Gender Medicine and Oncology: Report and consensus of an ESMO Workshop

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Abstract

Background: The importance of sex and gender as modulators of disease biology and treatment outcomes is well known in other disciplines of medicine, such as cardiology, but remains an undervalued issue in oncology. Considering the increasing evidence for their relevance, ESMO decided to address this topic and organized a multidisciplinary workshop in Lausanne, Switzerland, on November 30th and December 1st, 2018.

Design: 20 invited faculty members and 40 selected physicians / scientists participated. Relevant content was presented by faculty members on the basis of a literature review conducted by each speaker. Following a moderated consensus session, the final consensus statements are reported here.

Results: Clinically relevant sex differences include tumor biology, immune system activity, body composition and drug disposition and effects. The main differences between male and female cells are sex chromosomes and the level of sexual hormones they are exposed to. They influence both local and systemic determinants of carcinogenesis. Their effect on carcinogenesis in non-reproductive organs is largely unknown. Recent evidence also suggests differences in tumor biology and molecular markers. Regarding body composition, the difference in metabolically active, fat-free body mass is one of the most prominent :in a man and a woman of equal weight and height, it accounts for 80% of the man's and 65% of the woman's body mass, and is not taken into account in body-surface area based dosing of chemotherapy.

Conclusion: Sex differences in cancer biology and treatment deserve more attention and systematic investigation. Interventional clinical trials evaluating sex-specific dosing regimens are necessary to improve the balance between efficacy and toxicity for drugs with significant pharmacokinetic differences. Especially in diseases or disease subgroups with significant differences in epidemiology or outcomes, men and women with non-sex related cancers should be considered as biologically distinct groups of patients, for whom specific treatment approaches merit consideration.

Keywords: sex – gender – gender medicine – oncology – pharmacology

Key message: In oncology, sex and gender as modulators of disease biology and treatment outcomes are largely unexplored. Considering the increasing evidence for sex differences in cancer biology and drug effects, men and women with non-sex related cancers should no longer be considered as subgroups, but as biologically distinct groups of patients for whom specific treatment approaches merit consideration.

Introduction

What is gender medicine and why do we need it in oncology?

Sex and gender-sensitive medicine (SGSM) is an innovative approach to the practice of medicine that postulates that biological sex differences, gender identity, role, and relations all impact health and disease, and that these differences may have implications for prevention, screening, diagnosis, and treatment [1]. The ultimate goal of this field is to learn from these differences (or the absence thereof) and improve care and treatment for both men and women. 'Sex' refers to the biological bases that underlie female or male anatomy and physiology, while 'gender' is defined by the World Health Organization (WHO) as the socially constructed roles, behaviours, activities, and attributes that a given society considers appropriate for men and women. Hence, while every cell is sexed, every person is gendered (Canadian Institute of Health Research; CIHR)[2]. Within living human beings, there is a continuous interplay between the two [3]. In contrast to sex, which is generally classified as binary, gender is a continuum. While, as authors, we acknowledge gender identities as a non-binary concept, in this manuscript we limit our discussion to the male-female dichotomy.

While the role of sex differences as modulators of symptoms [4], access to therapy, [5] and incidence of serious side effects [6] has been extensively described in cardiology and pharmacology [7, 8], oncological research and practice is still largely sex- and gender-blind [9].

This paper provides an overview of sex and/or gender differences in:

1. Tumor biology
2. Immune system activity

3. Body composition
4. Pharmacology of anticancer drugs
5. Epidemiology, biology and treatment outcomes of melanoma, gastrointestinal cancers, and lymphoma as examples for sex and gender differences of non-sex-dependent cancers
6. Methodological challenges in the analyses of sex and gender differences in clinical trials in oncology

Data were presented and discussed during the European Society for Medical Oncology (ESMO) sponsored « Gender Medicine Meets Oncology » Workshop in Lausanne in 2018. Relevant content was presented by the faculty members on the basis of a literature review conducted by each speaker. No systematic literature review was conducted. Consensus questions were agreed upon by faculty members and the consensus statements reported here were elaborated during a moderated consensