression-free survival.

REVISION QUESTIONS

1. Summarise the features and risk factors that should be involved in your treatment decision.
2. Which criteria drive the treatment selection in the relapsed setting?
3. What is the role of ASCT in the relapsed setting?

Classical relapse regimens based on proteasome inhibitors and immunomodulatory drugs

Proteasome inhibitors (PIs) and immunomodulatory drugs (IMiDs) are two classes of drugs with high activity in the relapsed/refractory MM (RRMM) setting and represent the backbone of most relapsed myeloma treatment schemes.

PIs include bortezomib, ixazomib and carfilzomib. IMiDs include thalidomide, lenalidomide and pomalidomide, which has been recently approved for double-refractory patients.

Bortezomib was the first PI approved, it is administered subcutaneously and may induce significant peripheral neuropathy.

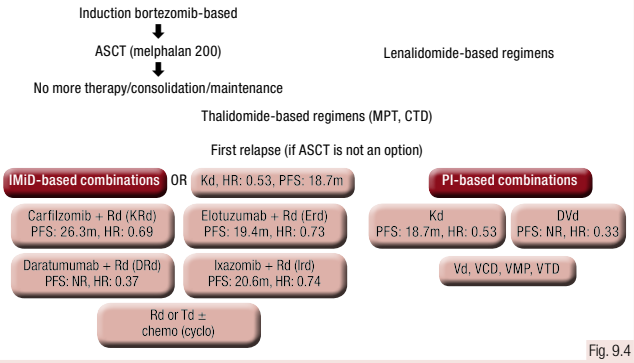


Fig. 9.4

ASCT, Autologous stem cell transplantation; CTD, cyclophosphamide/thalidomide/dexamethasone; DVd, daratumumab/bortezomib/dexamethasone; HR, hazard ratio; IMiD, immunomodulatory drug; Kd, carfilzomib/dexamethasone; MPT, melphalan/prednisone/thalidomide; NR, not reached; PFS, progression-free survival; PI, proteasome inhibitor; Rd, lenalidomide/dexamethasone; RRMM, relapsed/refractory multiple myeloma; Td, thalidomide/dexamethasone; VCD, bortezomib/cyclophosphamide/dexamethasone; Vd, bortezomib/dexamethasone; VMP, bortezomib/melphalan/prednisone; VTD, bortezomib/thalidomide/dexamethasone.

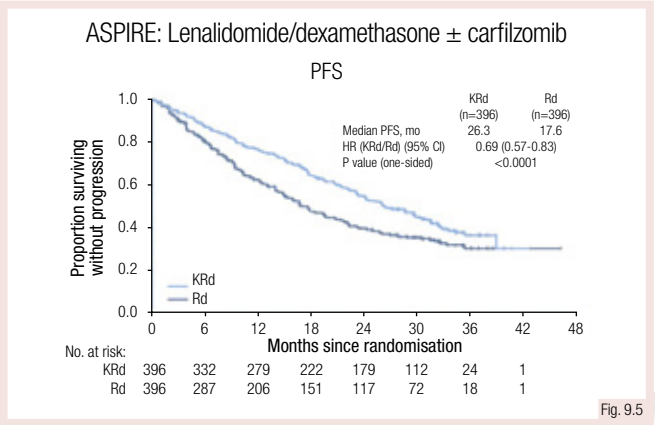


Fig. 9.5

CI, Confidence interval; HR, hazard ratio; KRd, carfilzomib/lenalidomide/dexamethasone; PFS, progression-free survival; Rd, lenalidomide/dexamethasone.

Carfilzomib is administered intravenously and is approved either combined with lenalidomide/dexamethasone (Rd) or with dexamethasone alone.

For patients who relapsed after 1–3 prior lines of therapy, the combination carfilzomib/dexamethasone was associated with a doubling of progression-free survival (PFS) when compared with bortezomib/dexamethasone (Vd), and demonstrated overall survival (OS) benefit (ENDEAVOR study).

The triplet combination carfilzomib/lenalidomide/dexamethasone (KRd) demonstrated a clear PFS benefit compared with Rd (ASPIRE study).

Ixazomib is an oral PI recently approved in combination with Rd, based on PFS benefit versus Rd alone after ≥1 prior line of therapy.

Several new treatment combinations, based on the PIs and IMiDs backbone along with novel drug agents, have been approved for the treatment of RRMM.

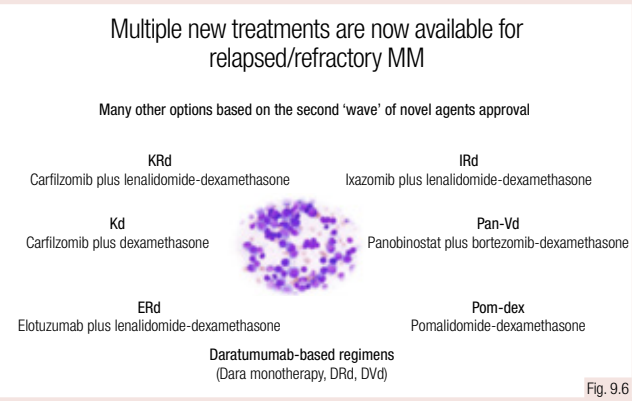


Fig. 9.6

DRd, Daratumumab/lenalidomide/dexamethasone; DVd, daratumumab/bortezomib/dexamethasone; MM, multiple myeloma.

REVISION QUESTIONS

1. Which are the main 'therapeutic class' agents used for the treatment of relapsed MM patients?
2. What is the role of carfilzomib in the RRMM setting?
3. Which are the most recent PIs and IMiDs approved for relapsed myeloma patients?

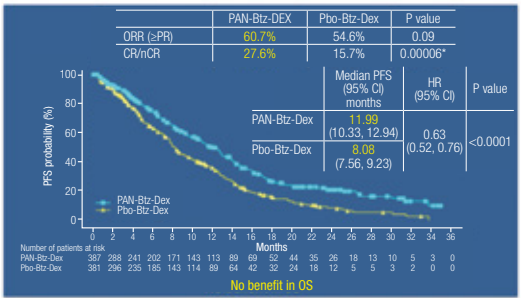
New relapse regimens based on antibodies and other targeted drugs

Drugs with different mechanisms of action such as monoclonal antibodies (mAbs), histone deacetylase (HDAC) inhibitors (HDACis), kinase inhibitors and inhibitors of different proteins or signalling pathways are currently either approved or under investigation.

Histone deacetylases are enzymes overexpressed in MM. HDACis are not effective as a monotherapy; however, they act synergistically with PIs.

Panobinostat is an HDACi approved in combination with Vd (PanoVd) for patients who have received ≥2 prior lines of therapy, including bortezomib and lenalidomide.

PANORAMA: Panobinostat + Btz + Dex vs Btz + Dex



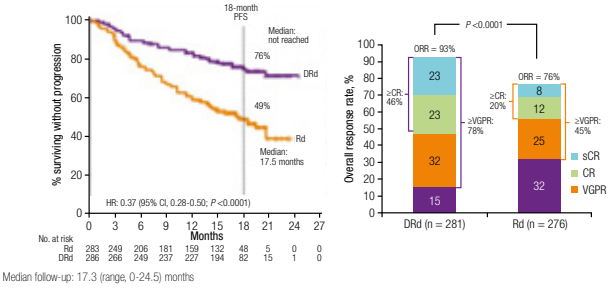
PAN-Btz-Dex-treated patients had a 37% reduction in the risk of disease progression or death in comparison with Btz-Dex

*Based on post-hoc testing

Fig. 9.7

Btz, Bortezomib; CI, confidence interval; CR, complete response; Dex, dexamethasone; HR, hazard ratio; nCR, near complete response; ORR, overall response rate; OS, overall survival; PAN, panabinostat; Pbo, placebo; PFS, progression-free survival; PR, partial response.

POLLUX (DRd + Rd): Updated efficacy



Median follow-up: 17.3 (range, 0-24.5) months

DRd-treated patients had a 63% reduction in the risk of disease progression or death in comparison with Rd

Responses continue to deepen in the DRd group with longer follow-up

Fig. 9.8

CI, Confidence interval; CR, complete response; DRd, daratumumab/lenalidomide/dexamethasone; HR, hazard ratio; ORR, overall response rate; PFS, progression-free survival; Rd, lenalidomide/dexamethasone; sCR, stringent complete response; VGPR, very good partial response.

Daratumumab is a human IgG1κ mAb that binds with high affinity to the CD38 molecule, which is highly expressed on the surface of the myeloma cells.

Daratumumab has been approved in combination with Rd (DRd) or Vd (DVd) in patients who have received ≥1 prior line of therapy.

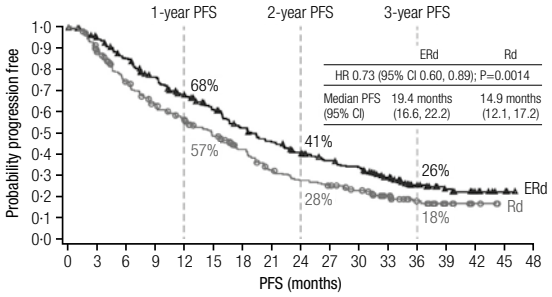
Daratumumab is also approved as a monotherapy for patients who have received ≥3 prior lines of therapy, including a PI and an IMiD, or who are double refractory to a PI and an IMiD.

DRd-treated patients had a 63% reduction in the risk of disease progression or death compared with Rd. DVd-treated patients had a 67% reduction in the risk of disease progression or death compared with Vd.

Following daratumumab approval in the refractory MM setting, other anti-CD38 mAbs such as isatuximab and MOR202 are currently under investigation.

Elotuzumab is an anti-SLAMF7 mAb recently approved in combination with Rd (ERd) for patients who have received ≥1 prior therapy. The PFS benefit with ERd was maintained over time.

ELOQUENT-2: Phase III study of elotuzumab + Rd vs Rd: extended PFS



PFS benefit with ERd maintained over time (vs Rd):
Overall 27% reduction in the risk of disease progression or death
Relative improvement in PFS of 44% at 3 years

Fig. 9.9

CI, Confidence interval; ERd, elotuzumab/lenalidomide/dexamethasone; HR, hazard ratio; PFS, progression-free survival; Rd, lenalidomide/dexamethasone.

REVISION QUESTIONS

1. Which mAbs have proven efficacy for relapsed MM?
2. What is the role of elotuzumab in the RRMM setting?
3. Which new molecules are currently being investigated in the RRMM setting in combination with a PI or an IMiD?

Practical management of relapsed myeloma

The comorbidity profile and any pre-existing toxicity should always be considered in the therapeutic approach.

For patients with significant cardiac dysfunction, caution should be taken with carfilzomib administration due to potential cardiotoxicity. For patients with peripheral neuropathy, bortezomib and ixazomib should be used cautiously.

For patients with chronic obstructive pulmonary disease (COPD) or asthma, daratumumab administration should be followed closely. For patients with history of thrombosis, thromboprophylaxis should be given when considered for IMiDs.

How are we going to proceed in clinical practice?

- Type of relapse: aggressive, …
  - KRd/DRd for aggressive relapse with rapid control required
- Age: all combinations work better in young patients
  - IMiD-based combos: DRd & ERd . 1st preference for elderly
  - PI-based combos: DVd & Kd ..... 1st preference for elderly
- Number and type of prior lines of therapy
- Cytogenetic abnormalities
- Comorbidities and/or cumulative toxicity: → **Be cautious with:**
  - Moderate/severe cardiac comorbidities: → Carfilzomib
  - Peripheral neuropathies: → Bortezomib/ixazomib
  - Severe COPD/asthma, … : → Daratumumab
  - Severe thrombotic events: → IMiDs

Fig. 9.10

COPD, Chronic obstructive pulmonary disease; DRd, daratumumab/lenalidomide/dexamethasone; DVd, daratumumab/bortezomib/dexamethasone; ERd, elotuzumab/lenalidomide/dexamethasone; IMiD, immunomodulatory drug; Kd, carfilzomib/dexamethasone; KRd, carfilzomib/lenalidomide/dexamethasone; PI, proteasome inhibitor.

Treatment choice	Prior line of therapy	
	Type	Number
KRd	After PIs/PI-sensitive	After 1 and ≥2 prior lines
IRd	After PIs/PI-sensitive – Primary refractory patients	After 2–3 prior lines
DRd	After PIs/regardless PI-sensitivity	After 1 and ≥2 prior lines
ERd	After PIs/regardless PI-sensitivity	Time from dx is >3.5 years (regardless 1 and ≥2 prior lines)
Kd	After PIs/IMiDs (s/r)	After 1 or ≥2 prior lines
DVd	After PIs/IMiDs (s/r)	After 1 prior line
REP	Len-refractory	

Fig. 9.11

DRd, Daratumumab/lenalidomide/dexamethasone; DVd, daratumumab/bortezomib/dexamethasone; ERd, elotuzumab/lenalidomide/dexamethasone; IMiD, immunomodulatory drug; IRd, isatuximab/lenalidomide/dexamethasone; Kd, carfilzomib/dexamethasone; KRd, carfilzomib/lenalidomide/dexamethasone; Len, lenalidomide; PI, proteasome inhibitor; REP, prednisone.

For elderly patients, DRd, ERd and IRd (ixazomib plus Rd) may be the IMiD-based regimens of choice, and DVd and Kd (carfilzomib plus dexamethasone) the PI-based regimens of preference.

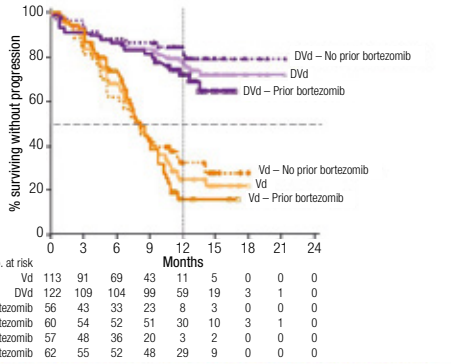
Triplet combinations (KRd/DRd/DVd) can be considered for aggressive relapses and whenever rapid control is required.

DRd is superior to Rd, regardless of time since the last therapy or bortezomib refractoriness. DVd provided clear treatment benefit regardless of prior bortezomib exposure or IMiD refractoriness.

Kd improves PFS especially in the patient group with 1 prior line of treatment, while KRd seems to be more beneficial in the group that received ≥2 previous lines of therapy.

ERd improves the outcome in the high-risk cytogenetics group in comparison with Rd. DVd improves outcomes regardless of cytogenetic risk. DRd improves outcomes in both high-risk and standard-risk patients. IRd achieves similar PFS in both high-risk and standard-risk patients.

CASTOR: PFS by prior bortezomib exposure (1 prior-line population)



No. at risk									
Vd	113	91	69	43	11	5	0	0	0
DVd	122	109	104	99	59	19	3	1	0
Vd – No prior bortezomib	56	43	33	23	8	3	0	0	0
DVd – No prior bortezomib	60	54	52	51	30	10	3	1	0
Vd – Prior bortezomib	57	48	36	20	3	2	0	0	0
DVd – Prior bortezomib	62	55	52	48	29	9	0	0	0

DVd provides treatment benefit regardless of prior bortezomib exposure

Fig. 9.12

DVd, Daratumumab/bortezomib/dexamethasone; PFS, progression-free survival; Vd, bortezomib/dexamethasone.

REVISION QUESTIONS

1. Which treatment strategy would you choose for elderly patients?
2. In which patients should carfilzomib administration be closely monitored?
3. When you treat a patient with daratumumab, which comorbidities should you always consider before administration?

New treatments for relapse

Several proteins have recently emerged as possible targets in MM, such as BCL-2 and XPO1. A BCL-2 inhibitor (venetoclax) has shown an overall response rate (ORR) of 21%.

Venetoclax seems to be more effective in patients harbouring *t(11;14)* (ORR 40%) and is currently being investigated in combination with Vd.

Selinexor is an XPO1 inhibitor; in combination with dexamethasone it has achieved an ORR of 20% in penta-refractory (IMiDs, PIs, anti-CD38 mAbs, alkylators) patients.

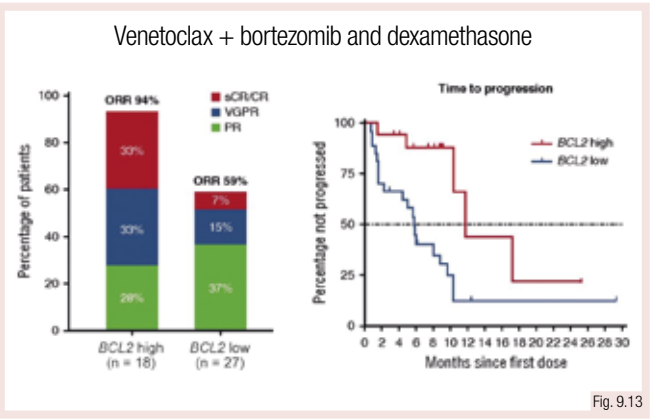


Fig. 9.13

CR, Complete response; ORR, overall response rate; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.

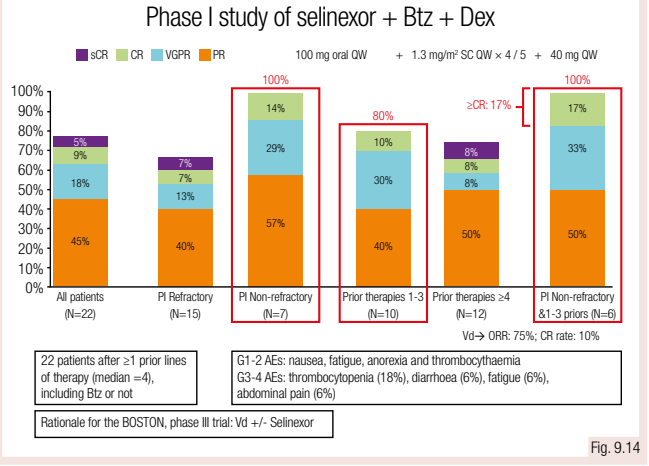


Fig. 9.14

AE, Adverse event; Btz, bortezomib; CR, complete response; Dex, dexamethasone; ORR, overall response rate; PI, proteasome inhibitor; PR, partial response; QW, once weekly; SC, subcutaneous; sCR, stringent complete response; Vd, bortezomib/dexamethasone; VGPR, very good partial response.

Immunotherapy is less developed in myeloma compared with other malignancies. Nevertheless, data are being generated with anti-programmed cell death protein 1 (PD-1) and with cell-based therapies.

Pembrolizumab is an anti-PD-1 mAb with no significant anti-myeloma activity as monotherapy. When combined with IMiDs, an ORR of approximately 36%–55% in double-refractory patients could be achieved.

Unmodified cells: marrow infiltrating lymphocytes (MILs) are cells that possess a broad endogenous tumour specificity and are enriched for central memory T cells that make them a more suitable source of cells for adoptive T cell approaches.

Autologous T cells can be reprogrammed by transducing them with a chimeric antigen receptor (CAR) which specifically targets tumour cells, and can thereby combine the specificity of an antibody with the potent cytotoxic and memory functions of a T cell.

CAR-T cells against CD19 or BCMA (B cell maturation antigen) are currently under investigation in MM patients. The cytokine release syndrome and neurological toxicity remain a concern.

Adoptive T cell immunotherapeutic strategies

1. **Unmodified cells:**
   Marrow infiltrating lymphocytes (MILs) → Broad endogenous tumour specificity, enriched for central memory T cells → more suitable for adoptive T cell approaches
2. **CAR-T cells:**
   ASCT plus CTL019 → Rescue therapy in 12 patients progressing within 1 year after ASCT. Median PFS: 6 months, all patients have progressed

   CAR-T-BCMA → Rescue therapy in 6 RRMM patients after a median of 9 prior lines. 1 sCR (+7 m), 1 VGPR (+5m) and 2 MR

   BCMA Ab (conjugated with auristatin) → 24 patients after more than 4 prior lines. 25% of unconfirmed responses

Fig. 9.15

Ab, Antibody; ASCT, autologous stem cell transplantation; BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; MR, minimal response; PFS, progression-free survival; RRMM, relapsed/refractory multiple myeloma; sCR, stringent complete response; VGPR, very good partial response.

REVISION QUESTIONS

1. What is a CAR-T cell?
2. What are the main concerns regarding CAR-T cell therapeutic strategy?
3. What is the mechanism of action of venetoclax?

Summary: Relapsed and refractory multiple myeloma

- Treatment of RRMM patients after 1–3 prior lines of therapy includes novel combinations with Rd or Vd as backbones (KRd, DRd, DVd, IRd, ERd and PanVd)
- Carfilzomib and ixazomib represent the second generation of PIs approved for RRMM treatment
- Kd is clearly superior to Vd in RRMM
- Pomalidomide is a third-generation IMiD approved for double-refractory MM
- Daratumumab is the first CD38 mAb approved for myeloma therapy
- DVd significantly improved PFS, time to progression and ORR in comparison with Vd
- DRd significantly improved PFS in comparison with Rd
- The HDACi panobinostat is approved in MM in combination with Vd
- Other novel agents targeting the BCL-2 family (venetoclax) and exportin-1 (selinexor), anti-PD-1/programmed death-ligand 1 and CAR-T cells are currently under investigation, especially in combination with backbone agents
- The use of the most effective combinations plus mAbs in the upfront setting will result in better outcomes with a significant proportion of patients being considered 'operationally cured'

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Symptomatic therapy and management of complications in myeloma

10

Symptomatology of myeloma patients

Multiple myeloma (MM) is characterised by: (i) malignant plasma cell infiltration in bone marrow; (ii) immune impairment; (iii) production of monoclonal protein.

Patients usually present with anaemia and pain due to bone destruction. Renal impairment can occur and there is an increased susceptibility to infections.

This can lead to impairment of the patient's quality of life and impacts life expectancy.

End-organ damage in myeloma

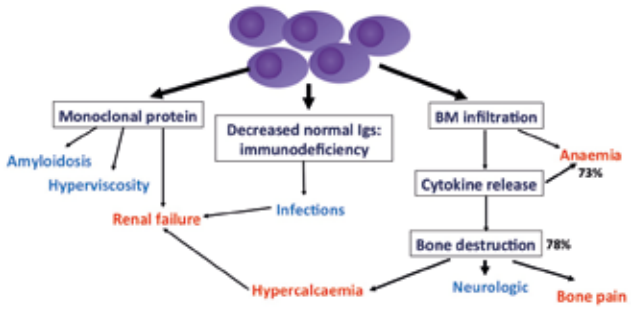

Fig. 10.1

BM, Bone marrow; Ig, immunoglobulin.

Myeloma-defining events

Evidence of end-organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:

- Hypercalcaemia: serum calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2.75 mmol/L (>11 mg/dL)
- Renal insufficiency: creatinine clearance <40 mL per minute or serum creatinine >177 µmol/L (>2 mg/dL)
- Anaemia: haemoglobin value of >20 g/L below the lower limit of normal, or a haemoglobin value <100 g/L
- Bone lesions: one or more osteolytic lesions on skeletal radiography, computed tomography (CT), or fluorodeoxyglucose (FDG)-positron emission tomography (PET)-CT

Any one or more of these biomarkers of malignancy:

- Clonal plasma cell bone marrow infiltration ≥60%
- Involved: uninvolved serum free-light chain ratio ≥100
- >1 focal lesion on magnetic resonance imaging studies

Fig. 10.2

Symptomatic therapy in MM includes the prevention and management of myeloma-defining events, present in almost all patients.

The disease definition is clinico-pathological; as a consequence, clinical manifestations of end-organ damage are required for diagnosis.

The definition of MM has been updated and includes the presence of some biomarkers predicting imminent risk of symptomatic MM; their early detection and treatment initiation can avoid the development of debilitating complications.

In recent years, several novel agents with different mechanisms of action have been incorporated into the treatment armamentarium of MM.

Although their overall toxicity profile is favourable, due to their complexity prolonged use requires attention to early and late side effects.

When drug-related specific side effects are known, it is possible to prevent them, detect them early and, if necessary, treat them appropriately.

Myeloma treatment (2000 - 2017)

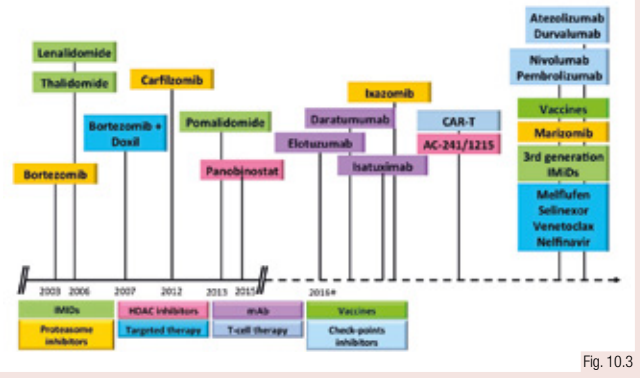

Fig. 10.3

CAR, Chimeric antigen receptor; HDAC, histone deacetylase; IMiD, immunomodulatory drug; mAb, monoclonal antibody.

REVISION QUESTIONS

1. What are the most frequent myeloma-related symptoms at the time of diagnosis?
2. Which are the newly identified biomarkers predicting imminent risk of progression to MM?
3. Cite three of the new drug classes for the treatment of MM patients.

Management of bone disease

Myeloma cells produce factors activating and enhancing osteoclast formation, leading to bone resorption, and also induce a decrease in bone formation through the impairment of osteoblasts function.

Bone destruction may lead to pathological fractures whereas neurological symptoms may warn of spinal cord compression.

The management of bone disease is focused on: (i) prevention and (ii) treatment of bone lesions. Bisphosphonates (BPs) are key for the prevention of bone disease.

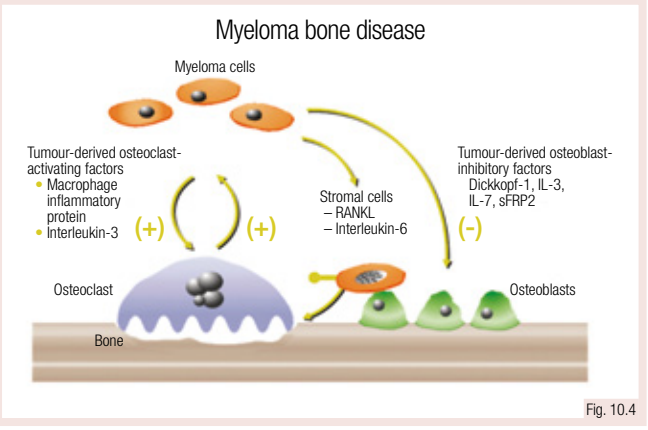

Fig. 10.4

IL, Interleukin; RANKL, receptor activator of nuclear factor kappa-B ligand.

Prevention of bone disease: Recommendations for use of bisphosphonates (BPs) in MM

Factor	Recommendations
Patient population	Newly diagnosed MM patients who require anti-myeloma treatment (regardless of bone status)
Duration/Frequency	• Monthly during initial therapy and continued in patients who are not in remission • After 2 years, discontinue if ≥ Very Good Partial Response
Choice	• **ZOL** (first option); **PAM** (second option); **CLO** (only in patients who cannot come to hospital or contraindications to ZOL and PAM) • **DENOSUMAB**: Recent results of a phase III → not inferior to ZOL in time to first on-study skeletal events, with a benefit in progression-free survival and specially in patients with renal impairment. Not approved yet

Fig. 10.5

CLO, Clodronate; MM, multiple myeloma; PAM, pamidronate; ZOL, zoledronic acid.

Zoledronic acid dose is 4 mg intravenous (i.v.) in at least 15 minutes infusion, every 3–4 weeks. Pamidronate dose is 90 mg i.v. in a 2–4 hour infusion, every 3–4 weeks.

Symptomatic patients without bone disease assessed by plain radiography can be treated with zoledronic acid. The benefit is not clear for patients without bone involvement assessed by computed tomography (CT).

Patients with monoclonal gammopathy of undetermined significance, smouldering myeloma or solitary plasmacytoma do not benefit from BPs.

Patients should receive calcium (600 mg/day) and vitamin D3 (400 IU/day) supplementation. Calcium supplementation should be used with caution in case of renal impairment.

Potential side effects associated with BPs include hypocalcaemia and hypophosphataemia, inflammatory reaction at the injection site, infusion-related reactions and osteonecrosis of the jaw.

If an invasive dental procedure is necessary, BPs should be stopped at least 90 days before and after the procedure. BPs do not need to be discontinued for routine dental procedures.

Prevention of bone disease

Practical recommendations during BP therapy
- Calcium and vitamin D3 should be used to maintain the calcium homeostasis
- All BP-treated patients should have creatinine clearance, serum electrolytes and urinary albumin monitored

Preventive strategies to avoid osteonecrosis of the jaw
- Comprehensive dental examination to treat all dental problems before initiating BP
- Educate about dental hygiene
- Unnecessary invasive dental procedures should be avoided
- If osteonecrosis occurs, BP therapy should be discontinued until healed

Fig. 10.6

BP, Bisphosphonate.

REVISION QUESTIONS

1. Describe briefly which cells are involved in the pathogenesis of bone disease in MM.
2. Which patients should receive preventive treatment with BPs?
3. What are the main practical recommendations during BP therapy?

Management of bone disease/Management of anaemia

Radiotherapy (RT) can be used for analgesic purposes or for the treatment of extramedullary disease or bone fractures. The most usual dose is 30 Gy in 10–15 fractions.

RT may cause delays in systemic anti-myeloma therapy with radio-sensitising drugs such as anthracyclines and proteasome inhibitors.

The administration of novel and very effective combinations as well as the implementation of preventive measures have reduced the need for surgery during the last decade.

Treatment of bone disease
Therapeutic strategies

Procedure	Recommendations
Balloon kyphoplasty	Painful vertebral compressive fractures
Vertebroplasty	Remains debatable in the absence of prospective trials
Radiotherapy	• Solitary plasmacytoma, symptomatic spinal cord compression, extremely painful lytic lesions • Prevention of pathological fractures
Surgery	• To fix pathological fractures of the long bones • To prevent and restore axial skeleton in cases of unstable spinal fractures • For spinal cord compression with bone fragments within the spinal route

Fig. 10.7

Pathogenesis of anaemia in MM

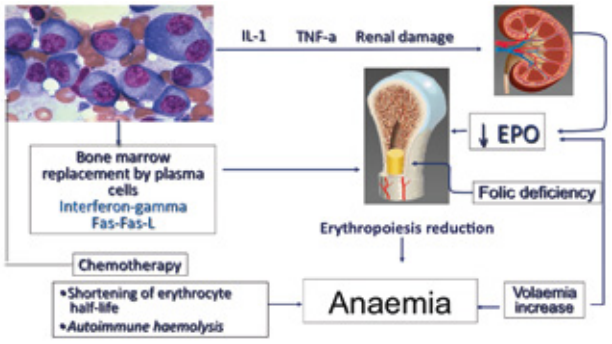

Fig. 10.8

EPO, Erythropoietin; IL, interleukin; MM, multiple myeloma; TNF, tumour necrosis factor.

Anaemia in MM is multifactorial. The major cause is the induction of erythroblast apoptosis by plasma cells, making anti-myeloma therapy with effective drugs crucial.

Anaemia is usually normochromic and normocytic. Other causes should be ruled out, such as iron, folic acid or vitamin B12 deficiency.

If iron deficiency is present, then iron must be supplied intravenously.

Erythropoiesis-stimulating agents (ESAs) mainly reduce the need for transfusions and improve quality of life.

Predictors of response to ESAs include: (i) observed to expected haemoglobin (Hb) ratios <0.9 and (ii) preserved bone marrow function, reflected by platelet counts >150x10^9/L.

The impact of ESAs on the outcome of MM patients is unclear. It is recommended to use them at the lowest possible dose to avoid transfusions.

Management of anaemia

Condition	Management

• Symptomatic anaemia or
• Asymptomatic anaemia with:
  ◦ cardiac disease
  ◦ chronic pulmonary disease
  ◦ cerebral vascular disease
	Transfusional support

• Persistent symptomatic anaemia, usually <10 g/dL with other causes of anaemia excluded	Use of erythropoiesis-stimulating agents (ESAs): Erythropoietin-α 40 000 UI/week ◦ Erythropoietin-β 30 000 UI/week ◦ Darbepoetin 150 μg/week or 500 μg/3 weeks

- Haemoglobin level should not increase more than 12 g/dL
- ESAs should be stopped after 6–8 weeks if adequate response is not achieved
- True or functional iron deficiency during treatment with an ESA should be treated with intravenous iron

Fig. 10.9

REVISION QUESTIONS

1. What are the indications for RT in myeloma?
2. What is the main cause of anaemia in myeloma?
3. In which situations would you prescribe red blood transfusion support to a patient with MM?

Management of renal disease

Cast nephropathy, a tubulo-interstitial injury, is the most common cause of severe acute kidney injury.

In patients with selective Bence Jones proteinuria, the diagnosis does not usually require renal biopsy unless the patient has non-selective proteinuria or if serum involved free light chain is <500 mg/L.

Early diagnosis and intervention remain key in the prevention of irreversible renal injuries in patients with MM.

How multiple myeloma affects the kidney

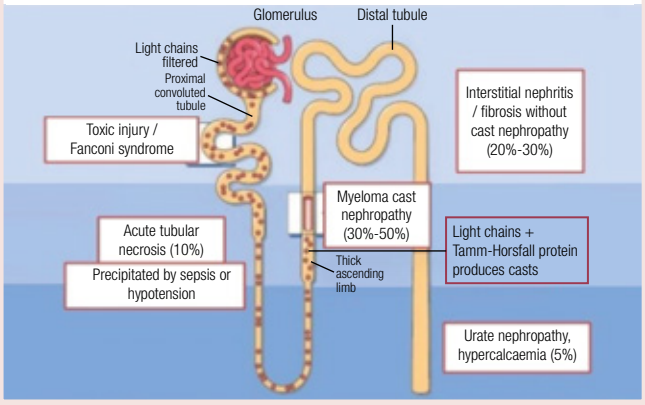

Fig. 10.10

Renal insufficiency diagnosis and management in MM

Myeloma-related renal insufficiency includes the presence of:
- Serum creatinine ≥2 mg/dL, or
- Estimated glomerular filtration rate (eGFR) <40 mL/minute

The patient has to present proteinuria, which consists mainly of light chains

Management:
- Effective therapy
- Adequate hydration
- Urine alkalinisation
- Treatment of hypercalcaemia if present
- Plasma exchange remains controversial
- Dialysis is required (conventional versus high cut-off dialysers is controversial)

MM, Multiple myeloma.

Fig. 10.11

Renal impairment at diagnosis should be considered a medical emergency in MM.

Mild renal impairment (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73m^2) can be observed in at least 25%–50% of patients.

The efficacy of mechanical approaches to remove free light chains is not well established and further investigation is required.

Bortezomib-containing regimens before and after autologous stem cell transplantation (ASCT) can overcome the poor prognosis of renal impairment.

ASCT can be performed in patients with renal impairment or under dialysis using melphalan at a reduced dose.

Immunomodulatory drugs can be also administered in case of renal impairment, with lenalidomide requiring dose adjustment. The most recent novel agents need further evaluation in this setting.

Recommendations for the general management of MM patients with renal impairment

Drugs	Dose adjustment
Proteasome inhibitors: bortezomib, carfilzomib or ixazomib	• No dose adjustment for bortezomib and carfilzomib • If haemodialysis, bortezomib after or at least 2 hours before haemodialysis. Carfilzomib should be given after dialysis • Ixazomib reduced to 3 mg in severe renal impairment or dialysis
Immunomodulatory drugs: thalidomide, lenalidomide or pomalidomide	• No dose adjustment for thalidomide and pomalidomide • Lenalidomide reduced to 10 mg/day (CrCl: 30–60 mL/min); 15 mg every other day (CrCl <30 mL/min and no dialysis); 5 mg/day after dialysis (CrCl <30 mL/min and dialysis)
Monoclonal antibodies	• No dose adjustment is required although further studies are needed in patients in dialysis

Fig. 10.12

CrCl: Creatinine clearance; MM, multiple myeloma.

REVISION QUESTIONS

1. In which situation would a kidney biopsy be necessary in a patient with MM and renal impairment?
2. What is the role of mechanical approaches for removing free light chains in MM patients with renal impairment?
3. Which drugs do not require any dose adjustment for renal function even in haemodialysis?

Management of hypercalcaemia and other novel agent-related side effects

One half of circulating calcium is free ionic calcium, the only one with physiological effects. The remainder is bound to albumin and other molecules.

Severe hypercalcaemia is a life-threatening emergency.

The best therapy for myeloma-related hypercalcaemia is to treat the disease.

Management of hypercalcaemia in MM

- **Definition:** Ionic calcium >11 mg/dL (mild <12 mg/dL; moderate 12–14 mg/dL; severe >14 mg/dL)
- **Pathogenesis:** Local resorption of bone induced by release of cytokines and production of humoural osteoclast activators
- **Symptoms:** Dehydration, lethargy and psychosis, malaise, fatigue, headaches, constipation, …
- Approaches to management:
  - **Increase urinary calcium excretion:** Isotonic saline with or without loop diuretics
  - **Diminish bone resorption:** bisphosphonates
  - **Decrease intestinal calcium absorption:** corticosteroids
  - **Dialysis** if required
  - **Active treatment** of myeloma

Fig. 10.13

MM, Multiple myeloma.

Prevention of novel treatment-related side effects

Side effect	Prevention
Infections • Herpes reactivation • Influenza • Bacterial	 • Aciclovir or derivative • Vaccination • Vaccination; growth factors if neutropaenia
Gastrointestinal disorders	• Diet and supportive care
Peripheral neuropathy	• Regular and careful monitoring of symptoms
Thrombotic events	• If only 1 risk factor, ASA (acetylsalicylic acid) • If ≥2 risk factors, LMWH (low molecular weight heparin) or warfarin
Infusion-related reactions	• Pre- and post-medication if required
Cardiovascular effects	• General risk assessment, good control of blood pressure

Fig. 10.14

Risk factors for thrombotic events: age, previous thrombotic events, immobilisation, inherited thrombophilia, central catheter, immunomodulatory drugs, high-dose dexamethasone, erythropoietin, anthracyclines, multichemotherapy, active uncontrolled disease and hyperviscosity

Antiviral prophylaxis is recommended with proteasome inhibitors and CD38 monoclonal antibodies within 1 week from the start of treatment, and must be continued for 3 months following treatment.

Antibacterial prophylaxis is mainly suggested for patients at high risk of infectious complications. Thromboprophylaxis is mandatory during treatment with immunomodulatory drugs and in patients with other high-risk features for thrombosis.

Proteasome inhibitors and immunomodulatory drugs induce diarrhoea and constipation. In case of proteasome inhibitor-related constipation, neuropathy should be ruled out.

In case of any toxicity of grade 3 or 4, it is recommended to temporarily discontinue the drug(s) until the toxicity is of grade 1 or 2, or resolved.

After any grade 3 or 4 toxicity, the treatment dose should be reduced by one level.

Dexamethasone is part of almost all novel agent-based combinations and its potential toxicity has to be considered.

Treatment of novel treatment-related side effects

Side effect	Treatment
Infections • Herpes reactivation, influenza or bacterial	 • Antivirals or antibiotics
Gastrointestinal disorders • Nausea/emesis • Constipation • Diarrhoea	 • Metoclopramide; if severe: 5-HT3 antagonists, neurokinin-1 antagonists or both. Consider also dexamethasone • Osmotic or stimulant laxatives; in case of opioid-induced bowel atony: naltrexone or naloxone • Loperamide. If severe, long-acting somatostatin
Peripheral neuropathy	• Prompt action reducing dose or modifying the scheme • If pain, gabapentin, pregabalin, duloxetine, opioids or lidocaine cream
Thrombotic events	• LMWH or warfarin at therapeutic doses
Infusion-related reactions	• Stop the infusion and start supportive treatment

Fig. 10.15

5-HT3, 5-Hydroxytryptamine; LMWH; low molecular weight heparin.

REVISION QUESTIONS

1. Under which form is calcium physiologically active?
2. What is the best way to prevent drug-related peripheral neuropathy?
3. Which prophylaxis should be prescribed to a MM patient receiving immunomodulatory drugs?

Summary: Symptomatic therapy and management of complications in myeloma

- Symptomatic therapy includes prevention and management of myeloma-related symptomatology
- Anaemia and bone pain are present in two-thirds of newly diagnosed myeloma patients
- Symptomatic therapy also includes prevention and treatment of novel agent-related side effects
- To avoid bone disease, all myeloma patients receiving active treatment require supportive care with BPs
- Kyphoplasty, RT and/or surgery can be used to treat myeloma-related bone disease
- Anaemia is multifactorial and can be treated with transfusional support and/or ESAs
- Spinal cord compression, hypercalcaemia and renal insufficiency are medical emergencies
- The best approach is to start effective anti-myeloma therapy, adjusting doses if necessary
- In case of hypercalcaemia, enhance calcium excretion and decrease bone resorption and intestinal absorption
- Proteasome inhibitors require antiviral prophylaxis and immunomodulatory drugs thromboprophylaxis

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B

More advanced knowledge

11 Molecular biology of leukaemia

Leukaemia: a heterogeneous disease

Leukaemia originates from white blood cell precursors (lymphoid or myeloid) arising in the bone marrow or thymus. Lineage and maturation stage translate into leukaemia classification: acute lymphoblastic (ALL), acute or chronic myeloid (AML, CML) and chronic lymphocytic (CLL).

Leukaemogenesis is a multistep process of accumulation and cooperation of genetic and epigenetic lesions, which directly/indirectly affects: cell cycle, proliferation, differentiation and apoptosis of blood precursors (blasts).

Differentiation arrest and enhanced proliferation of leukaemic blasts result in an abnormal number of non-functional white blood cells and translate into the symptoms of leukaemia.

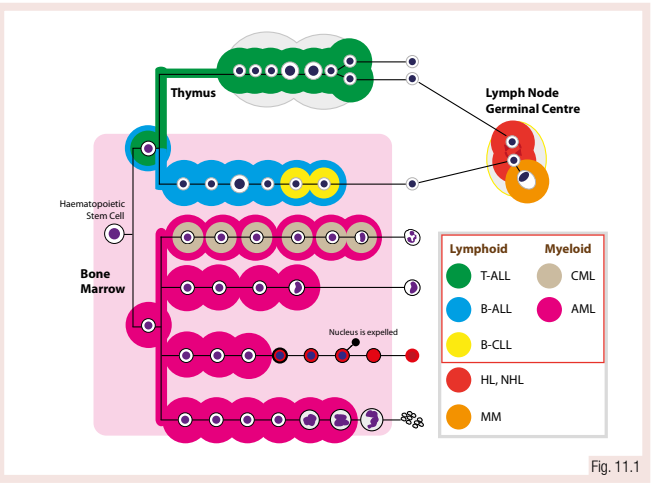

Fig. 11.1

AML, Acute myeloid leukaemia; B-ALL, B cell acute lymphoblastic leukaemia; B-CLL, B cell chronic lymphocytic leukaemia; CML, chronic myeloid leukaemia; HL, Hodgkin lymphoma; MM, multiple myeloma; NHL, Non-Hodgkin lymphoma; T-ALL, T cell acute lymphoblastic leukaemia.

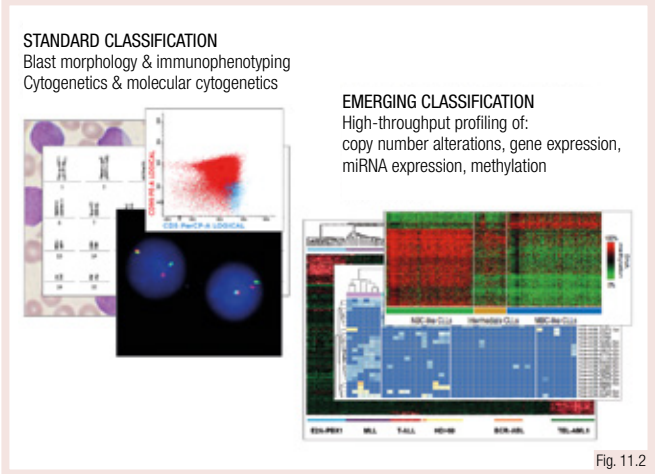

Fig. 11.2

CLL, Chronic lymphocytic leukaemia; HD, hyperdiploidy; MBC, memory B cell; miRNA, micro RNA; NBC, naïve B cell; T-ALL, T cell acute lymphoblastic leukaemia.

Biological and clinical heterogeneity of leukaemia subtypes stem from the underlying heterogeneity of the molecular mechanisms and genes/pathways affected. Heterogeneity is also seen across patients with the same leukaemia subtype.

High-throughput techniques (microarrays and next generation sequencing [NGS]) revealed this (epi-)genetic heterogeneity and enabled the identification of molecular subtypes of leukaemia.

Leukaemia classification based on morphology, immunophenotype and cytogenetics is gradually being enhanced by data on copy number alterations, expression profiles of messenger RNA (mRNA), non-coding RNA (e.g. micro RNA [miRNA]) and methylation profile.

Most leukaemia cases represent a mixture of heterogeneous clones of leukaemic cells, differing in proliferation rate, drug response, survival etc.

These clones arise due to clonal evolution, caused by: genomic instability of highly proliferating leukaemic cells and selective pressure exerted by treatment and the microenvironment.

The 'best suited' clones survive and constitute minimal residual disease (MRD). These residual cells emerge as a relapse, if not eradicated by further treatment and the immune system. MRD level is a powerful prognostic marker.

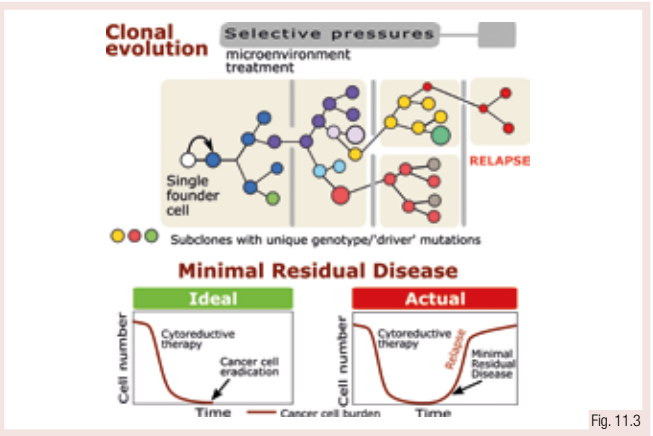

Fig. 11.3

REVISION QUESTIONS

1. Is leukaemia due to a genetic aberration affecting a single gene/pathway?
2. How can the use of advanced genomic approaches explain clinical and biological heterogeneity of leukaemias?
3. What is the link between clonal heterogeneity, MRD and relapse?

The genetic landscape of leukaemia

Gross chromosomal aberrations and multiple submicroscopic genetic lesions (sequence mutations) are present at diagnosis in most leukaemia cases.

In ALL, AML and CLL, certain genetic aberrations are recurrent (some of these have prognostic significance), others are rare. CML is the exception, with *t(9;22)*, causing *BCR-ABL1* fusion, being the hallmark of this leukaemia (detected in most patients as the only genetic aberration at diagnosis).

Chromosomal aberrations are mostly 'early events' in leukaemogenesis, while DNA copy number alterations and most sequence mutations are acquired later.

The whole spectrum of chromosomal aberrations is found in leukaemia: translocations, deletions, inversions, amplifications and numerical abnormalities.

Leukaemia	Main recurrent genetic aberrations in leukaemia in adults (frequency at diagnosis ≥5%)	
	Chromosomal aberrations	Gene mutations
ALL	Hyperdiploidy Hypodiploidy *t(9;22)/BCR-ABL1* *t(4;11)/MLL-AF4* Deletions of 9p incl. *CDKN2A/B* (9p21.3) *t(1;19)/TCF3-PBX* *t(12;22)/EP300-ZNF384*	*FAT1, SF1, CRLF2, TET2, PTPN11, CREBBP, MLL2, PAX5, SETD2, FLT3, RUNX1, DIS3, MPL, NRAS, KRAS, JAK2* *IKZF1* deletions and mutations *NOTCH1, FBXW7, JAK3, DNM2* (specifically in T-ALL)
AML	*t(8;21)/RUNX1-RUNX1T1* *inv(16)* or *t(16;16)/CBFB-MYH11* *t(15;17)/PML-RARA* Deletions of: 7q, 5q	*NPM1, DNMT3A, CEBPA, TET2, IDH1, IDH2, FLT3-ITD* (internal tandem duplication), FLT3-TKD (tyrosine kinase domain), *MLL*-PTD (partial tandem duplication), *ASXL1, NRAS, KRAS, TP53, WT1, PTPN11, RUNX1*
CLL	Deletions of: 13q14, 11q23, 17p Trisomy of chromosome 12 Rearrangements involving: 3p21, 11q23, 13q14, 14q32 and 18q21	*NOTCH1, ATM, PAX5, SF3B1, BIRC3, CHD2, TP53*
CML	*t(9;22)/BCR-ABL1*	*ABL1*-TKD (tyrosine kinase domain) Cause resistance to TKI; Not extensively studied for other mutations at diagnosis

Fig. 11.4

ALL, Acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; CLL, chronic lymphocytic leukaemia; CML, chronic myeloid leukaemia; T-ALL, T cell acute lymphoblastic leukaemia; TKI, tyrosine kinase inhibitor.

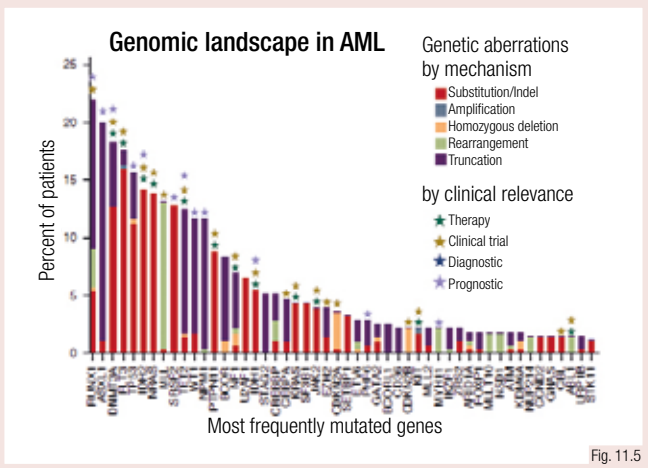

Fig. 11.5

AML, Acute myeloid leukaemia.

Though by different mechanisms, functionally both chromosomal aberrations and sequence mutations cause activation of oncogenes and inactivation of tumour suppressors.

Most frequently, oncogenes are activated by chromosomal translocations, inversions or activating sequence mutations. Tumour suppressors are lost or inactivated by gross chromosomal deletions or inactivating sequence mutations.

The frequency of somatic sequence mutations in leukaemia is relatively low, when compared with other malignancies (<20 non-silent mutations/case).

Rare exceptions are relapsed cases with hypermutator phenotype (>100 non-silent mutations/case). These are due to mutations in genes responsible for DNA damage repair.

Mutations in certain genes are recurrent in ALL, AML and CLL (putative 'driver mutations'), others are random 'passenger mutations'. In CML, mutations affecting *BCR-ABL1* cause resistance to tyrosine kinase inhibitors (TKIs).

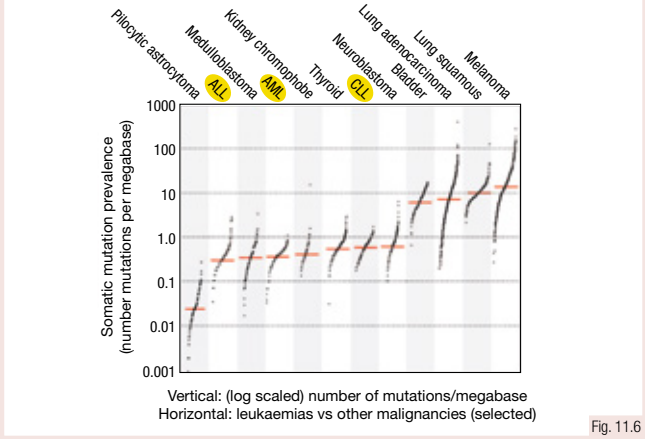

Fig. 11.6

ALL, Acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; CLL, chronic lymphocytic leukaemia.

REVISION QUESTIONS

1. What are the most frequent mechanisms affecting oncogenes and tumour suppressor genes in leukaemia?
2. How is CML different from other leukaemias in terms of genetic landscape?
3. What is the difference between driver mutations and passenger mutations?

Beyond the protein-coding genes

The genetic landscape of leukaemia has widened with the use of next generation whole exome sequencing (WES). Many new putative oncogenes and tumour suppressors, involved by mutation in leukaemogenesis, have been identified.

But it is not only genetic aberrations affecting protein-coding genes that contribute to leukaemia. Whole genome sequencing (WGS) and non-coding RNA sequencing (ncRNA-seq) further unravel the genomic landscape of leukaemia.

The epigenetic landscape of leukaemia appears to be equally important and is now available for study with the use of advanced approaches.

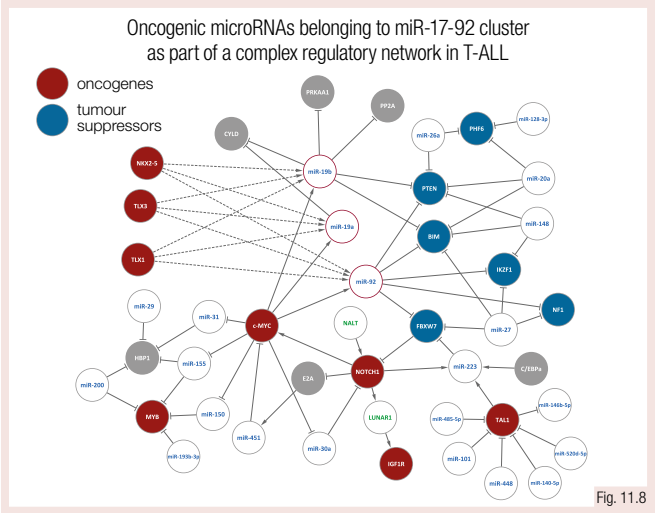

Fig. 11.8

T-ALL, T cell acute lymphoblastic leukaemia.

Methylation abnormalities are extensively studied epigenetic aberrations in leukaemia. Global hypomethylation (resulting in genomic instability) and selective hypermethylation of promoter regions of tumour suppressor genes (resulting in gene silencing) are observed in leukaemia.

Distinct methylation profiles have been identified in molecular genetic subtypes of leukaemia. Methylation profiling has prognostic potential and correlates with leukaemia progression and treatment response.

Unravelling the complex interplay of genetic aberrations (affecting both protein-coding and non-coding sequences) and epigenetic aberrations is the emerging concept of integrated 'omics-based' research in leukaemia.

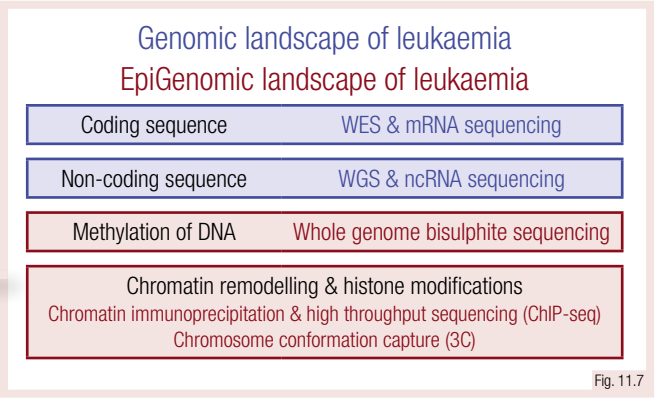

Fig. 11.7

mRNA, messenger RNA; ncRNA, non-coding RNA; WES, whole exome sequencing; WGS, whole genome sequencing.

miRNAs are extensively studied non-coding RNAs in leukaemia. By targeting specific sequences in the mRNA of protein-coding genes, miRNAs are involved in time- and context-specific regulation of gene expression.

miRNAs are crucial regulators in normal and malignant haematopoiesis involved in complex regulatory networks: single miRNA targets multiple mRNAs; single mRNA is targeted by several miRNAs. In leukaemia, miRNA-coding genes themselves are affected by genetic and epigenetic lesions.

Oncogenic miRNAs are miRNAs negatively regulating the expression of tumour suppressors; tumour suppressor miRNAs are negative regulators of oncogenes. miR-15a and miR-16a were the first miRNAs identified to be involved in cancer. These tumour suppressor miRNAs are located in locus 13q14, deleted in >50% of CLL patients. Many new oncogenic and tumour suppressor miRNAs are being identified in leukaemia.

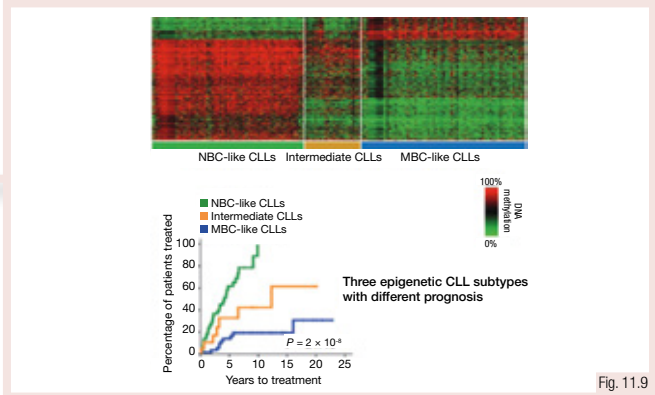

Fig. 11.9

CLL, Chronic lymphocytic leukaemia; MBC, memory B cell; NBC, naïve B cell.

REVISION QUESTIONS

1. What is the scope of genetic and epigenetic research in leukaemia?
2. What is the nature of miRNA involvement in complex regulatory networks in leukaemia?
3. Which methylation abnormalities, at a global and a single gene level, are observed in leukaemia?

Summary: Molecular biology of leukaemia

- Leukaemia is a very heterogeneous disease: classified into four major types and many molecular subtypes of different clinico-biological characteristics
- Leukaemia heterogeneity stems from a diversity of genetic and epigenetic aberrations that accumulate and cooperate in the process of leukaemogenesis
- Leukaemia heterogeneity is also seen in individual patients: heterogeneous clones of leukaemic cells undergo clonal evolution leading to the selection of clones with survival advantage
- Residual cells that survive treatment constitute 'minimal residual disease', which is used as a prognostic marker
- Genetic aberrations identified in leukaemia include chromosomal aberrations and submicroscopic lesions, affecting both oncogenes and/or tumour suppressors
- Only a fraction of genetic aberrations are recurrent in leukaemia patients. The exception is *t(9;22)* and the resulting *BCR-ABL1* fusion, which represent the hallmarks of CML
- A relatively low number of somatic sequence mutations are identified in leukaemia patients
- Aberrant expression of miRNAs is implicated in leukaemogenesis; oncogenic and tumour suppressor miRNAs are identified in leukaemia
- Aberrant epigenetic regulation, especially aberrant methylation profile, is also implicated in leukaemogenesis, and has prognostic potential

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Acknowledgement

The authors' work on this chapter was supported by The National Science Centre, Poland; grant: 2014/15/B/NZ2/03394 and The National Centre for Research and Development, Poland; grant: STRATEGMED3/304586/5/NCBR/2017.

12 Molecular biology of myeloma

Disease initiation and progression

Two types of disease-initiating events (DIEs) have been identified in the molecular pathogenesis of multiple myeloma (MM):

1. Hyperdiploidy (HD), involving ≥2 trisomies.
2. IgH translocations (IgHtxs), putting an oncogene under the control of the IgH enhancer: *t(4;14)*: FGFR3/MMSET, *t(6;14)*: CCND3, *t(11;14)*: CCND1, *t(14;16)*: MAF or *t(14;20)*: MAFB.

Despite their molecular diversity, DIEs share one common aberration: (in)direct overexpression of ≥1 cyclin D (*CCND*) gene(s).

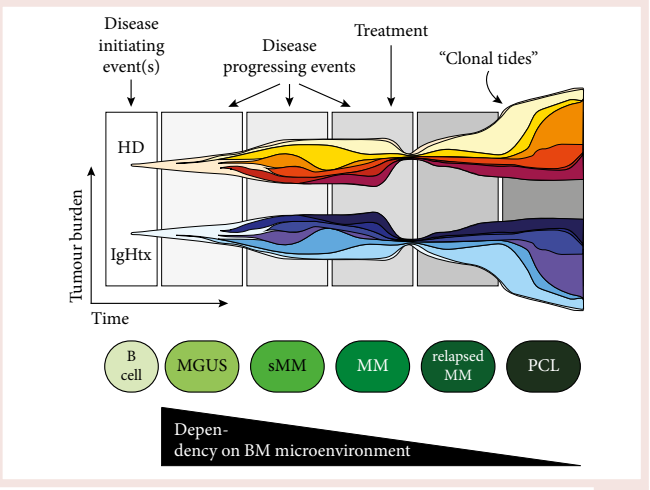

Fig. 12.1

BM, Bone marrow; HD, hyperdiploidy; IgHtx, IgH translocations; MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma; PCL, plasma cell leukaemia; sMM, smouldering multiple myeloma.

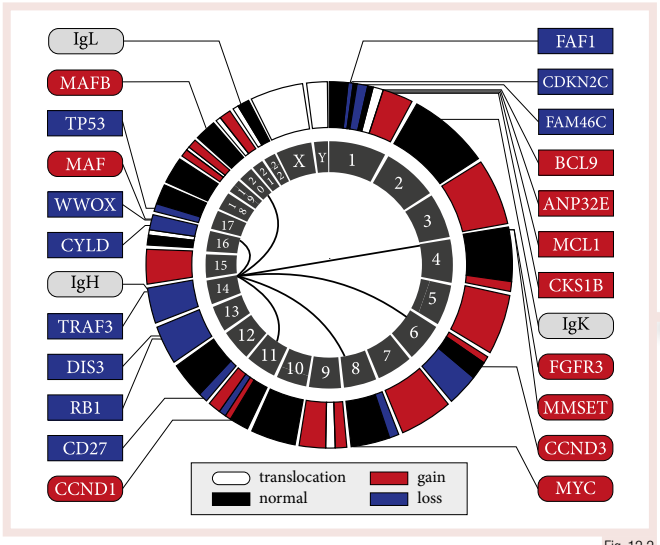

Fig. 12.2

IgH, Immunoglobulin H; IgK, immunoglobulin K; IgL, immunoglobulin L.

The MM cell of origin is unknown, but may be a pro-B cell or germinal centre B cell, as primary IgHtxs seem to have occurred during VDJ/class switch recombination or somatic hypermutation.

As the MM genome evolves, disease-progressing events (DPEs) such as *del(17p)*, *del(1q)*, *1q* gain and *t(8;14)* (involving MYC) are being selected for. These therefore usually also confer an inferior prognosis.

Disease progression in MM is characterised by a decreased bone marrow (BM) microenvironment dependency, caused by deletions and mutations that result in intrinsic activation of the NFκB pathway.

The mutational load of the MM genome is in the middle of a spectrum, with infrequently mutated paediatric cancers at one end and carcinogen-induced, hypermutated tumours at the other.

MM lacks any disease-defining mutations and only a few genes are recurrently mutated. Still, ~40% of patients have an *NRAS* and/or *KRAS* mutation. *TP53* mutations have prognostic value.

The MAPK/ERK, DNA damage response, NFκB, RNA processing, plasma cell differentiation, cell cycle control and MYC pathways are recurrently disrupted in MM.

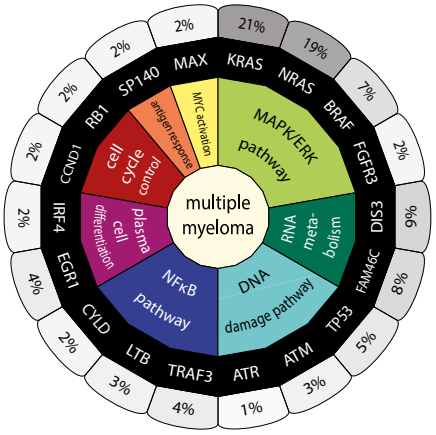

Fig. 12.3

REVISION QUESTIONS

1. What are the two major clonal disease-initiating events in MM and what do they have in common?
2. Which DNA-editing processes in B cell development have been found to be involved in MM pathogenesis?
3. Which pathways are primarily disrupted in MM cells?

Inter- and intra-tumour heterogeneity and prognostic implications

Unsupervised clustering of gene expression profiles (GEPs) has led to the identification of six robust MM subgroups that show a strong correlation with DIEs.

GEP-classified high-risk MM is enriched for DIEs *t(4;14)*, *t(14;16)*, and *t(14;20)*, and DPEs *1q gain*, *del(17p)* and *del(13p)*, generally identifying highly proliferative tumour biology.

Therefore, MM is not one disease, but many, being characterised by large inter-tumour variation (and hence a variable clinical disease course).

Fig. 12.4

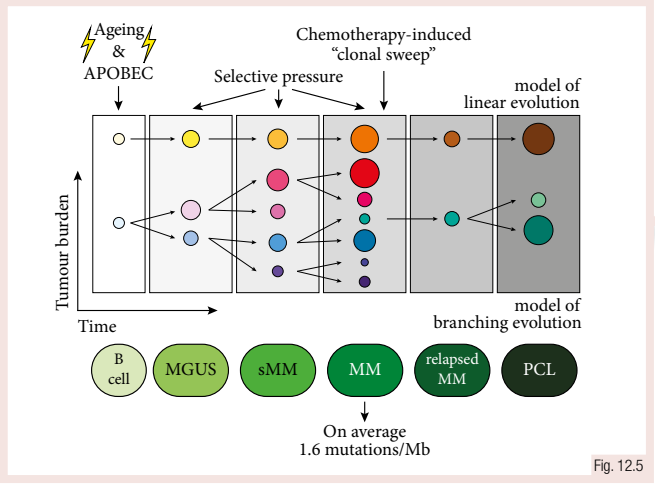

Fig. 12.5

MGUS, Monoclonal gammopathy of undetermined significance; MM, multiple myeloma; PCL, plasma cell leukaemia; sMM, smouldering multiple myeloma.

Two mutational aetiologies have been identified in MM: (a) an ageing signature, and (b) an *APOBEC* signature.

MM can show large intra-tumour heterogeneity, as is evidenced by the 'waxing and waning' of subclones during disease progression. The evolutionary pattern can be linear and/or branching.

Research is ongoing to define the level of spatial heterogeneity (between focal lesions), which may be a third dimension of genomic complexity in MM.

The International Myeloma Working Group (IMWG) has proposed a set of prognostic biomarkers to assess high-risk MM biology: *del(17p)*, *t(4;14)* and/or *t(14;16)*, which may be combined with a GEP-based high-risk classifier.

The International Staging System (ISS) classification reflects tumour burden and patient condition. The Revised ISS (R-ISS) classification also incorporates tumour biology (i.e. cytogenetics and lactate dehydrogenase [LDH]) in its risk score.

A pitfall of current molecular biomarkers is that an invasive BM aspiration is needed. This may be overcome by novel, sensitive blood tests.

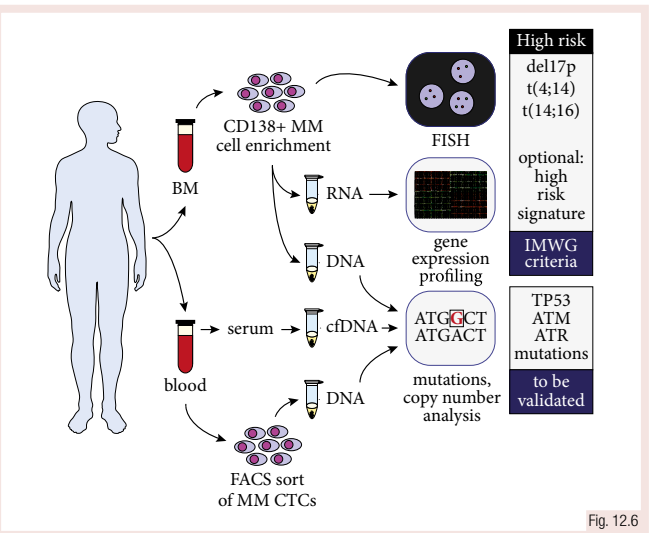

Fig. 12.6

BM, Bone marrow; CTC, circulating tumour cell; FACS, fluorescence activated cell sorting; FISH, fluorescent *in situ* hybridisation; IMWG, International Myeloma Working Group; MM, multiple myeloma.

REVISION QUESTIONS

1. What are the most common genetic aberrations associated with high-risk MM?
2. What can be considered classical tumour suppressor genes in MM, as these are often affected by bi-allelic hits (e.g. one allele is deleted and the other mutated)?
3. Is it necessary to perform a BM aspiration to be able to calculate an R-ISS score? How may this change in the future?

Molecular rationale for treatment

The chemotherapeutic treatment of MM consists of three major components:

1. Alkylating agents (AAs), which cause intrastrand linking and crosslinking of DNA.

2. Glucocorticoids (GCs), which induce apoptosis in lymphocytes by a currently unknown mechanism.

3. Proteasome inhibitors (PIs), which inhibit proteasomal degradation of misfolded and unneeded proteins. Plasma cells are particularly sensitive, as these produce large amounts of proteins (antibodies).

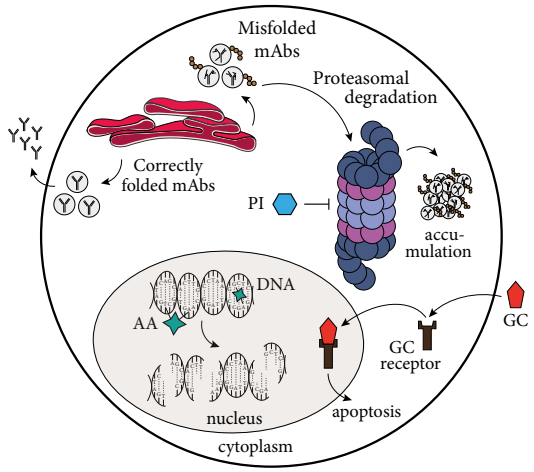

Fig. 12.7

AA, Alkylating agent; GC, glucocorticoid; mAb, monoclonal antibody; PI, proteasome inhibitor.

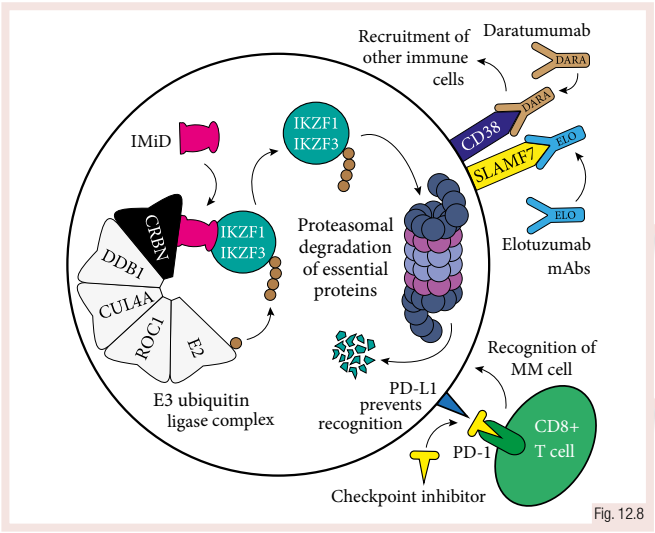

Fig. 12.8

CRBN, Cereblon; DARA, Daratumumab; ELO, elotuzumab; IMiD, immunomodulatory drug; mAb, monoclonal antibody; MM, multiple myeloma; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.

Immune therapies also play a central role in the treatment of MM. These target typically both the MM cell and its microenvironment.

Immunomodulatory drugs (IMiDs) bind to cereblon, which induces selective proteasomal degradation of IKZF1 and IKZF3 (essential transcriptional regulators of T and B cells).

Many novel immune therapies are being tested in MM clinical trials such as monoclonal antibodies (mAbs) against CD38 and SLAMF7 and immune checkpoint inhibitors (e.g. programmed cell death protein 1 [PD-1]/ programmed death-ligand 1 [PD-L1] inhibitors).

Treatment is currently only aimed at general MM vulnerabilities. With personalised medicine, patients could benefit from targeted therapies against their tumour-specific driver aberrations and avoid the side effects of ineffective agents.

Targeted therapy trials are currently being conducted in MM patients with so-called 'actionable alterations'.

A better understanding of the subclonal dynamics after treatment will be essential to guide rational decision-making on therapeutic choice and order.

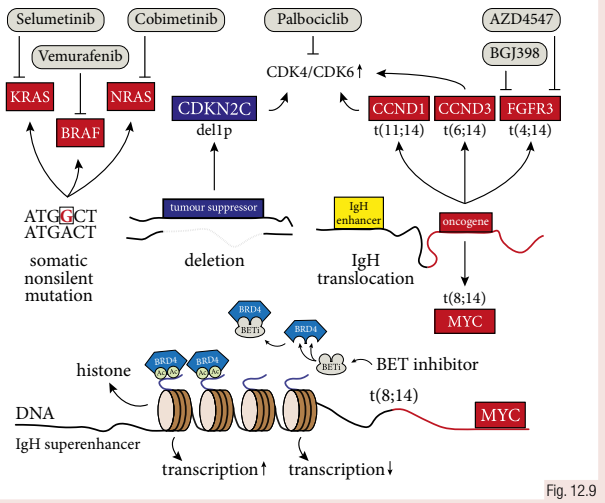

Fig. 12.9

BET, Bromodomain and Extra-Terminal motif; IgH, immunoglobulin H.

REVISION QUESTIONS

1. In what maturation stage would B cells be most sensitive to PIs and why?
2. What other cells in the BM microenvironment would respond to treatment with an IMiD, based on their mechanism of action in MM cells?
3. Would a differential response be expected, if a therapy aimed at mutation χ is given to a patient with a clonal versus a subclonal mutation χ?

Summary: Molecular biology of myeloma

- DIEs in MM can be divided into two classes: hyperdiploidy and IgH translocations
- DPEs in MM are numerous and show a positive correlation with advanced-disease stage
- MM shows large inter-tumour heterogeneity, yet many pathways (rather than genes) are recurrently disrupted by somatic variants, such as the MAPK/ERK, DNA damage response, NFκB, RNA processing, plasma cell differentiation, cell cycle control and MYC pathways
- Intra-tumour heterogeneity in MM is evidenced by an alternating dominance of different clones during disease progression, corresponding to differential treatment sensitivities and clonal outgrowth rates
- MM has an intermediate mutational load in the spectrum of cancer types, for which two main biological processes are responsible: ageing and increased *APOBEC* gene activity
- Prognosis in MM is determined by both patient- and tumour-related factors, which are combined in the R-ISS classification
- Classic molecular prognostic biomarkers are obtained from BM and investigated with FISH (with GEP and NGS being validated)
- PIs prevent proteasomal degradation of misfolded and unneeded proteins. Plasma cells are particularly sensitive to this treatment, as these are highly dependent on the efficient removal of misfolded antibodies
- IMiDs cause specific degradation of IKZF1 and IKZF3, which are two essential transcription factors in plasma cells
- As yet, MM is treated irrespective of its specific genetic aberrations, but with further development of targeted therapies and molecular markers, patients could benefit from personalised medicine

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13 Allogeneic transplantation and graft-versus-host disease

Principles of allogeneic stem cell transplantation

Allogeneic stem cell transplantation (alloSCT) is the replacement of the patients' haematopoietic stem cells (HSCs) with stem cells from a donor. The process requires the ablation of the patient's own haematopoiesis and immune system (to avoid rejection).

In vitro colony assays demonstrated the pluripotency of HSCs and the monophyletic origin of blood cells.

In murine models, lethally irradiated mice could be protected by bone marrow (BM) cell infusion but with subsequent development of graft-versus-host disease (GvHD).

World Marrow Donor Agency (WMDA) data describing the stem cell sources used for allogeneic stem cell transplantation

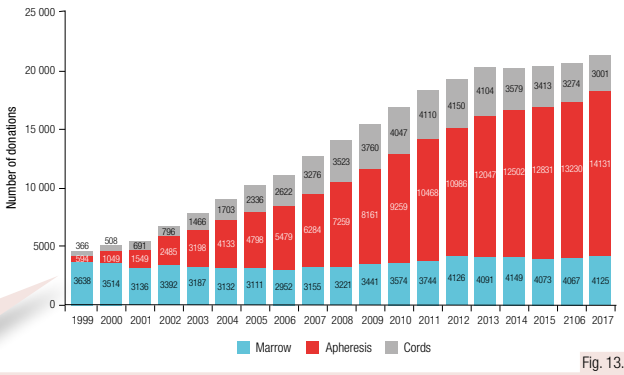


Fig. 13.1

Over the years, peripheral stem cells and cord blood stem cells have replaced bone marrow as a source of stem cells for transplantation

The human HLA Class I (A, B and C) and Class II (DR, DP and DQ) genes

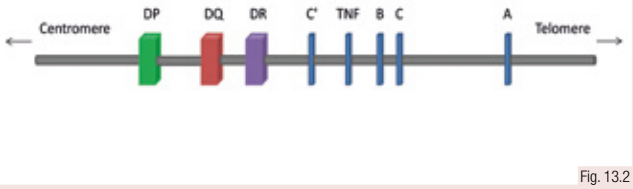


Fig. 13.2

HLA, Human leukocyte antigen.

HSCs can be extracted from BM by repeated aspiration of the posterior iliac crests, under general or local anaesthesia.

When stimulated with granulocyte colony-stimulating factor (G-CSF), stem cells can be mobilised into, and easily collected from, peripheral blood by leukapheresis.

Cord blood (CB) cells, collected and cryopreserved at birth, can also be used as a stem cell source for allogeneic transplants, in both children and adults.

To be transplanted, stem cells from donor and recipient must be compatible. This is determined by comparing the human leukocyte antigen (HLA) profiles of both donor and patient.

Suitable donors can be: matched related (HLA identical siblings or syngeneic twins), matched unrelated or mismatched related (haploidentical, sharing only one HLA haplotype).

Currently, 30 million healthy volunteers are registered by the World Marrow Donor Agency (WMDA). Matched unrelated donors include those with a molecularly defined 10/10 matching of A, B, C, DRB1 and DQ loci.

Total number of stem cell donors

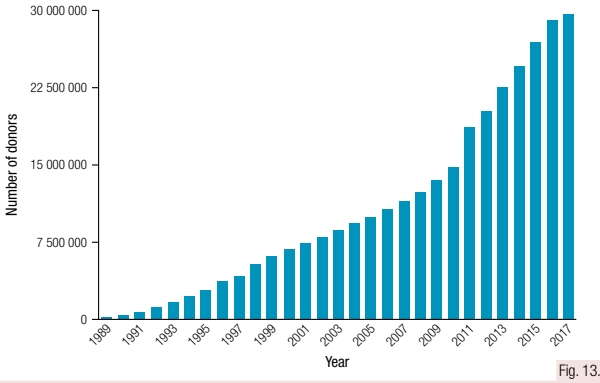


Fig. 13.3

REVISION QUESTIONS

1. What should be done to avoid the rejection of transplanted BM?
2. Which are the possible sources of stem cells for transplantation?
3. How is the compatibility evaluated between donor and recipient?

Indications and administration of allogeneic transplantation

The therapeutic principle of the transplant is twofold: on the one hand, the myeloablative conditioning regimen should eliminate all chemosensitive tumour cells; on the other, transplantation of the donor's immune system should eliminate the remaining chemo-resistant disease.

Allogeneic transplantation can therefore be seen as a combination of high-dose anti-cancer therapy and immunotherapy.

HSC transplantation (HSCT) is used primarily to treat myeloid and lymphoid malignancies, but also many other non-neoplastic diseases.

Clinical indication to allogeneic transplantation	
A. Haematological neoplastic diseases	
• Acute myeloid leukaemia	• Juvenile chronic myeloid leukaemia
• Acute lymphoid leukaemia	• Non-Hodgkin lymphoma
• Myelodysplastic syndromes	• Hodgkin lymphoma
• Myeloproliferative disorders	• Chronic lymphocytic leukaemia
• Chronic myeloid leukaemia	• Multiple myeloma
B. Other non-neoplastic diseases	
• Thalassaemia major	• Fanconi's anaemia
• Sickle cell anaemia	• Blackfan–Diamond anaemia
• Aplastic anaemia	• Severe combined immunodeficiency
• Paroxysmal nocturnal haemoglobinuria	• Wiskott–Aldrich syndrome
	• Inborn errors of metabolism

Fig. 13.4

Need of stem cell support infusion to overcome the bone marrow aplasia induced by the conditioning regimen

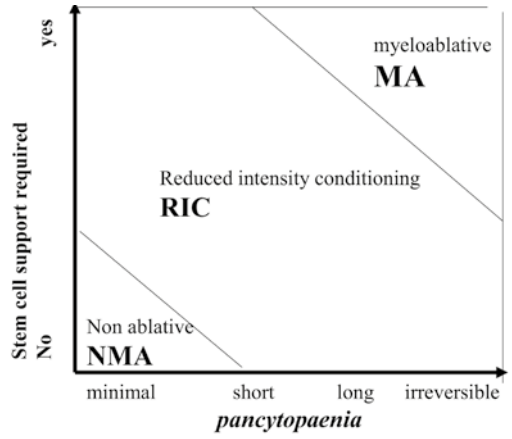


Fig. 13.5

MA, Myeloablative; NMA, non-myeloablative; RIC, reduced-intensity conditioning.

Conditioning regimens aim to provide immune-ablation to prevent graft rejection and, in patients with malignant disorders, to eradicate or minimise the tumour burden.

They are based on chemotherapy (ChT) alone or combined ChT and radiotherapy (RT).

The intensity of conditioning can vary significantly and can be classified as myeloablative (MA), reduced-intensity conditioning (RIC), and non-myeloablative (NMA).

The development of RIC regimens, characterised by a reduced toxicity compared with MA conditioning (MAC), has made alloSCT accessible to older patients, including those with comorbidities.

MA regimens cause irreversible cytopaenia and stem cell support is mandatory. RIC regimens also induce cytopaenia, not always irreversible. NMA regimens cause minimal cytopaenia.

The most common acute non-haematological toxicities include nausea, vomiting, xerostomia, mucositis, diarrhoea, veno-occlusive liver disease and opportunistic infections.

Oral mucositis

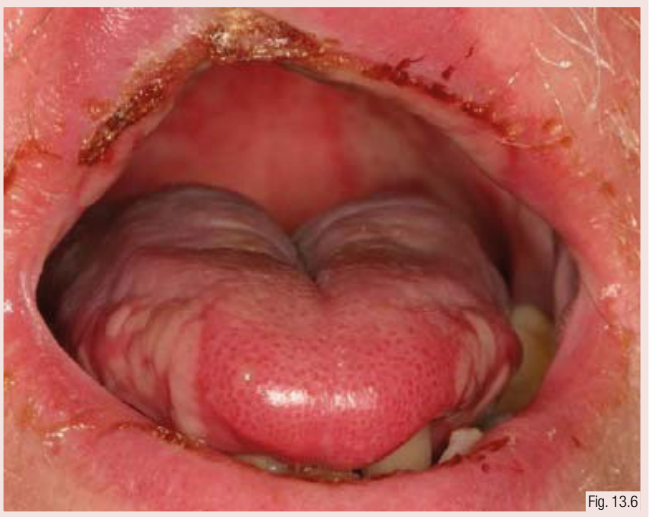


Fig. 13.6

REVISION QUESTIONS

1. Why is it necessary to give a conditioning treatment prior to transplantation?
2. What is a reduced intensity transplant?
3. What are the usual toxicities induced by conditioning regimens?

Graft-versus-host disease

The main complication of HSCT is GvHD, an immunological disorder that affects many organ systems (gastrointestinal tract, liver, skin and lung).

The pathophysiology of acute GvHD (aGvHD) is due to the allogeneic recognition of the patient's tissue antigens by donor lymphocytes.

The recipient's tissues, damaged by the conditioning regimens, enhance cross-presentation of histocompatibility antigens to the donor immune cells.

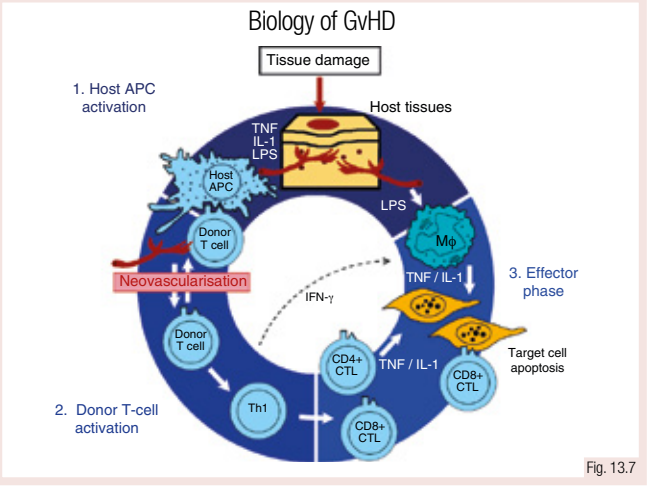


Fig. 13.7

APC, Antigen-presenting cell; CTL, cytotoxic T lymphocyte; GvHD, graft-versus-host disease; IFNγ, interferon gamma; IL-1, interleukin 1; LPS, lipopolysaccharide; Th1, T helper 1; TNF, tumour necrosis factor.

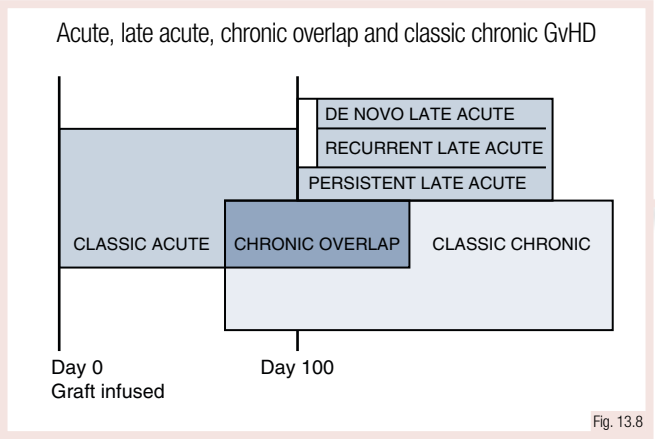


Fig. 13.8

GvHD, Graft-versus-host disease

Historically, aGvHD has been defined as a manifestation occurring in the first 100 days after HSCT, while chronic GvHD (cGvHD) refers to signs occurring after 100 days.

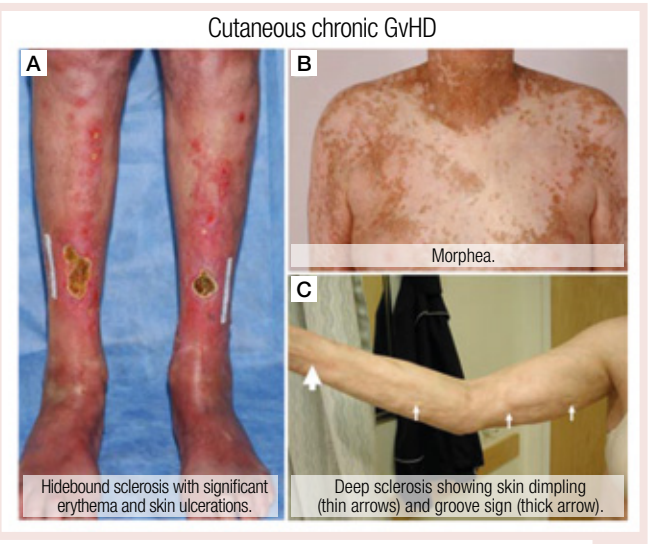
In 2005, the National Institutes of Health (NIH) classification included late-onset aGvHD (after day 100) as an overlap syndrome with features of both acute and chronic disorder.

Most common clinical manifestations of aGvHD affect: skin (maculopapular rash), gastrointestinal tract (nausea, anorexia, diarrhoea [>500 mL], abdominal pain, ileus) and liver (cholestasis).

The usual features of cGvHD include skin pathologies varying from lichen planus–like lesions to full sclerosis, bronchiolitis obliterans and oral lichen planus lesions.

cGvHD occurs as a continuum in time with clinical features that are distinct from, but not mutually exclusive to, those seen in aGvHD.

Steroids remain the gold standard for treatment of GvHD. New approaches primarily target allo-reactive donor T cells, allo- and auto-reactive B cells, or T regulatory cells.



GvHD, Graft-versus-host.

Fig. 13.9

REVISION QUESTIONS

1. What are the main clinical manifestations of GvHD?
2. How can GvHD be classified?
3. What is the standard treatment for GvHD?

Summary: Allogeneic transplantation and graft-versus-host disease

- Allogeneic transplant is used primarily to treat myeloid and lymphoid malignancies
- HSCs can derive from the BM, or be collected from peripheral blood after stimulation with G-CSF by leukapheresis or from CB at birth
- Patients who are candidates for allogeneic transplantation are matched with eligible donors by HLA typing
- HLA typing identifies two categories: Class I (HLA A, B, C antigens expressed by most nucleated cells) and Class II (HLA DR, DQ, DP antigens expressed by antigen-presenting cells and activated T cells)
- Possible donors can be matched related (HLA identical siblings or syngeneic twins), mismatched related (haploidentical, sharing only one HLA haplotype) or unrelated (matched and mismatched unrelated or CB)
- For those patients without a matched family donor, currently 30 million healthy volunteers are registered by the WMDA and more than 700 000 CB units are stored worldwide
- Conditioning regimens provide immuno-ablation, to prevent graft rejection and to minimise tumour burden
- The development of RIC regimens made alloSCT accessible to older patients
- The main serious complication of allogeneic transplants is GvHD. This is an immune reaction whereby cells from the donor's immune system recognise the patient's body as foreign and attack it
- GvHD most commonly attacks the skin, liver and digestive system

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14 Myeloproliferative neoplasms other than CML: essential thrombocythaemia, polycythaemia vera and myelofibrosis

Essential thrombocythaemia

Essential thrombocythaemia (ET) is a myeloproliferative neoplasm (MPN) characterised by persistent thrombocytosis, with a tendency to thrombosis and frequent microvascular symptoms. 10% of patients are under 40 years old.

Mutations are detected in 80%–90% of patients. Frequencies are: *JAK2 V617F* 60%, calreticulin (*CALR*) 20%–25%, *MPL* 1%–4% and triple negative 10%–20%.

BCR/ABL1 rearrangement should be discarded in triple-negative cases. Red cell mass measurement may help excluding polycythaemia vera (PV) in *JAK2 V617F*-positive patients.

Proposed revision of the WHO criteria: ET diagnosis requires meeting all four major criteria or the first three major criteria and the minor criterion
Major criteria
1. Platelet count >450 × 10^9/L
2. Bone marrow biopsy showing proliferation mainly of the megakaryocyte lineage with increased numbers of enlarged, mature megakaryocytes with hyperlobulated nuclei. No left-shift in neutrophil granulopoiesis or erythropoiesis and very rarely minor (grade 1) increase in reticulin fibres
3. Not meeting WHO criteria for BCR-ABL1+ CML, PV, PMF, myelodysplastic syndromes or other myeloid neoplasms
4. Presence of *JAK2 V617F*, *CALR* or *MPL* mutation
Minor criterion
1. Presence of a clonal marker or absence of evidence for reactive thrombocytosis

CML, Chronic myeloid leukaemia; ET, essential thrombocythaemia; PMF, primary myelofibrosis; PV, polycythaemia vera; WHO, World Health Organization.

Fig. 14.1

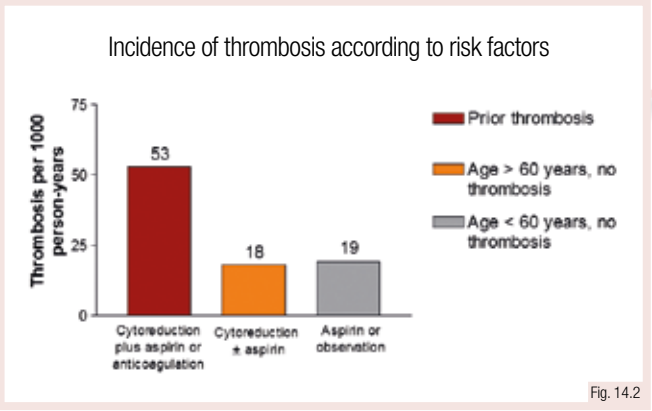


Fig. 14.2

Age over 60 years and history of thrombosis are the main risk factors for thrombosis; these patients are candidates for cytoreduction plus antiplatelet therapy.

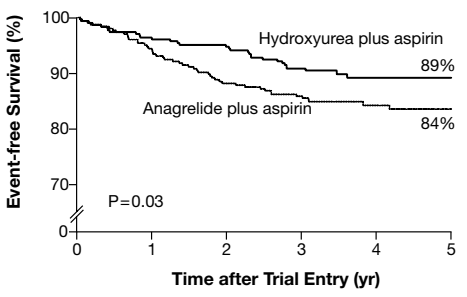
In low-risk patients, thrombosis incidence is similar to that in a matched healthy population. They can be managed with careful observation or low-dose aspirin.

Extreme thrombocytosis (>1500 x 10^9/L) is a risk factor for bleeding. Antiplatelet therapy should be avoided in such cases.

Hydroxyurea and anagrelide are equally effective in controlling platelets; hydroxyurea results in a lower thrombosis rate whereas anagrelide lacks leukaemogenic potential.

The most frequent side effects of therapy are leg and oral ulcers for hydroxyurea and headache and palpitations for anagrelide.

Low-dose aspirin is recommended in low-risk patients with microvascular symptoms, cardiovascular risk factors or positive for the *JAK2 V617F* mutation.



No. at Risk

Hydroxyurea plus aspirin	404	388	298	204	129	57
Anagrelide plus aspirin	405	379	272	190	119	52

Fig. 14.3

REVISION QUESTIONS

1. What are the frequencies of the three MPN driver mutations in ET?
2. In which situation should antiplatelet therapy be avoided in ET patients?
3. Which are the cytoreductive treatment modalities usually employed in ET?

Polycythaemia vera

PV is a *BCR/ABL*-negative MPN characterised by an increased red cell mass with frequent leukocytosis and thrombocytosis.

An elevated haematocrit level in the presence of the *JAK2 V617F* mutation is the basis of PV diagnosis.

Patients with erythrocytosis and low erythropoietin levels who are negative for the *JAK2 V617F* mutation should be screened for mutations in exon 12 of the *JAK2* gene.

Proposed revision of the WHO criteria: PV diagnosis requires meeting either all three major criteria or the first two major criteria and one minor criterion
Major criteria
1. Hb >16.5 g/dL (men) or Hb >16 g/dL (women) or HTC >49% (men) or HTC >48% (women) or Increased red cell mass by isotopic assessment
2. Bone marrow: trilineage proliferation with pleomorphic megakaryocytes (BM not necessary if Hb >18.5 g/dL in men or >16.5 g/dL in women or demonstration of increased red cell mass)
3. Presence of *JAK2 V617F* or *JAK2* exon 12 mutation
Minor criterion
1. Serum erythropoietin below the normal reference range

BM, Bone marrow; Hb, haemoglobin; HTC, haematocrit; PV, polycythaemia vera; WHO, World Health Organization.

Fig. 14.4

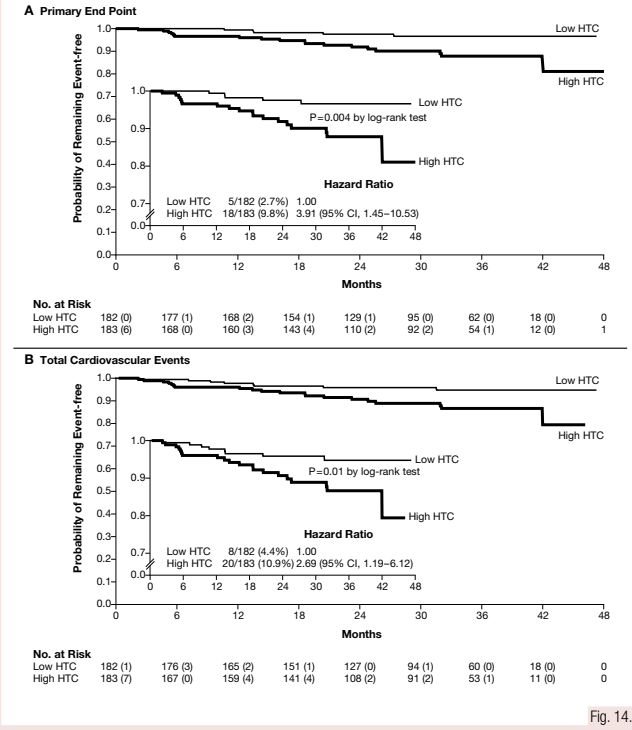


Fig. 14.5

CI, Confidence interval; HTC, haematocrit.

Cytoreductive therapy is indicated for high-risk patients (age >60 years or history of thrombosis). Hydroxyurea is the first choice for the majority of such patients.

Young PV patients without a history of thrombosis can be controlled with phlebotomy and low-dose aspirin only; interferon can be given in case of thrombosis.

Ruxolitinib (a *JAK* inhibitor) is an effective therapy for PV patients with resistance or intolerance to hydroxyurea.

PV treatment aims to control the symptoms and prevent thrombotic and haemorrhagic complications.

The aim of therapy is to maintain the haematocrit level below 45%, since this results in a lower rate of thrombosis.

Low-dose aspirin and strict control of cardiovascular risk factors are important complementary measures.

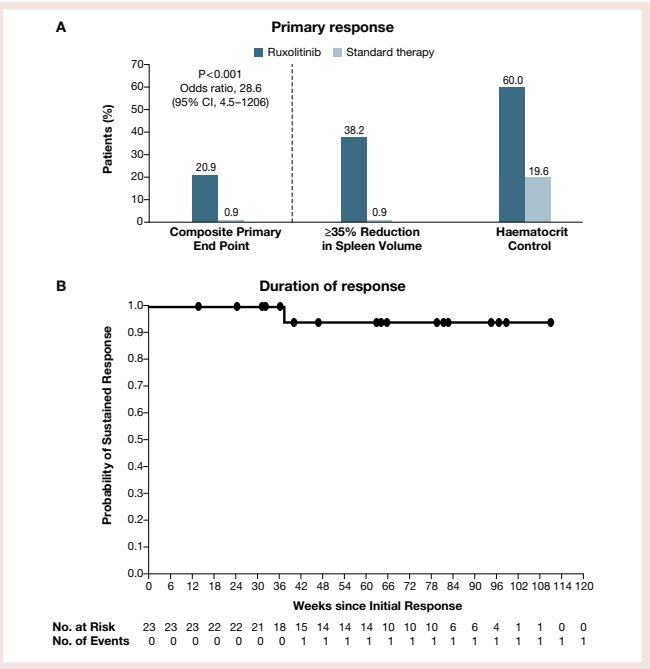


Fig. 14.6

CI, Confidence interval.

REVISION QUESTIONS

1. What is the molecular abnormality commonly observed in patients with PV?
2. At which level should the haematocrit be maintained to better prevent thrombosis in PV patients?
3. Which PV patients would be candidates to receive the *JAK* inhibitor ruxolitinib?

Myelofibrosis

Myelofibrosis (MF) is characterised by anaemia, splenomegaly, constitutional symptoms, leukoerythroblastosis, increased lactate dehydrogenase (LDH) level, clusters of dysplastic megakaryocytes and marrow fibrosis.

The current WHO classification also recognises a 'prefibrotic' form of MF, with absent or mild fibrosis and clusters of dysplastic megakaryocytes in the bone marrow.

60% of patients with MF harbour the *JAK2 V617F* mutation, 20%–25% have *CALR* mutations and 5%–8% *MPL* mutations. Triple negativity is associated with poor prognosis.

Proposed revision of the WHO criteria: diagnosis of overt PMF requires all three major criteria, and at least one minor criterion
Major criteria
1. Presence of megakaryocytic proliferation and atypia, accompanied by either reticulin and/or collagen fibrosis grades 2 or 3
2. Not meeting WHO criteria for ET, PV, *BCR-ABL1*+ CML, myelodysplastic syndromes or other myeloid neoplasms
3. Presence of *JAK2*, *CALR* or *MPL* mutation or, in the absence of these mutations, presence of
4. Another clonal marker or absence of reactive myelofibrosis
Minor criteria
A. Anaemia not attributed to a comorbid condition
B. Leukocytosis >11 x 10^9/L
C. Palpable splenomegaly
D. Increased LDH
E. Leukoerythroblastosis

Fig. 14.7

CML, Chronic myeloid leukaemia; ET, essential thrombocythaemia; LDH, lactate dehydrogenase; PMF, primary myelofibrosis; PV, polycythaemia vera; WHO, World Health Organization.

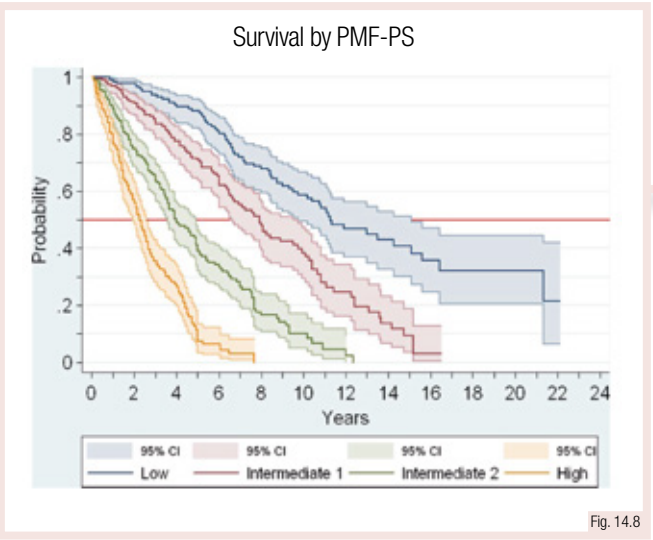


Fig. 14.8

CI, Confidence interval; PMF-PS, primary myelofibrosis prognostic score.

Median survival is 7 years. The International Prognostic Scoring System (IPSS), based on age >65 years, constitutional symptoms, haemoglobin <10 g/dL, white blood cells >25 x 10^9/L and blood blasts, identifies four risk groups.

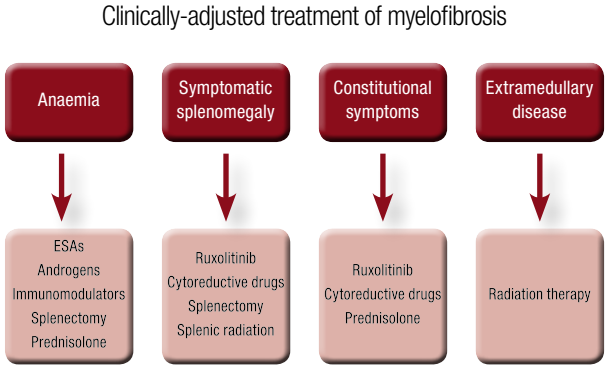
The Dynamic IPSS (DIPSS, based on the same prognostic factors) is used to assess prognosis during the patient's evolution.

Treatment is aimed at alleviating symptoms. In patients below 65–70 years with intermediate-2 or high-risk MF, allogeneic transplantation can be considered.

First-choice therapy for anaemia of MF is driven by erythropoietin (EPO) levels. Erythropoiesis-stimulating agents (ESAs) are given if EPO levels are inadequate, and danazol if levels are adequate.

Immunomodulatory agents such as thalidomide or lenalidomide, combined with prednisone, are the third-line option for MF anaemia.

The *JAK* inhibitor ruxolitinib is the more effective therapy for symptomatic splenomegaly and constitutional symptoms.



ESA, Erythropoiesis-stimulating agent.

Fig. 14.9

REVISION QUESTIONS

1. What are the two most frequent molecular markers of MF?
2. For which of the clinical manifestations of MF is ruxolitinib highly effective?
3. In which MF risk groups is allogeneic stem cell transplantation recommended in patients under 65–70 years old?

Summary: Myeloproliferative neoplasms other than CML: ET, PV, MF

- ET, PV and MF are Philadelphia-negative MPNs characterised by overproduction of mature myeloid cells of clonal origin
- Diagnosis is based on blood counts, mutational status of *JAK2*, *CALR* or *MPL* genes and bone marrow histology
- The goals of treatment in ET and PV are controlling symptoms and preventing vascular complications
- PV and ET patients older than 60 years or with history of thrombosis are candidates for cytoreduction, usually with hydroxyurea
- Young patients without previous history of thrombosis have a low risk of developing thrombosis and can be managed with careful observation in ET and with phlebotomies in PV
- Low-dose aspirin is usually indicated in PV patients and in *JAK2 V617F*-positive ET
- MF is characterised by a high symptom burden, mostly derived from anaemia, splenomegaly and constitutional symptoms
- Median survival in MF patients is around 7 years, but there is wide heterogeneity
- Treatment choice in MF is driven by the predominant symptoms. Main therapeutic modalities are anaemia-treating agents and hydroxyurea or ruxolitinib for splenomegaly and constitutional symptoms
- In MF patients under 65–70 years with poor prognosis features, allogeneic transplantation can be considered

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15 Myelodysplastic/myeloproliferative diseases

Introduction to myelodysplastic/myeloproliferative neoplasms

Myelodysplastic/myeloproliferative neoplasms (MDS/MPN) encompass diseases sharing both myelodysplastic (cytopaenia, myeloid lineage dysplasia) and myeloproliferative features (myeloid proliferation, organomegaly).

The most frequent entity is chronic myelomonocytic leukaemia (CMML), with an incidence of 4 per million per year, mostly affecting patients older than 65 years.

Other MDS/MPN are juvenile myelomonocytic leukaemia (JMML), atypical chronic myeloid leukaemia (aCML), MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T) and unclassifiable-MDS/MPN.

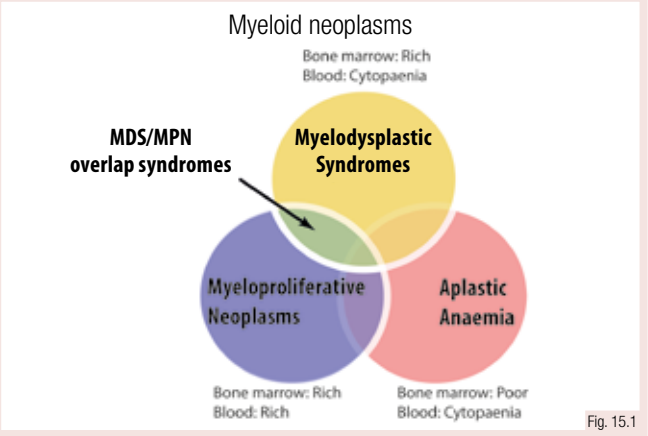


Fig. 15.1

MDS/MPN, Myelodysplastic/myeloproliferative neoplasms.

Criteria	CMML	JMML	aCML	MDS/MPN-RS-T
Age (years)	~72	<14	~70	~72
Monocytes (x 10^9/L)	>1 (>10% WBCs)	>1	<1 (<10% WBCs)	-
Myelaemia (%)	<10%	Present	>10%	-
WBCs (x 10^9/L)	-	-	>13	-
Platelets (x 10^9/L)	-	-	-	>450
Ring sideroblasts >15%	No	No	No	Yes
Medullary/peripheral blasts (%)	<20%	<20%	<20%	<20%
Dysplasia	≥1	Minimal	Dysgranulopoiesis	≥1
BCR-ABL1, PDGFRA/B, FGFR1, PCM1-JAK2 rearrangements	No	No	No	No

Fig. 15.2

aCML, Atypical chronic myeloid leukaemia; CMML, chronic myelomonocytic leukaemia; JMML, juvenile myelomonocytic leukaemia; MDS/MPN, myelodysplastic/myeloproliferative neoplasms; MDS/MPN-RS-T, MDS/MPN with ring sideroblasts and thrombocytosis; WBC, white blood cell.

MDS/MPN diagnosis is mostly based on complete blood count and bone marrow (BM) exploration, showing proliferation and dysplasia of myeloid lineages, sometimes leading to anaemia or thrombocytopaenia.

MDS/MPN diagnosis requires exclusion of other myeloproliferative neoplasms (chronic myeloid leukaemia [CML], neoplasms associated with eosinophilia) and of acute myeloid leukaemia (AML).

Recurrent somatic mutations are frequent in MDS/MPN, and though their repartition is characteristic, none is specific of a particular entity.

CMML arises from the transformation of a haematopoietic stem or progenitor cell (HSPC) that linearly acquires somatic mutations with an early clonal dominance.

CMML progenitors are hypersensitive to growth factors, especially granulocyte–macrophage colony-stimulating factor (GM-CSF), mostly in patients harbouring signalling mutations, with a differentiation skewing toward granulomonocytic lineage.

Monocytes accumulate in peripheral blood together with dysplastic granulocytes and sometimes immature myeloid cells.

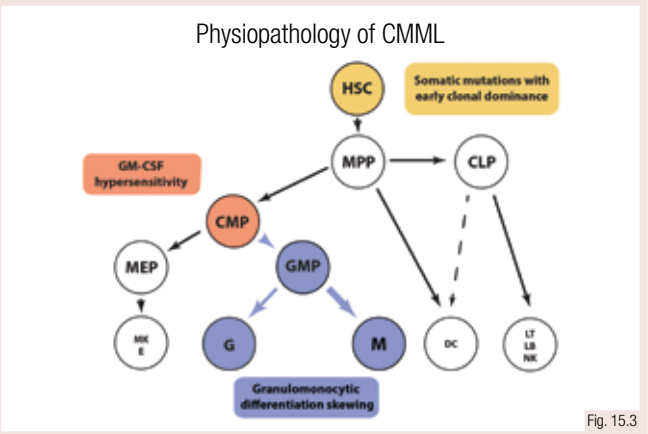


Fig. 15.3

CLP, Common lymphoid progenitor; CMML, chronic myelomonocytic leukaemia; CMP, common myeloid progenitor; DC, dendritic cell; E, erythrocyte; G, granulocyte; GM-CSF, granulocyte–macrophage colony-stimulating factor; GMP, granulocyte monocyte progenitor; HSC, haematopoietic stem cell; LB, B lymphocyte; LT, T lymphocyte; M, monocyte; MEP, megakaryocyte erythrocyte progenitor; MK, megakaryocyte; MPP, multipotent progenitor; NK natural killer.

REVISION QUESTIONS

1. What are the five MDS/MPN subtypes?
2. What are the main differential diagnoses of MDS/MPN?
3. What is the cell of origin in CMML?

Chronic myelomonocytic leukaemia

CMML diagnostic criteria are: a persistent monocytosis ≥1 x 10^9/L (and ≥10% white blood cells [WBCs]), with exclusion of other MPN, <20% blasts in BM and blood, and presence of dysplasia.

If dysplasia is absent, a clonal cytogenetic abnormality (~30%) or a clonal somatic mutation (~100%) should be identified in haematopoietic cells, or the monocytosis should persist ≥3 months.

CMML is characterised by the accumulation of classical monocytes (MO1), with a MO1 fraction ≥94% of total monocytes.

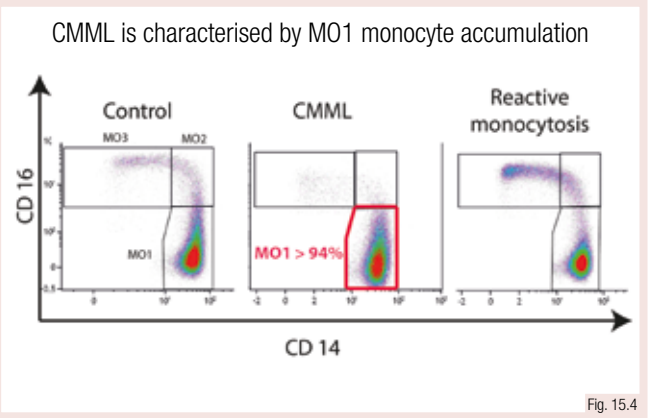


Fig. 15.4

CMML, Chronic myelomonocytic leukaemia.

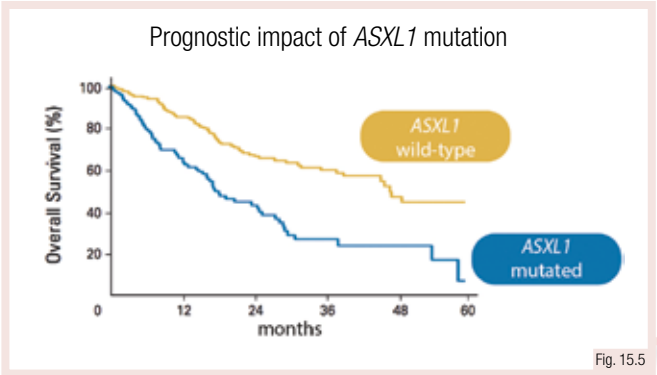


Fig. 15.5

CMML prognosis is heterogeneous and several prognostic scores have been proposed to assess the risk and guide the treatment.

A CMML-specific prognostic scoring system (CPSS) score is based on WBCs, BM blast count, cytogenetic risk and red blood cells (RBCs) transfusion dependency. It categorises CMML patients into 4 groups with significant differences in overall survival (OS).

Frameshift and nonsense mutations of *ASXL1*, a transcription regulator, are associated with poorer outcome.

Patients with low-risk CMML require symptomatic treatment (erythropoiesis-stimulating agents [ESAs], thrombopoietin agonists, transfusion support) and clinical/biological monitoring.

When possible, patients with high-risk CMML should receive an allogeneic stem cell transplantation (alloSCT), which remains the only curative treatment.

Patients with high-risk CMML unfit to receive alloSCT are treated with hypomethylating agents (azacitidine if myelodysplastic CMML according to European Medicines Agency [EMA] label, otherwise as part of clinical trials).

		CPSS risk category	
		Lower-risk	**Higher-risk**
FAB category	MD-CMML (WBCs < 13 g/L)	• Anaemia: Erythropoiesis-stimulating agents (ESA) • Thrombocytopaenia: Thrombopoietin agonists?	• AlloSCT if possible • Azacitidine
	MP-CMML (WBCs ≥ 13 g/L)	• Constitutive symptoms: *JAK* inhibitors? • Myeloproliferation: Hydroxyurea	• AlloSCT if possible • Decitabine?

Fig. 15.6

AlloSCT, Allogeneic stem cell transplantation; CMML, chronic myelomonocytic leukaemia; CPSS, CMML-specific prognostic scoring system; FAB, French-American-British; MP-CMML, myeloproliferative CMML; MD-CMML, myelodysplastic CMML; WBC, white blood cell.

REVISION QUESTIONS

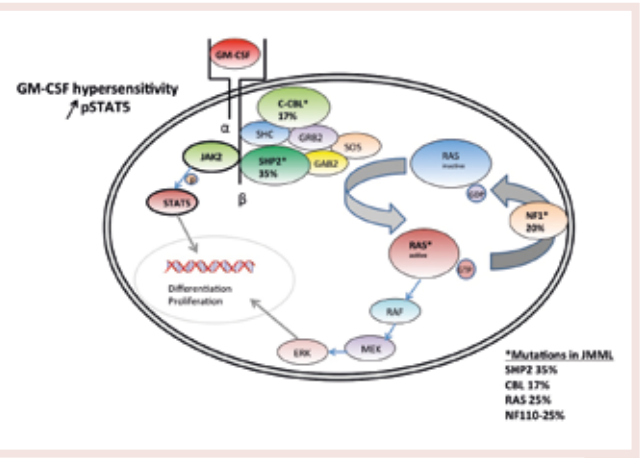
1. List the diagnostic criteria of CMML.
2. What are the main variables predicting outcome in CMML patients?
3. What is the standard treatment for a patient with a high-risk CMML, unfit to receive alloSCT?

Other main MDS/MPN

JMML is an MDS/MPN of infancy characterised by granulomonocytic expansion and dismal prognosis without treatment (median survival 10–12 months). Somatic or germline mutations in *RAS* pathway genes are found in >90% of cases.

JMML diagnostic criteria include: peripheral blood (PB) monocytes >10^9/L, splenomegaly and either a somatic mutation in *PTPN11*, *NF1*, *CBL*, *KRAS* or *NRAS* or two of the following criteria: increased haemoglobin F, erythromyeloid precursors on PB smear, GM-CSF hypersensitivity in colony assays or STAT5 hyperphosphorylation.

AlloSCT is the curative treatment of JMML. Selected patients (e.g. patients with *CBL* mutations and non-proliferative disease) may benefit from a 'watch and wait' policy as spontaneous regression may occur.



GM-CSF, Granulocyte–macrophage colony-stimulating factor; JMML, juvenile myelomonocytic leukaemia. Fig. 15.7

Left panels: Abnormal megakaryocytes;
right panels: Ring sideroblasts (Perls' staining)

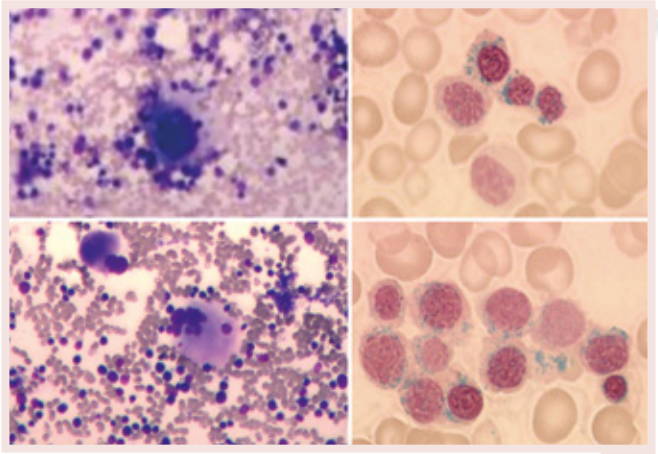


Fig. 15.8

MDS/MPN-RS-T is characterised by refractory anaemia, medullar dyserythropoiesis with ring sideroblasts accounting for >15% of erythroid precursors, thrombocytosis with platelet count >450×10^9/L and <5% blasts on BM smear.

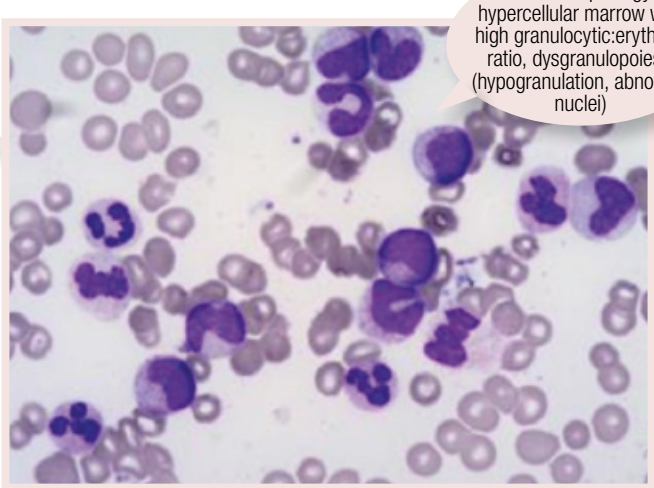
MDS/MPN-RS-T is characterised by the combination of *SF3B1* (70%–90% of cases) and *JAK2/MPL/CALR* (50%–70%) mutations. Prognosis is usually better than in other MDS/MPN.

Clinical management includes ESAs ± transfusions to treat anaemia, iron chelation (as established for low-risk MDS) in frequently transfused patients and low-dose aspirin (as established for essential thrombocytosis).

aCML is a rare disease of the elderly with a dismal prognosis (median survival ~24 months) and frequent (40%) transformation to AML.

Diagnostic criteria include hyperleukocytosis with >10% neutrophil precursors, dysgranulopoiesis, no or minimal basophilia and monocytosis, hypercellular BM with granulocytic proliferation and dysplasia. Classical MPN, including *BCR-ABL* CML and AML, must all be excluded.

SETBP1 and *ETKN1* mutations are found in up to one third of cases. *CSF3R* mutations are rare and warrant exclusion of chronic neutrophilic leukaemia.



aCML morphology: hypercellular marrow with high granulocytic:erythroid ratio, dysgranulopoiesis (hypogranulation, abnormal nuclei)

aCML, Atypical chronic myeloid leukaemia. Fig. 15.9

REVISION QUESTIONS

1. Which signalling pathway is involved in JMML physiopathology?
2. What are the two mutations most frequently found in MDS/MPN-RS-T?
3. What is the treatment of JMML?

Summary: Myelodysplastic/myeloproliferative diseases

- MDS/MPN are rare myeloid neoplasms characterised by overlapping features with myelodysplastic syndromes and myeloproliferative neoplasms
- Their diagnosis requires exclusion of typical myeloproliferative neoplasms and acute myeloid leukaemia
- CMML is the most frequently diagnosed MDS/MPN
- CMML is characterised by a persistent monocytosis with specific accumulation of the classical CD14+/CD16- subset
- CMML prognosis is heterogeneous and is influenced by myeloproliferation, cytopaenias, blast excess, cytogenetics and gene mutations
- The only curative treatment of MDS/MPN is alloSCT
- Treatment of CMML is not well codified and may include cytoreductive agents and hypomethylating agents
- JMML, a MDS/MPN of early childhood characterised by monocytosis, is driven by mutations of genes of the RAS pathway
- Overall, prognosis of aCML is poor, with no codified treatment
- Prognosis of MDS/MPN-RS-T is better than for other MDS/MPN entities

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16 New drugs and novel treatment strategies in acute leukaemia

New drugs for acute myeloid leukaemia

To make it more efficient, the classical combination of cytarabine and daunorubicin was included into a nanoscale liposomal delivery complex, named CPX-351.

CPX-351 liposomes contain a 5:1 molar ratio of cytarabine to daunorubicin; 1 unit = 1.0 mg cytarabine plus 0.44 mg daunorubicin.

A randomised phase III study comparing liposomal formulation with standard induction in 300 patients >60 years old showed better response and survival with the liposomal drug.

Typical liposomal drug carrier structure

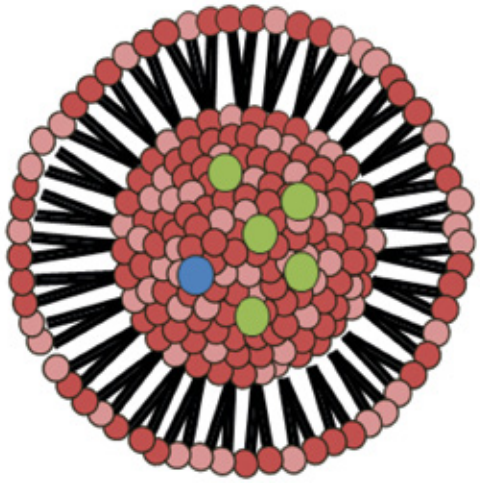


Fig. 16.1

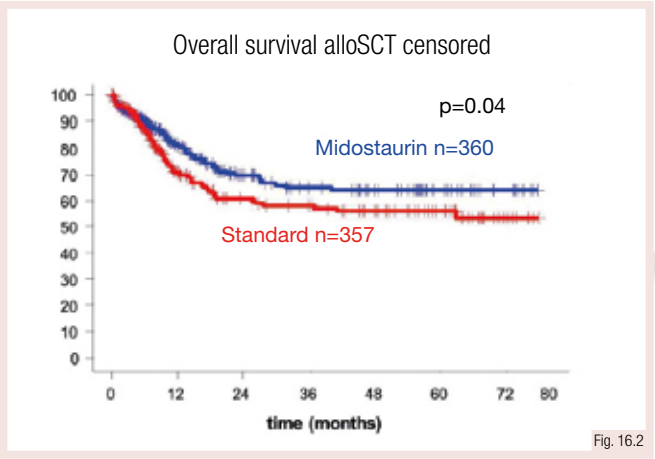


Fig. 16.2

AlloSCT, Allogeneic stem cell transplantation.

A new strategy is to target specific mutations, such as *FLT3* internal tandem duplication (up to 30% of acute myeloid leukaemia [AML] patients). Several drugs inhibit the *FLT3* tyrosine kinase. Of these, midostaurin was recently approved.

In a randomised trial including 717 patients with *FLT3* mutation, patients received induction chemotherapy (ChT) with or without midostaurin.

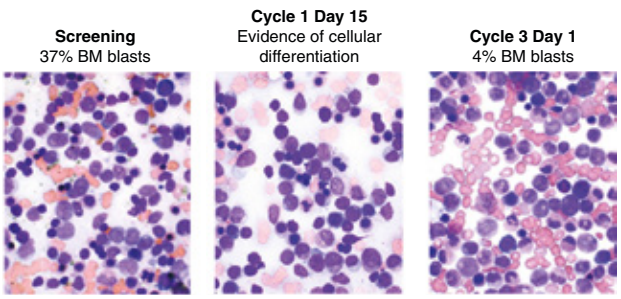
Overall survival (OS) was improved with midostaurin, and the best results were obtained in patients with midostaurin + allogeneic transplant. *FLT3* inhibitors may also benefit *FLT3*-unmutated patients.

Another example of a potential target is the mutation in isocitrate dehydrogenase 1 or 2 *(IDH1/IDH2)*, found in 10%–15% of AML patients.

Mutated *IDH* produces 2-hydroxyglutarate and blocks cellular differentiation. In *IDH*-mutated AML cells, *IDH* inhibitors were shown *in vitro* to induce differentiation.

Clinical use of *IDH* inhibitors is associated with a differentiation syndrome. Some responses in single-agent use have been observed and some patients received prolonged treatment.

Differentiation effects in the bone marrow



Differentiation syndrome is an inflammatory state associated with terminal differentiation of tumour cells, including fever, oedema, dyspnoea and renal failure

BM, Bone marrow.

Fig. 16.3

REVISION QUESTIONS

1. How can liposomes be used to treat acute leukaemia?
2. Which *FLT3* inhibitors have shown therapeutic value in AML?
3. What is the differentiation syndrome?

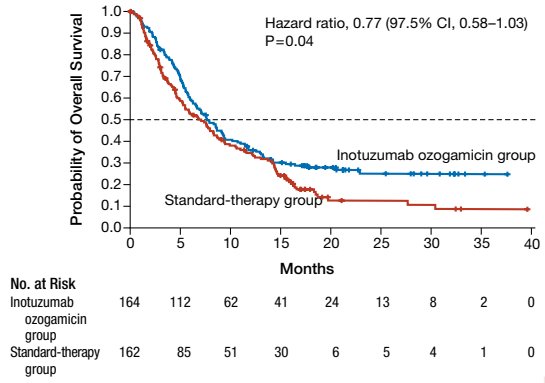
New drugs for acute lymphoblastic leukaemia

Inotuzumab ozogamicin (IO) is a monoclonal anti-CD22 antibody conjugated to calicheamicin, an anthracycline-like cytotoxic antibiotic.

A study randomised 326 patients with relapsed/refractory acute lymphoblastic leukaemia (ALL) to ChT or IO. With IO, OS was longer and both remission rates and minimal residual disease (MRD)-negative remission rates were higher.

Major side effects included severe sinusoidal obstruction syndrome, occurring in up to 9% of patients. This side effect is known from other calicheamicin conjugates.

Survival in patients with relapsed/refractory ALL treated with inotuzumab vs. standard therapy regimens



No. at Risk									
Inotuzumab ozogamicin group	164	112	62	41	24	13	8	2	0
Standard-therapy group	162	85	51	30	6	5	4	1	0

Fig. 16.4

ALL, Acute lymphoblastic leukaemia; CI, confidence interval.

Bispecific antibody linking the T lymphocyte to the CD19-carrying B lymphoblast

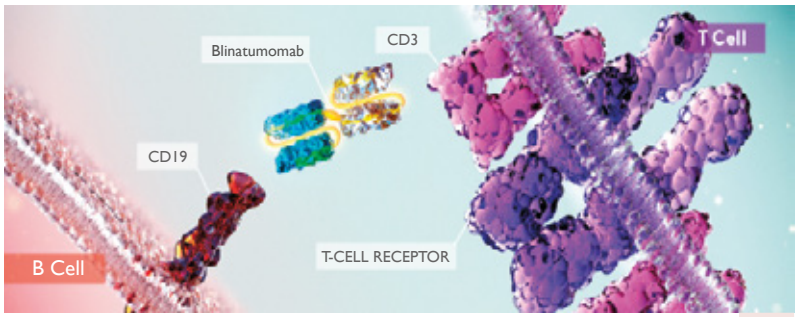


Fig. 16.5

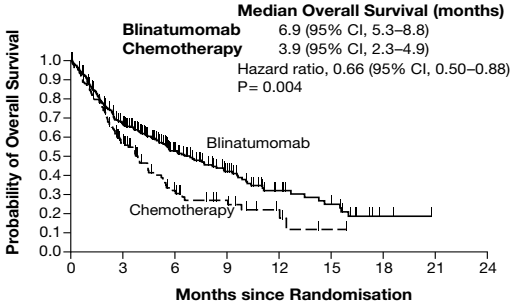
Bispecific antibodies (bAbs) consist of a moiety targeting tumour cells (e.g. CD19) and a second moiety targeting the CD3 antigen to recruit T cells to attack tumour cells.

This concept was shown to be effective in B cell ALL (B-ALL). A randomised trial with 405 relapsed/refractory patients showed higher remission rates and significantly longer survival with blinatumomab monotherapy, as compared with ChT.

Blinatumomab is administered as a 28-day continuous infusion to compensate for renal loss of this small molecule. Side effects include cytopaenia, cytokine-release syndrome (CRS) and neurotoxicity.

Of note: bAbs change tumour immunotherapy, not only by targeting tumour cells but also by redirecting immune effectors to the target.

Survival in patients with relapsed/refractory ALL treated with blinatumomab compared with chemotherapy



No. at Risk									
Blinatumomab	271	163	80	44	21	13	2	0	0
Chemotherapy	134	56	21	12	5	1	0	0	0

Fig. 16.6

ALL, Acute lymphoblastic leukaemia; CI, confidence interval.

REVISION QUESTIONS

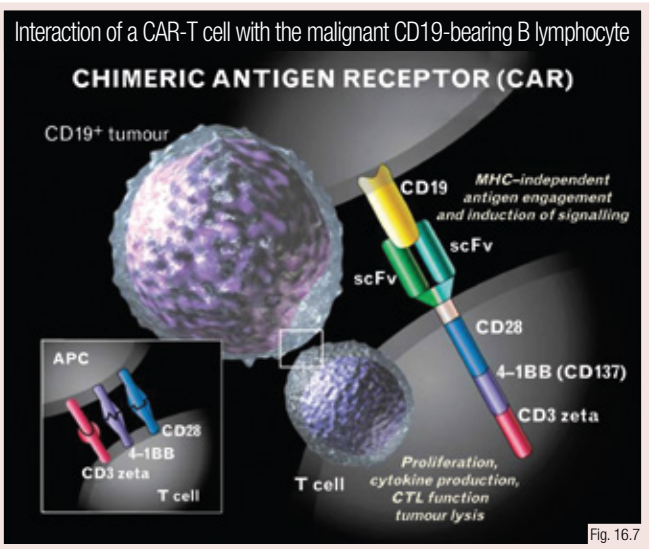
1. What is the structure of IO?
2. What is the mechanism of action of blinatumomab?
3. Why is blinatumomab administered using a continuous infusion?

Treatment of acute leukaemia with chimeric antigen receptor-T cells

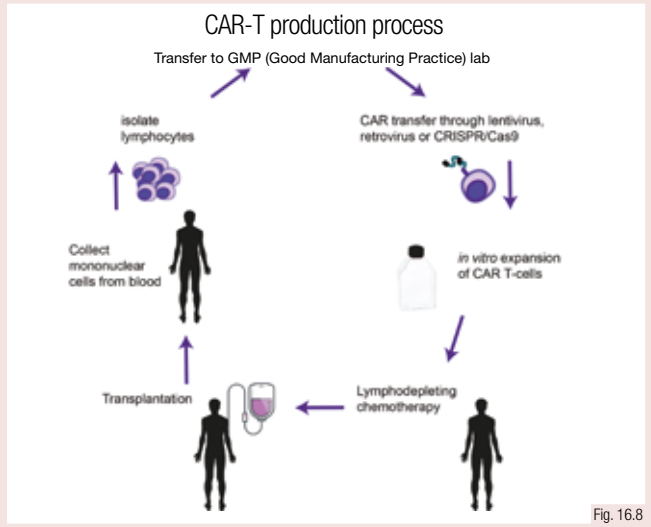
Chimeric antigen receptor (CAR)-T cells were recently approved by the Food and Drug Administration (FDA) to treat relapsed refractory ALL in young patients.

Autologous T cells are engineered to express a CD19-CAR incorporating an anti-CD19 single-chain variable fragment capable of recognising and binding the CD19 expressed on tumour cells, so that effector cells are recruited to the tumour.

This process is now feasible on an industrial scale, and after 3 weeks of cell collection, the anti-CD19-expressing autologous cells are ready to be reinfused into the patient, following a cytotoxic conditioning treatment.



APC, Antigen-presenting cell; CTL, cytotoxic T lymphocyte; MHC, major histocompatibility complex; scFv, single-chain variable fragment.



CAR, Chimeric antigen receptor; GMP, Good Manufacturing Practice.

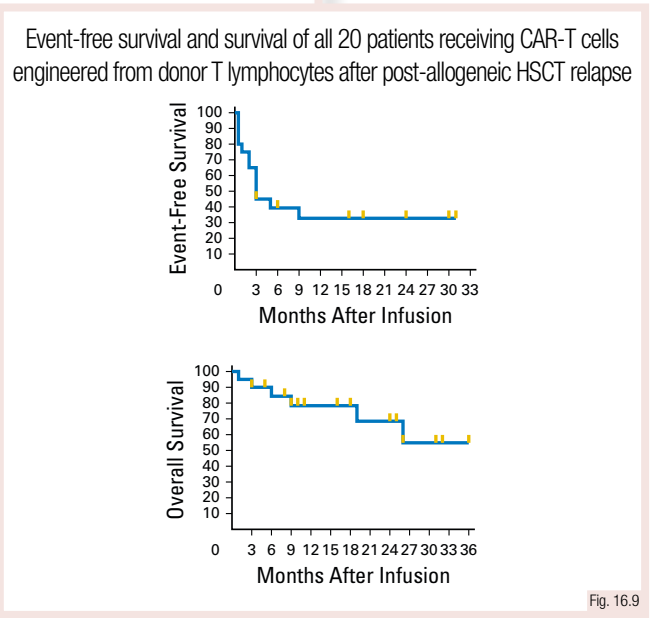
Novel toxicities emerge. The CRS includes symptoms such as fever, hypotension and skin reactions, as well as laboratory abnormalities.

CRS is induced by high cytokine levels and can occur after monoclonal antibody (mAb) or bAb treatment targeting immune effectors and tumour cells as well as with CAR-T cell treatment.

bAb and CAR-T cell treatment can also induce central nervous system toxicity (encephalopathy, cerebellar alteration, disturbed consciousness) of unknown pathophysiology.

In the last few years, several series have been reported but no large study has yet been published comparing CD19-CAR-T cell approaches to other forms of treatment.

20 patients with variable lymphoid malignancies were treated; 4 out of 5 patients with ALL achieved MRD-negative complete remission.



CAR, Chimeric antigen receptor; HSCT, haematopoietic stem cell transplantation.

REVISION QUESTIONS

1. Which of the following treatment approaches requires genetic engineering: rituximab, IO calicheamicin, blinatumomab, CAR-T cells?
2. Against which antigen are CAR-T cells directed in ALL treatment?
3. What toxicity has been reported with CAR-T cell treatment?

Summary: New drugs and novel treatment strategies in acute leukaemia

- In AML, new approaches include packaging conventional ChT in liposomes, although the value of these therapies needs confirmation
- Major advances are likely to come from targeting mutated proteins with small molecules such as *FLT3* inhibitors or *IDH1/2* inhibitors. These are under development
- In ALL, most approaches are of immunotherapeutic nature; the value of anti-CD20 antibodies has been shown recently
- Other immunotherapeutic agents include bAbs for T cell recruitment, anti-CD22 antibody drug conjugates and, most interestingly, CAR-engineered T cells
- bAbs represent a new immunotherapeutic principle targeting tumour cells and potentially tumouricidal immune cells
- CAR-T cells are even more novel as these may bring new concepts of engineered cellular therapies into the therapeutic armamentarium. Where effects have been shown in studies, it was mostly in advanced disease stages. Confirming the data and incorporating these agents into first-line treatment will await future studies
- Many additional approaches are underway targeting mechanisms of leukaemogenesis, abnormal gene regulation and others

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17 New drugs and novel treatment strategies in multiple myeloma treatment

Improving survival in multiple myeloma

Survival in multiple myeloma (MM) patients has significantly increased in the last 15 years, thanks to the availability of new drugs.

Proteasome inhibitors (PIs) and immunomodulatory drugs (IMiDs) are the two first novel classes of drugs with high activity in relapsed/refractory (RR) and newly diagnosed patients. They represent the backbone of most myeloma treatment regimens.

Other classes of drugs with different mechanisms of action include: histone deacetylase (HDAC) inhibitors, kinase inhibitors, inhibitors of different proteins or signalling pathways and monoclonal antibodies (mAbs).

Improving survival in MM: changes in OS from 1960–2010

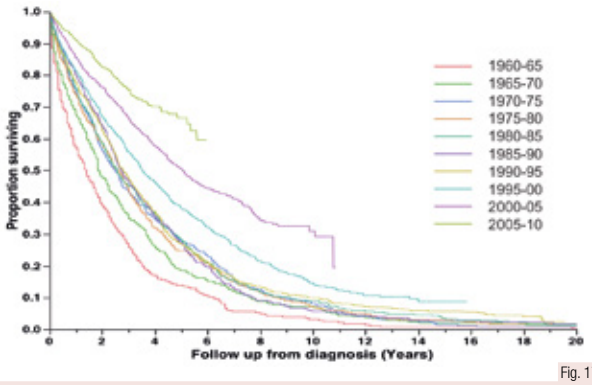
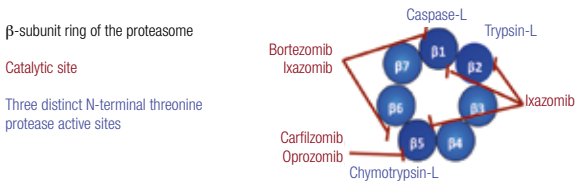


Fig. 17.1

MM, Multiple myeloma; OS, overall survival.

Proteasome inhibitors (PIs)



	Type	Reversibility	po/iv	Dosing	Phase
Bortezomib	Boronic	Reversible	iv	1, 4, 8, 11	Approved
Carfilzomib	Epoxi-ketone	Irreversible	iv	1–2, 8-9, 15-16	Approved
Ixazomib (MLN-9708)	Boronic	Reversible	po	1, 4, 8, 11	Approved
Ixazomib (NPI-0052)	Salinospore	Irreversible	iv	1, 4, 8, 11	I/II
Oprozomib (PR-047)	Epoxi-ketone	Irreversible	po	BID	I/II

Fig. 17.2

BID, Twice daily; iv, intravenous; po, orally.

PIs differ in their chemical structure, catalytic site for inhibition, binding reversibility and route of administration (iv/sc/oral). Following bortezomib (Btz), both carfilzomib (Cfz) and ixazomib have been approved for relapsing patients, and marizomib and oprozomib are in early-phase trials.

Ixazomib is an oral PI with a very good safety profile and, in combination with Len-Dex (lenalidomide-dexamethasone) yielded a longer progression-free survival (PFS) than Len-Dex alone, but with no significant difference in overall survival (OS).

Cfz-dex achieves twice the PFS as Btz-dex, and the triplet Cfz+Len-Dex (KRd) also results in significantly superior PFS and OS when compared with Len-Dex. Cfz does not induce significant peripheral neuropathy but is associated with some cardiovascular toxicity.

Thalidomide, lenalidomide and pomalidomide are IMiDs. Small changes in their chemical structure lead to differences in the immunomodulatory and antiangiogenic effects and toxicity profile.

Pomalidomide, a third-generation IMiD, in combination with low-dose dexamethasone has been approved for the treatment of double-refractory patients.

Pomalidomide is becoming a backbone for drug combinations with cyclophosphamide, PIs and mAbs. A new generation of more potent and specific IMiDs is under development.

Novels IMiDs in MM

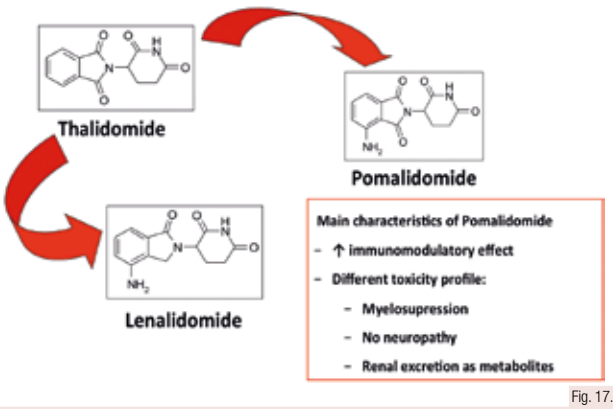


Fig. 17.3

IMiD, Immunomodulatory drug; MM, multiple myeloma.

REVISION QUESTIONS

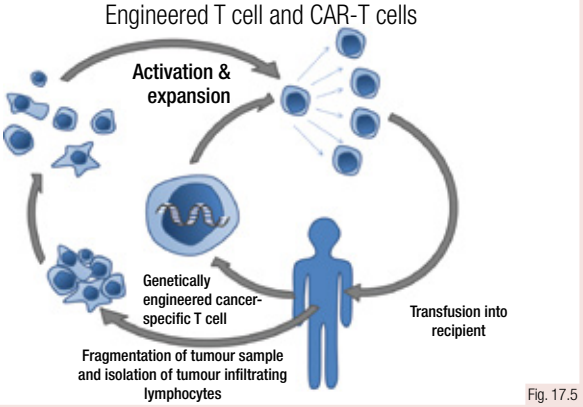
1. What are the two backbone classes of drugs for MM treatment?
2. What is the oral PI used in clinical practice?
3. What is the name of the third-generation IMiD approved for the treatment of MM patients?

Novel immunotherapy strategies for the treatment of multiple myeloma

The use of mAbs represents a major step forward in the treatment of MM, with 5 potential modes of action (shown in Fig. 17.4). As opposed to daratumumab, elotuzumab (SLAMF7) has no activity as a single agent but the combination of elotuzumab with Len-Dex is significantly superior to Len-Dex alone.

CD38 mAbs (daratumumab, isatuximab, MOR202), show activity as monotherapies, with an approximately 30% response rate in relapsed and refractory patients.

Daratumumab in combination with Len-Dex and Btz-dex reduces the risk of progression or death by two-thirds in relapsed MM patients, as compared with the standard Len-Dex / Btz-dex.



MM, Multiple myeloma; NK, natural killer.

Fig. 17.4

Fig. 17.5

CAR, Chimeric antigen receptor.

The bispecific antibodies (targeting both the tumour and T cells) may overcome the limitations of an immunosuppressive tumour microenvironment and could be an alternative to CAR therapy for RRMM patients. Several mAbs targeting BCMA are under investigation in early-phase trials but no clinical data are available at the time of publication.

Conjugated antibodies are also under development. Anti-BCMA antibody conjugated with Auristatin-F has shown promising single-agent activity (60% responses) in refractory patients and 40% in patients previously exposed to daratumumab.

Immune checkpoints, such as the programmed cell death protein 1 (PD-1) pathway, are often exploited by tumours to escape immune surveillance. Despite initial good results with PD-1 inhibitors in MM, all trials have been halted due to safety concerns.

Patients' autologous T cells can be reprogrammed by transducing them with a chimeric antigen receptor (CAR) to specifically target tumour cells, thereby combining the specificity of an antibody with the potent cytotoxic and memory functions of a T cell.

CARs are engineered fusion proteins that contain an extracellular antigen-binding domain (single-chain variable fragment [scFv], derived from an antibody), linked in tandem to the CD3z chain of the T cell receptor (TCR) complex and the endo-domain of costimulatory molecules (CD28/CD137).

CAR-T against CD19, BCMA (B-cell maturation antigen) or SLAMF-7 are being tested in MM. Anti-BCMA has shown an overall response rate (ORR) of ~90% (50% complete response [CR] including minimal residual disease [MRD] negativity) with a median PFS of 12 months in the most mature trial. However, the toxicity (mainly cytokine-release syndrome and neurological toxicity) is still a concern.

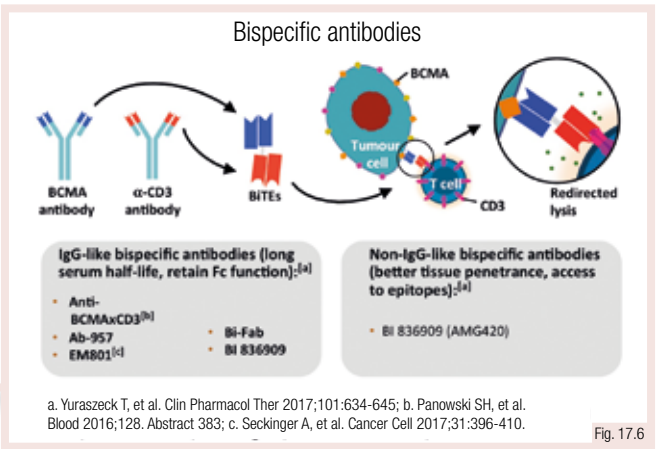


Fig. 17.6

BCMA, B-cell maturation antigen; BiTE, bispecific T cell engager; IgG, immunoglobulin G.

REVISION QUESTIONS

1. Which mAb achieves 30% positive response as a single agent in refractory MM?
2. What is the structure of CAR?
3. What are the potential alternatives to CAR-T therapies in MM patients?

New drugs with novel mechanisms of action

A large number of novel agents targeting different pathogenic mechanisms of the plasma cell have been tested both pre-clinically and clinically.

As MM is a polygenic entity with no single pathogenic mechanism, the activity of these novel agents with one single target is limited, and they usually need to be combined among themselves or with other backbones to show clinically significant results.

The future (and it has already started) would probably be to characterise the key pathogenic mechanisms of every patient, and adapt the therapy based on his/her biology in what is called personalised or precision medicine.

New drugs and mechanisms of action in MM

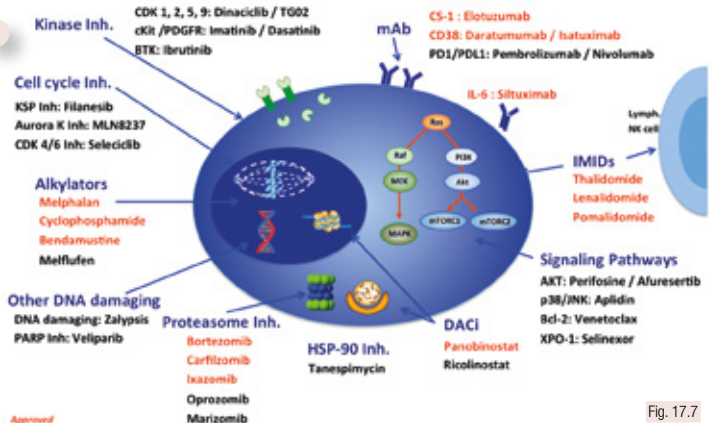


Fig. 17.7

BTK, Bruton's tyrosine kinase; CDK, cyclin-dependent kinase; DACi, deacetylase inhibitor; HSP, heat shock protein; IL, interleukin; IMiD, immunomodulatory drug; KSP, kinesin spindle protein; mAb, monoclonal antibody; MM, multiple myeloma; mTORC1/C2; mechanistic target of rapamycin complex 1/2; NK, natural killer; PARP, poly(adenosine diphosphate-ribose) polymerase; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PDGFR, platelet-derived growth factor receptor.

Rationale for combining DACi + bortezomib

Inhibition of the aggresome and proteasome pathways causes a build-up of intracellular misfolded cytotoxic proteins, leading to MM cell apoptosis

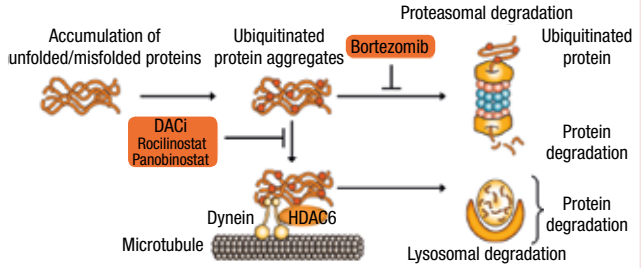


Fig. 17.8

DACi, Deacetylase inhibitor; HDAC, histone deactylase; MM, multiple myeloma.

HDACs are enzymes overexpressed in several cancers including MM, and their inhibition with specific agents (HDAC inhibitors [HDACis]) has shown antitumoural activity in some malignancies.

Although they do not have anti-MM activity as monotherapy, these drugs synergise with PIs, favouring the accumulation of toxic misfolded proteins, which leads to myeloma cell death.

Panobinostat has been approved in combination with Btz-dex for patients who have received at least two lines of treatment, including Btz and len. More selective deacetylase (DAC) inhibitors, such as the HDAC-6 inhibitor ricolinostat with better tolerability, are under investigation.

Some proteins that have recently emerged as targets in MM are the pro-survival protein BCL2 and XPO1 (exportin-1), which transfer proteins from the cell nucleus to the cytoplasm.

The BCL2 inhibitor venetoclax has shown an ORR of 21%, with more specific activity in patients harbouring *t(11;14)* (40% responses), and is also being investigated in combination with Btz-dex.

Selinexor (XPO1 inhibitor) with dexamethasone yielded 20% ORR in penta-refractory patients, and is synergistic with PIs and IMiDs in the clinical setting.

BCL2 inhibitor venetoclax

Venetoclax induces cell death in MM, particularly in *t(11;14)* MM, associated with higher ratios of BCL2 expression

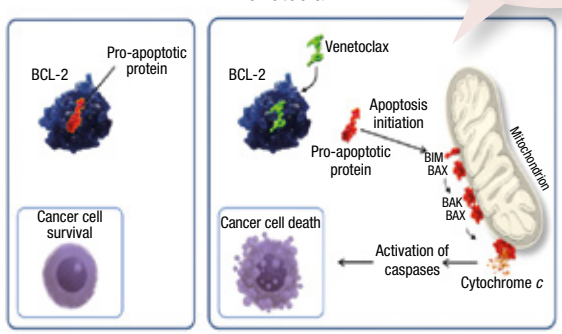


Fig. 17.9

MM, Multiple myeloma.

REVISION QUESTIONS

1. List some novel targets that could potentially be effective in MM.
2. What is the rationale for combining HDACi and PI in MM?
3. Which specific subsets of MM patients may benefit the most from BCL2 inhibition?

Summary: New drugs and novel treatment strategies in multiple myeloma treatment

- PIs and IMiDs represent the backbone of myeloma treatment
- Cfz and ixazomib are the second generation of PIs approved for relapsed/refractory MM
- Pomalidomide is a third-generation IMiD approved for double-refractory MM
- Immunotherapy is a very attractive therapeutic avenue for MM patients
- CD38 mAb has activity as a single agent in relapsed/refractory MM, and in combination with len or Btz reduces the risk of progression by 62%
- Anti-BCMA CAR-T cells induced positive responses in highly refractory myeloma patients
- Targeted agents in MM usually induce few responses, of short duration, but their action might be substantially enhanced within combination therapies
- HDACis were the first novel family of agents to be approved (after PIs and IMiDs) in MM, in combination with Btz and dex
- Other novel targets are the BCL2 family (venetoclax) and exportin-1 (selinexor), particularly in combination with backbone agents

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18 Systemic immunoglobulin light-chain amyloidosis

Amyloidosis – Background and diagnosis

Amyloidosis is a rare group of diseases caused by extracellular deposition of amyloid fibrils.

Systemic immunoglobulin light-chain (AL) amyloidosis is the most common type of amyloidosis in the western world.

Wild-type (wt) 'senile systemic' transthyretin (ATTR) amyloidosis is an increasingly recognised entity and may become the most common type of amyloidosis in the elderly.

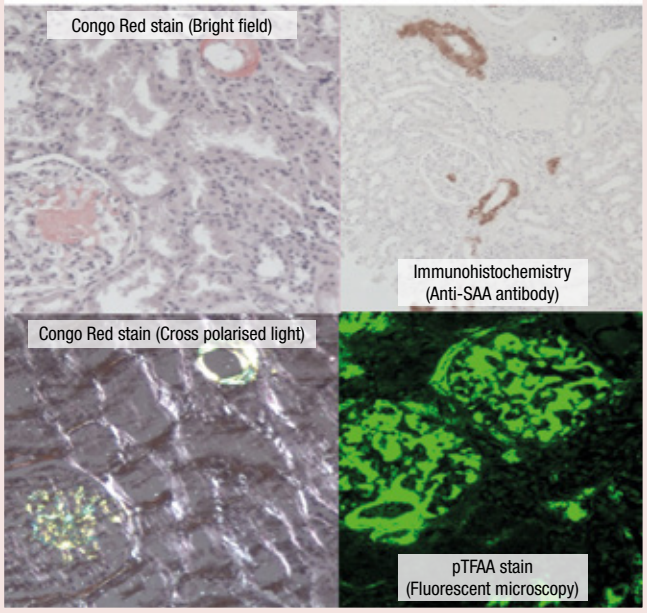
The most common types of amyloidosis and organ involvement

Amyloid type	Heart	Kidneys	Liver/GI tract	PNS	ST
AL	++	++	+	+	+
ATTRm	++	–	–	++	–
ATTRwt	+++	–	–	–	Carpal tunnel
AFib	–	+++	–	–	–
AApoA1	+	++	++	+	–
ALys	–	+	++	–	–

AApoA1, Apolipoprotein A1 amyloidosis; AFib, fibrinogen amyloidosis; AL, Light chain amyloidosis; ALys, lysozyme amyloidosis; ATTR, transthyretin amyloidosis; GI, gastrointestinal; m, mutant; PNS, peripheral nervous system; ST, soft tissue; wt, wild-type.

Fig. 18.1

Congo Red staining and immunohistochemistry



pTFAA, Probe heptameric formic thiophene acetic acid; SAA, serum amyloid A.

Fig. 18.2

Demonstration of amyloid deposition in a tissue biopsy by characteristic birefringence under cross-polarised light with Congo Red staining remains the gold standard.

Laser capture of amyloid deposits followed by proteomics is the current gold standard for amyloid fibril protein identification.

Amyloidotic tissue is captured from formalin-fixed sections, cut with a laser capture microscope, subjected to tryptic digestion and analysed by mass spectrometry.

Early diagnosis is key. During routine follow-up of patients with MGUS (monoclonal gammopathy of undetermined significance), two simple tests – measurement of NT-proBNP (N-terminal pro-brain natriuretic peptide [and, if indicated, of cardiac troponin-T]) and urine for protein – would detect >90% of such cases very early, potentially improving outcomes.

3 key steps to diagnosing AL amyloidosis:

1. Histologically prove amyloid deposition and confirm the fibril type causing amyloidosis
2. Assess the underlying disease (in case of AL amyloidosis – the monoclonal disease)
3. Define the extent of systemic damage, including risk stratification/staging.

Proteomic analysis showing amyloid fibril proteins (blue box)

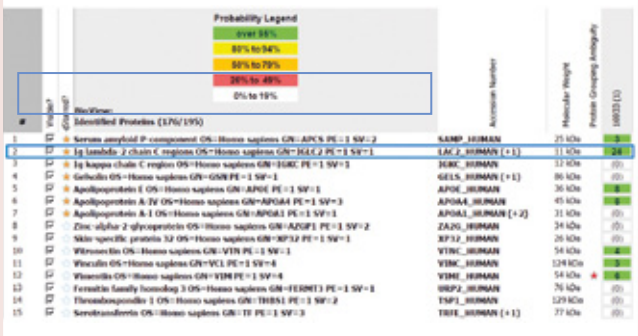


Fig. 18.3

REVISION QUESTIONS

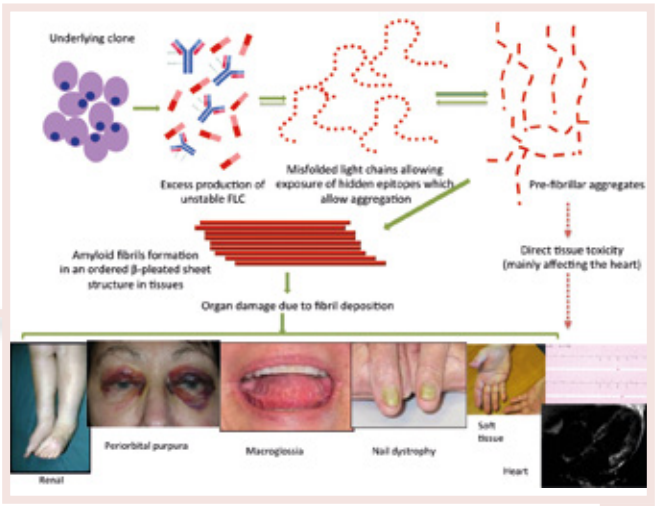
1. What is the most common type of amyloidosis?
2. What is the method to prove amyloid deposits on histology?
3. Which technique is best for amyloid fibril typing?

Clinical presentation and imaging

The majority of patients present with an underlying plasma cell dyscrasia, which produces unstable monoclonal immunoglobulin light chains.

These light chains not only deposit in the tissues but are also tissue-toxic, resulting in multi-organ involvement.

Heart, kidney and liver involvement is seen in 70%, 65% and 30% of patients, respectively. Soft tissue involvement with macroglossia is seen in nearly 25% of patients and is almost pathognomonic of AL amyloidosis. Nail dystrophy and deposits in other soft tissue sites are seen in 15% of patients.



FLC, Free light chain.

Fig. 18.4

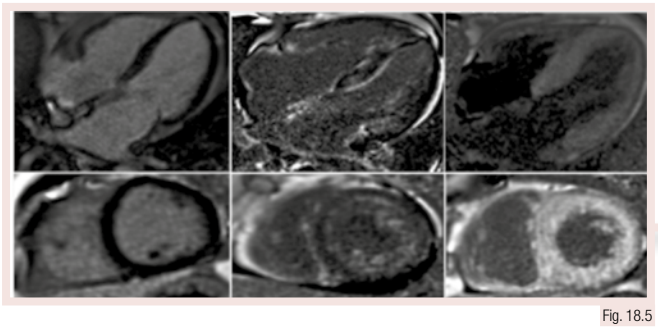


Fig. 18.5

Heart involvement is the main cause of morbidity and mortality. Echocardiography demonstrates a thick-walled left ventricle typically with dilated atria and marked diastolic dysfunction.

Cardiac magnetic resonance imaging (MRI) with gadolinium contrast is more useful in this regard – late enhancement after gadolinium contrast is characteristic of amyloidosis, and a transmural pattern of enhancement is associated with poor outcomes.

^{99m}Tc-DPD is a bone scanning agent that is highly specific for cardiac amyloid deposits and shows high-grade uptake in ATTR amyloidosis, whereas it is negative in half of all cases with AL amyloidosis – and when positive uptake is low grade. This allows it to be a very useful tool to differentiate the two amyloid types in older patients.

Early mortality remains a major medical concern. 30%–40% of all patients with AL amyloidosis and cardiac involvement will succumb to disease-related complications in the first few months following diagnosis.

Outcome of patients with newly diagnosed AL amyloidosis has improved from 1.5 years in the early part of the last decade to nearly 5 years for more recently diagnosed patients.

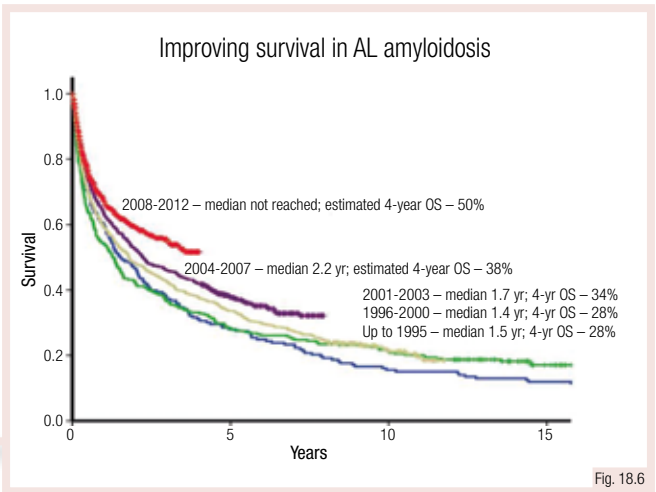


Fig. 18.6

AL, Light chain; OS, overall survival.

REVISION QUESTIONS

1. What is the ongoing challenge in cardiac amyloidosis?
2. Which organs are commonly affected in AL amyloidosis?
3. What are the best tools for the diagnosis of cardiac amyloidosis?

Treatment of AL amyloidosis

The mainstay of therapy remains treatment directed towards the plasma cell clone, using effective chemotherapy (ChT) or autologous stem cell transplantation (ASCT). This achieves a good response in 60%–70% of treated patients, translating into an organ response.

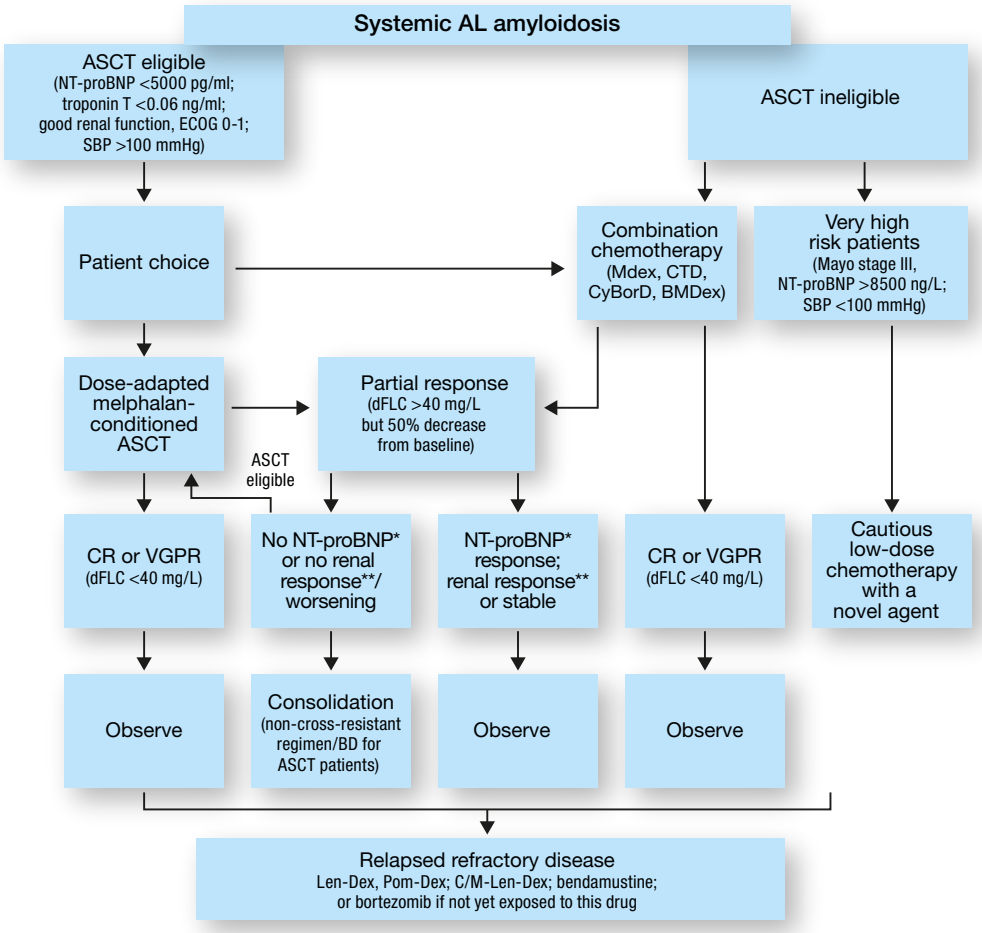


Fig. 18.7

*Reduction of 30% and 300 ng/L
** 50% decrease in proteinuria with stable or < 25% increase in serum creatinine
AL, Light-chain; ASCT, autologous stem cell transplantation; BD, bortezomib/dexamethasone; BMDex, bortezomib/melphalan/dexamethasone; C/M-Len-Dex, cyclophosphamide/melphalan/lenalidomide/dexamethasone; CR, complete response; CTD, cyclophosphamide/thalidomide/dexamethasone; CyBorD, cyclophosphamide/bortezomib/dexamethasone; dFLC, difference between involved minus uninvolved serum free light chains; ECOG, Eastern Cooperative Oncology Group; Len-Dex, lenalidomide/dexamethasone; Mdex, melphalan/dexamethasone; NT-proBNP, N-terminal pro-brain natriuretic peptide; Pom-Dex, pomalidomide/dexamethasone; SBP, systolic blood pressure; VGPR, very good partial response.

At baseline, all patients need to be assessed for ASCT suitability. Patients with good organ function and limited or no cardiac involvement are potential candidates (15% of all patients are eligible). Such patients should be considered for a melphalan 200 mg/m^2-conditioned stem cell transplant.

All other patients are candidates for ChT-based treatment. Bortezomib is the backbone of AL ChT. Addition of either cyclophosphamide or melphalan (CyBorD [cyclophosphamide, bortezomib, dexamethasone] or BMdex [bortezomib, melphalan, dexamethasone]) is considered as first-line standard of care in AL amyloidosis. Patients with neuropathy are best treated with either an alkylator-based regimen or lenalidomide-based regimens.

Therapies directly targeting the amyloid deposits are becoming available and aim to accelerate amyloid removal from tissues.

REVISION QUESTIONS

1. What is the mainstay of treatment in AL amyloidosis?
2. What is the key baseline decision when faced with a newly diagnosed patient with AL amyloidosis?
3. If the patient is not suitable for an autologous transplant, what is the best first-line treatment regimen?

Summary: Systemic immunoglobulin light-chain amyloidosis

- AL amyloidosis is the most frequent of the rare protein deposition diseases
- It should be suspected in any patient with a monoclonal protein presenting with unexpected cardiac, renal, liver or neurological symptoms
- NT-proBNP and urine assessment for albuminuria will detect 90% of suspected cases
- Amyloid deposition is confirmed by Congo Red staining, and fibril typing is done by immunohistochemistry or mass spectrometry
- Imaging is critical in the assessment process
- Cardiac echography and MRI are useful for diagnosis of heart involvement
- ^{99m}Tc-DPD scintigraphy is useful for differentiating between AL and ATTR amyloidosis
- Treatment is based on strategies to eliminate the plasma cell clone in the bone marrow with either an ASCT or with combination ChT
- Achieving a haematological complete or very good partial response is the goal of treatment
- Patient outcomes are improving and novel anti-amyloid therapies are in the pipeline, aiming to change the outlook for this disease

Further Reading

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Appendix 1: WHO 2016 Classification of Myeloid Neoplasms and Acute Leukaemia

Myeloproliferative neoplasms (MPN)

- Chronic myeloid leukaemia (CML), *BCR-ABL1*$^{+}$
- Chronic neutrophilic leukaemia (CNL)
- Polycythaemia vera (PV)
- Primary myelofibrosis (PMF)
  - PMF, prefibrotic/early stage
  - PMF, overt fibrotic stage
- Essential thrombocythaemia (ET)
- Chronic eosinophilic leukaemia, not otherwise specified (NOS)
- MPN, unclassifiable

Mastocytosis

Myeloid/lymphoid neoplasms with eosinophilia and rearrangement of *PDGFRA, PDGFRB,* or *FGFR1,* or with *PCM1-JAK2*

- Myeloid/lymphoid neoplasms with *PDGFRA* rearrangement
- Myeloid/lymphoid neoplasms with *PDGFRB* rearrangement
- Myeloid/lymphoid neoplasms with *FGFR1* rearrangement
- *Provisional entity: Myeloid/lymphoid neoplasms with PCM1-JAK2*

Myelodysplastic/myeloproliferative neoplasms (MDS/MPN)

- Chronic myelomonocytic leukaemia (CMML)
- Atypical chronic myeloid leukaemia (aCML), *BCR-ABL1*$^{-}$
- Juvenile myelomonocytic leukaemia (JMML)
- MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T)
- MDS/MPN, unclassifiable

Myelodysplastic syndromes (MDS)

- MDS with single lineage dysplasia
- MDS with ring sideroblasts (MDS-RS)
  - MDS-RS and single lineage dysplasia
  - MDS-RS and multilineage dysplasia
- MDS with multilineage dysplasia
- MDS with excess blasts
- MDS with isolated *del(5q)*
- MDS, unclassifiable
- *Provisional entity: Refractory cytopaenia of childhood*

Myeloid neoplasms with germ line predisposition

Acute myeloid leukaemia (AML) and related neoplasms

- AML with recurrent genetic abnormalities
  - AML with *t(8;21)(q22;q22.1);RUNX1-RUNX1T1*
  - AML with *inv(16)(p13.1q22)* or *t(16;16)(p13.1;q22);CBFB-MYH11*
  - APL with *PML-RARA*
  - AML with *t(9;11)(p21.3;q23.3);MLLT3-KMT2A*
  - AML with *t(6;9)(p23;q34.1);DEK-NUP214*
  - AML with *inv(3)(q21.3q26.2)* or *t(3;3)(q21.3;q26.2); GATA2, MECOM*
  - AML (megakaryoblastic) with *t(1;22)(p13.3;q13.3);RBM15-MKL1*
  - *Provisional entity: AML with BCR-ABL1*
  - AML with mutated *NPM1*
  - AML with biallelic mutations of *CEBPA*
  - *Provisional entity: AML with mutated RUNX1*
- AML with myelodysplasia-related changes
- Therapy-related myeloid neoplasms
- AML, NOS
  - AML with minimal differentiation
  - AML without maturation
  - AML with maturation
  - Acute myelomonocytic leukaemia
  - Acute monoblastic/monocytic leukaemia
  - Pure erythroid leukaemia
  - Acute megakaryoblastic leukaemia
  - Acute basophilic leukaemia
  - Acute panmyelosis with myelofibrosis
- Myeloid sarcoma
- Myeloid proliferations related to Down syndrome
  - Transient abnormal myelopoiesis (TAM)
  - Myeloid leukaemia associated with Down syndrome

Blastic plasmacytoid dendritic cell neoplasm

Acute leukaemias of ambiguous lineage

- Acute undifferentiated leukaemia
- Mixed phenotype acute leukaemia (MPAL) with *t(9;22)(q34.1;q11.2); BCR-ABL1*
- MPAL with *t(v;11q23.3); KMT2A* rearranged
- MPAL, B/myeloid, NOS
- MPAL, T/myeloid, NOS

B-lymphoblastic leukaemia/lymphoma

- B-lymphoblastic leukaemia/lymphoma, NOS
- B-lymphoblastic leukaemia/lymphoma with recurrent genetic abnormalities
- B-lymphoblastic leukaemia/lymphoma with *t(9;22)(q34.1;q11.2);BCR-ABL1*
- B-lymphoblastic leukaemia/lymphoma with *t(v;11q23.3); KMT2A* rearranged
- B-lymphoblastic leukaemia/lymphoma with *t(12;21)(p13.2;q22.1); ETV6-RUNX1*
- B-lymphoblastic leukaemia/lymphoma with hyperdiploidy
- B-lymphoblastic leukaemia/lymphoma with hypodiploidy
- B-lymphoblastic leukaemia/lymphoma with *t(5;14)(q31.1;q32.3); IL3-IGH*
- B-lymphoblastic leukaemia/lymphoma with *t(1;19)(q23;p13.3);TCF3-PBX1*
- *Provisional entity: B-lymphoblastic leukaemia/lymphoma, BCR-ABL1–like*
- *Provisional entity: B-lymphoblastic leukaemia/lymphoma with iAMP21*

T-lymphoblastic leukaemia/lymphoma

- *Provisional entity: Early T-cell precursor lymphoblastic leukaemia*

Provisional entity: Natural killer (NK) cell lymphoblastic leukaemia/lymphoma

Further Reading

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Appendix 2: Selected treatment schedules

Acute myeloid leukaemia

REGIMEN	TREATMENT/DRUG	DOSE	ROUTE	SCHEDULE
3+7 [1, 2]	Daunorubicin (OR idarubicin) Cytarabine	60–90 mg/m^2 (12 mg/m^2) 100–200 mg/m^2	i.v. (i.v.) i.v. as c.i.	Days 1–3 * (Days 1–3 *) Days 1–7 * q 4–6 weeks
Midostaurin in patients with *FLT3* mutation [3]	Midostaurin (added to standard chemotherapy)	50 mg BID	p.o.	Days 8–21 during induction and consolidation Days 1–28 during maintenance (12 cycles) q 28 days
HDAC [4] IDAC	Cytarabine Cytarabine	3000 mg/m^2 BID 1000 mg/m^2 BID	i.v. i.v.	Days 1, 3, 5 Days 1–6 q 4–6 weeks
ATRA/ATO (APL) [5]	ATRA Arsenic trioxide	45 mg/m^2 0.15 mg/kg	p.o. i.v.	Day 1 Day 1
Decitabine [6, 7]	Decitabine	20 mg/m^2	i.v.	Days 1–5 [6] (10 [7]) q 28 days
Azacitidine [8]	Azacitidine	75 mg/m^2	s.c.	Days 1–7 q 28 days
Low-dose AraC [9]	Cytarabine	20 mg BID	s.c.	Days 1–10 q 28 days

Footnotes: * The treatment depends on the protocol and on the remission after the first cycles. If patients are in remission, most protocols go to HDAC/IDAC as consolidation. If patients are not in remission, some protocols repeat another 3+7, usually 4–6 weeks after the first cycle.

Abbreviations: APL, Acute promyelocytic leukaemia; ATO, Arsenic trioxide; ATRA, all-trans retinoic acid; BID, twice daily; c.i. continuous infusion; HDAC, high-dose Ara-C; IDAC, intermediate-dose Ara-C; i.v., intravenous; p.o., oral; s.c., subcutaneous.

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Chronic myeloid leukaemia in chronic phase

REGIMEN	TREATMENT/DRUG	DOSE	ROUTE	SCHEDULE [e]
First-line treatment	Imatinib	400 mg/d	p.o.	1×/d, independent from food intake
First-line treatment Second-line treatment	Nilotinib Nilotinib	2 × 300 mg/d 2 × 400 mg/d [a]	p.o.	2×/d, no food intake 2 h before & 1 h after drug intake
First-line AND second-line treatment	Dasatinib	1 × 100 mg/d	p.o.	1×/d, independent from food intake
First-line treatment Second-line treatment	Bosutinib [b] Bosutinib	1 × 400 mg/d 1 × 500 mg/d	p.o.	1x/d, with food
First-line treatment AND Second-line treatment	Ponatinib [c] Ponatinib [d]	1 × 45 mg/d	p.o.	1×/d, independent from food intake

Footnotes: [a] In case of intolerance 2 × 300 mg/d according to European LeukemiaNet (ELN) 2013 recommendations; [b] So far, for first-line treatment, only approved by the US Food and Drug Administration (FDA); [c] In any treatment line with a *T315I* mutation; [d] According to the European Medicines Agency (EMA): only in second line, if resistance or intolerance to nilotinib or dasatinib; [e] Treatment is recommended life-long with optimal response and acceptable tolerability, otherwise re-evaluation of treatment needed; in case of deep molecular response: ongoing studies are evaluating when and in which patients it would be safe and most promising to stop tyrosine kinase inhibitors (TKIs). In individual patients, stopping TKI may be considered if proper, high-quality and certified monitoring can be ensured and certain prerequisites are given – for details, please see references.

Abbreviations: d, Day; h, hour; p.o., oral.

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Chronic myeloid leukaemia in accelerated or blast phase

REGIMEN	TREATMENT/DRUG	DOSE	ROUTE	SCHEDULE [e]
First-line treatment	Imatinib	1 × 600 mg/d	p.o.	1x/d, independent from food intake
Second-line treatment	Nilotinib	2 × 400mg/d [a]	p.o.	2x/d, no food intake 2 h before & 1 h after drug intake
Second-line treatment	Dasatinib	2 × 70mg/d [b]	p.o.	2x/d, independent from food intake
Second-line treatment [c]	Bosutinib	1 × 500mg/d [b]	p.o.	1x/d, with food
Second-line treatment [c, d]	Ponatinib	1 × 45mg/d	p.o.	1x/d, independent from food intake

Footnotes: [a] Only for accelerated phase, not for blast crisis; [b] For accelerated phase and blast crisis; [c] If no other *BCR-ABL1*, tyrosine kinase inhibitors (TKIs) can be used; [d] With any line of treatment in case of a T315I mutation; [e] Treatment is recommended life-long with optimal response and acceptable tolerability, otherwise re-evaluation of treatment needed; independently from the TKI treatment, the patient should already initially be evaluated for a potential allogeneic haematopoietic stem cell transplantation.

Abbreviations: d, Day; h, hour; p.o, oral.

Note: For paediatric patients, please consider specific indications and dosages.

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Newly diagnosed myeloma, transplant-eligible patients

REGIMEN	TREATMENT/DRUG	DOSE	ROUTE	SCHEDULE
VTD [1]	Bortezomib	1.3 mg/m^2	s.c.	Days 1, 4, 8, 11 q 3 weeks
	Thalidomide	100 mg	p.o.	Daily q 3 weeks
	Dexamethasone	40 mg	p.o.	Days 1–2, 4–5, 8–9 and 11–12 q 3 weeks
VCD [2]	Bortezomib	1.3 mg/m^2	s.c.	Days 1, 4, 8, 11 q 3 weeks
	Cyclophosphamide	900 mg/m^2	i.v.	Day 1 q 3 weeks
	Dexamethasone	40 mg	p.o.	Days 1–2, 4–5, 8–9 and 11–12 q 3 weeks
VRD [3]	Bortezomib	1.3 mg/m^2	s.c.	Days 1, 4, 8, 11 q 3 weeks
	Lenalidomide	25 mg	p.o.	Days 1–14 q 3 weeks
	Dexamethasone	20 mg	p.o.	Days 1–2, 4–5, 8–9 and 11–12 q 3 weeks
PAD [4]	Bortezomib	1.3 mg/m^2	s.c.	Days 1, 4, 8, 11 q 4 weeks
	Doxorubicin	9 mg/m^2	i.v.	Days 1–4 q 4 weeks
	Dexamethasone	40 mg	p.o.	Days 1–4, 9–12 and 17–20 q 4 weeks
High-dose melphalan	Melphalan	200 mg/m^2	i.v.	1 or 2 days before ASCT
Lenalidomide maintenance [5]	Lenalidomide	10–15 mg	p.o.	Days 1–21 or 1–28 q 4 weeks

Abbreviations: ASCT, Autologous stem cell transplantation; i.v., intravenous; p.o., oral; s.c., subcutaneous.

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Newly diagnosed myeloma, transplant-ineligible patients

REGIMEN	TREATMENT/DRUG	DOSE	ROUTE	SCHEDULE
VMP	Bortezomib Melphalan Prednisone	1.3 mg/m^2 9 mg/m^2 60 mg/m^2	s.c. p.o. p.o.	Days 1, 4, 8, 11, 22, 25, 29, 32 * Days 1–4 Days 1–4 q 6 weeks 9 cycles
Rd	Lenalidomide Dexamethasone	25 mg 40 mg	p.o. p.o.	Days 1–21 Days 1, 8, 15, 22 q 4 weeks 18 cycles or until progression
VRd followed by Rd	Bortezomib Lenalidomide Dexamethasone	1.3 mg/m^2 25 mg 20 mg	s.c. p.o. p.o.	Days 1, 4, 8, 11 Days 1–21 Days 1, 2, 4, 5, 8, 9, 11, 12 q3 weeks 8 cycles of VRd, followed by Rd until progression (see Rd schedule)
Daratumumab-VMP	Daratumumab Bortezomib Melphalan Prednisone	16 mg/kg 1.3 mg/m^2 9 mg/m^2 60 mg/m^2	i.v. s.c. p.o. p.o.	Cycle 1: once weekly Cycles 2–9: every 3 weeks Cycles 10 & next: every 4 weeks Cycle 1: days 1, 4, 8, 11, 22, 25, 29, 32 Cycles 2–9: days 1, 8, 22, 29 Days 1–4 Days 1–4 q 6 weeks 9 cycles of daratumumab-VMP, thereafter daratumumab only, until progression

Footnotes: * First 4 cycles bortezomib twice a week, last 5 cycles bortezomib once a week (according to the VISTA study).
Note: Dose modifications are required in patients with renal failure, comorbidities and frailty – please refer to SmPCs and Reference 5.

Abbreviations: i.v., intravenous; p.o., oral; s.c., subcutaneous; SmPC, summary of product characteristic.

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Relapsed/refractory multiple myeloma

REGIMEN	TREATMENT/DRUG	DOSE	ROUTE	SCHEDULE
Kd	Carfilzomib	20 mg/m^2 on Days 1, 2 of cycle 1; 56 mg/m^2 thereafter	i.v.	Days 1, 2, 8, 9, 15 & 16
	Dexamethasone	20 mg p.o. or i.v.		Days 1, 2, 8, 9, 15, 16, 22 & 23 q 4 weeks *
KRd [1]	Carfilzomib	20 mg/m^2 on Days 1, 2 of cycle 1; 27 mg/m^2 thereafter	i.v.–p.o.	Cycles 1–12: Days 1, 2, 8, 9, 15 & 16 Cycles 13–18: Days 1, 2, 15 & 16; then discontinuation
	Lenalidomide	25 mg		Days 1–21 of each cycle *
	Dexamethasone	40 mg		Days 1, 8, 15 & 22 of each cycle * q 4 weeks
IRd [2]	Ixazomib	4 mg	p.o.	Days 1, 8 & 15
	Lenalidomide	25 mg [a]		Days 1–21 of each cycle
	Dexamethasone	40 mg		Days 1, 8, 15 & 22 of each cycle q 4 weeks *
Pom-Dex [3]	Pomalidomide	4 mg	p.o.	Days 1–21
	Dexamethasone	40 mg		Days 1, 8, 15 & 22 q 4 weeks *
PanVd [4]	Panobinostat	20 mg	i.v.–p.o.	Days 1, 3, 5, 8, 10 & 12
	Bortezomib	1.3 mg/m^2		Cycles 1–8: Days 1, 4, 8, 11 + Dex on the days of and after Btz administration Cycles 9–16 (only in responding patients): Days 1, 8 + Dex on the days of and after Btz
	Dexamethasone	20 mg		q 3 weeks, 8 cycles[c]
Daratumumab monotherapy	Daratumumab	16 mg/kg	i.v.	Cycles 1 & 2: once weekly Cycles 3–6: every 2 weeks Cycle 7 & following: every 4 weeks q 4 weeks *
ERd [5]	Elotuzumab	10 mg/kg	i.v.–p.o.	Cycles 1–2: Days 1, 8, 15 & 22 Cycle 3 & next: Days 1 & 15
	Lenalidomide	25 mg		Days 1–21 of each cycle
	Dexamethasone	40 mg p.o. on the week without Elo, or 8 mg i.v. + 28 mg p.o. on the day of Elo administration		p.o. on the week without Elo, and i.v. + p.o. on the day of Elo administration q 4 weeks *
DVd [6]	Daratumumab	16 mg/kg (i.v.)	i.v.–s.c.–p.o.	Cycles 1–3: 1×/week i.v. (Days 1, 8 & 15) Cycles 4–8: every 3 weeks (Day 1) Cycle 9 & next: every 4 weeks *
	Bortezomib	1.3 mg/m^2 (s.c.)		Cycles 1–8: Days 1, 4, 8 & 11; then discontinuation
	Dexamethasone	20 mg (p.o.)		Cycles 1–8: Days 1, 2, 4, 5, 8, 9, 11 & 12; then discontinuation q 3 weeks
DRd [7]	Daratumumab	16 mg/kg	s.c.–p.o.	Cycles 1 & 2: 1×/week (Days 1, 8, 15 & 22) Cycles 3–6: every 2 weeks (Days 1 & 15) Cycle 7 & next: every 4 weeks
	Lenalidomide	25 mg [b]		Days 1–21 of each cycle
	Dexamethasone	40 mg		Days 1, 8, 15 & 22 q 4 weeks *

Footnotes: [a] 10 mg for patients with a creatinine clearance of ≤60 ml/minute; [b] 10 mg for patients with a creatinine clearance of 30–60 ml/minute; [c] In responding patients additional 8 cycles; * Until disease progression.

Abbreviations: Btz, Bortezomib; Dex, dexamethasone; Elo, elotuzumab; i.v., intravenous; p.o., oral; s.c., subcutaneous.

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Myeloproliferative neoplasms other than CML: Essential thrombocythaemia, polycythaemia vera and myelofibrosis

A. HIGH-RISK ESSENTIAL THROMBOCYTHAEMIA

REGIMEN	TREATMENT/DRUG	DOSE	ROUTE	SCHEDULE
Hydroxyurea	Hydroxyurea	1000 mg/d	p.o.	Continuous [a]
Anagrelide	Anagrelide	0.5 mg BID initially [b]	p.o.	Continuous [a]
Interferon	Interferon-α	3 MU	s.c.	Three times a week [a]
Pegylated interferon	Pegylated interferon-α	45 µg initially [b]	s.c.	Weekly [a]

Footnotes: [a] Until treatment failure; [b] Progressive dose increase until platelet count normalisation.

Abbreviations: BID, Twice daily; d, day; MU, million units; p.o., oral; s.c., subcutaneous.

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B. HIGH-RISK POLYCYTHAEMIA VERA

REGIMEN	TREATMENT/DRUG	DOSE	ROUTE	SCHEDULE
Hydroxyurea	Hydroxyurea	1000 mg/d	p.o.	Continuous [a]
Interferon	Interferon-α	3 MU	s.c.	Three times a week [a]
Pegylated interferon	Pegylated interferon-α	45 µg initially [b]	s.c.	Weekly [a]
JAK inhibitor therapy [c]	Ruxolitinib	10 mg BID	p.o.	Continuous [a]

Footnotes: [a] Until treatment failure; [b] Progressive dose increase based on response and tolerability; [c] Only for resistance or intolerance to hydroxyurea.

Abbreviations: BID, Twice daily; d, day; JAK, janus kinase; MU, million units; p.o., oral; s.c., subcutaneous.

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C. MYELOFIBROSIS

REGIMEN	TREATMENT/DRUG	DOSE	ROUTE	SCHEDULE
JAK inhibitor therapy	Ruxolitinib	15-20 mg BID [a]	p.o.	Continuous [b]
Androgens	Danazol	600 mg/d initially	p.o.	Progressive dose reduction after 6 months [b,c]
ESA	Darbepoetin-α	300 µg	s.c.	Weekly [b,d]

Footnotes: [a] 15 mg if platelets 100–200 × 10^9/L, 20 mg if platelets >200 × 10^9/L; [b] Until treatment failure; [c] In case of response, a maintenance dose is necessary; [d] The dose or schedule must be adjusted to the achieved response.

Abbreviations: BID, Twice daily; d, day; ESA, erythropoiesis-stimulating agents; JAK, janus kinase; p.o., oral; s.c., subcutaneous.

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AL amyloidosis

REGIMEN	TREATMENT/DRUG	DOSE [a,b]	ROUTE	SCHEDULE [c]
CyBorD [1]	Cyclophosphamide Bortezomib Dexamethasone	500 mg 1.3 mg/m^2 10–20 mg	p.o./i.v. s.c. p.o.	Days 1, 8, 15, 22 Days 1, 8, 15, (22) Days 1, 2, 8, 9, 15, 16, 22, 23
Mel-Dex [2]	Melphalan Dexamethasone	0.22 mg/kg 20–40 mg	p.o. p.o.	Days 1–4 Days 1–4
Len-Dex [3]	Lenalidomide Dexamethasone	5–15 mg 20–40 mg	p.o. p.o.	Days 1–21 Days 1, 8, 15, 22
Pom-Dex [4]	Pomalidomide Dexamethasone	4 mg 20–40 mg	p.o. p.o.	Days 1–21 Days 1, 8, 15, 22
Ixa-Dex [5]	Ixazomib Dexamethasone	4 mg 20–40 mg	p.o. p.o.	Days 1, 8, 15 Days 1, 8, 15
CTDa [6]	Cyclophosphamide Thalidomide Dexamethasone	500 mg 50–100 mg 20–40 mg	p.o. p.o. p.o.	Days 1, 8, 15, 22 Days 1–28 Days 1, 2, 8, 9, 15, 16, 22, 23

Footnotes: [a] Drug doses should be adapted, based on renal function following the recommendation from the manufacturer; [b] Patients with advanced cardiac amyloidosis need dose reduction, and gentle dose increase can be considered based on tolerance; [c] All schedules are 28-day cycles. Maximum number of cycles: CyBorD/CTDa – 6-8 cycles (but can continue longer as maintenance in selected cases); Mel-Dex – 9 cycles; Len-Dex/Pom-Dex/Ixa-Dex – ongoing until progression or intolerance or toxicity (consider dose reduction of dexamethasone after 6 cycles).

Abbreviations: AL, Amyloid light-chain; i.v., intravenous; p.o., oral; s.c., subcutaneous.

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Image sources

The authors acknowledge with gratitude the following sources of the images used in this publication.

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Declarations of interest

A Álvarez-Larrán: No conflicts of interest.

H Avet-Loiseau: No conflicts of interest.

U Bacher: No conflicts of interest.

GM Baerlocher: Advisory Boards for Novartis, Bristol-Myers Squibb, Pfizer, Ariad, Incyte; research funding from Geron Corporation.

M Cavo: Honoraria from and advisory boards for Celgene, Janssen, Takeda, Amgen, Bristol-Myers Squibb.

F Cervantes: No conflicts of interest.

J Corre: No conflicts of interest.

M Dawidowska: No conflicts of interest.

MA Dimopoulos: Consultancy for Janssen, Genesis, Celgene, Onyx, Amgen, Novartis.

M Duchmann: No conflicts of interest.

P Fenaux: No conflicts of interest.

M Gavriatopoulou: No conflicts of interest.

N Gökbuget: Advisory boards / honoraria for Amgen, Pfizer, Novartis, Kite, Incyte, Servier; research support from Amgen, Pfizer, Incyte Novartis, Servier.

V González-Calle: No conflicts of interest.

A Grassi: No conflicts of interest.

T Haferlach: Equity ownership of Munich Leukemia Laboratory (MLL), Munich, Germany.

D Hofste op Bruinink: No conflicts of interest.

A Höllein: Employed by Munich Leukemia Laboratory (MLL).

R Itzykson: No conflicts of interest.

E Kastritis: Honoraria from Janssen, Genesis Pharma, Amgen, Takeda.

C Lengerke: No conflicts of interest.

N Lucas: No conflicts of interest.

F Lussana: No conflicts of interest.

MV Mateos: Consultancy for Janssen, Celgene, Takeda, Amgen.

M Medinger: No conflicts of interest.

IS Nijhof: No conflicts of interest.

EM Ocio: Consultancy for or honoraria from Mundipharma, Celgene, Amgen, Novartis, Takeda, AbbVie, Bristol-Myers Squibb, Janssen.

T Pabst: No conflicts of interest.

JR Passweg: No conflicts of interest.

A Rambaldi: No conflicts of interest.

P Rodríguez-Otero: No conflicts of interest.

JF San Miguel: Consultancy for Janssen, Celgene, Takeda, Amgen, MSD, Bristol-Myers Squibb, Novartis.

E Solary: No conflicts of interest.

P Sonneveld: Research support from Amgen, Celgene, Janssen, Karyopharm, SkylineDx; Advisory boards for Amgen, Bristol-Myers Squibb, Celgene, Janssen, Karyopharm.

C Stege: No conflicts of interest.

G Stüssi: No conflicts of interest.

P Tacchetti: No conflicts of interest.

AD Wechalekar: No conflicts of interest.

M Witt: No conflicts of interest.

E Zamagni: No conflicts of interest.

S Zweegman: Advisory boards for Celgene, Janssen, Takeda, Amgen; research support from Celgene, Janssen, Takeda.

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LEUKAEMIA AND MYELOMA

ESSENTIALS *for* CLINICIANS

edited by

Veronika Ballová, Michele Ghielmini, Meletios-Athanasios Dimopoulos

Depending on the country, leukaemias and myeloma are treated either by haematologists or by medical oncologists, and in some cases by both. Acute leukaemia patients may need several months of in-patient treatment, sometimes ending with allogeneic transplantation; therefore, management of these patients requires specialist knowledge and expertise. On the other hand, the majority of chronic leukaemia and multiple myeloma patients can easily be treated in the outpatient setting and they are thus often seen by oncologists and haematologists in medical practice. As it is the case with other titles in this series, this book is composed of a first section on "What every oncologist should know" and a second section on "More advanced knowledge". In a concise and easy-to-read format, the basics of pathology, diagnosis, presentation of disease, treatment and complications are given. The balance between text and illustrations, as well as the review questions at the end of each page, make these basic concepts easy to assimilate, while the further reading suggestions at the end of each chapter allow those who are interested to explore the subject in more depth. The "Essentials for Clinicians" series wouldn't have been complete without this haemato-oncology volume, as leukaemias and myeloma are relatively frequent malignancies.

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ESMO Press · ISBN 978-88-941795-6-9

9 788894 179569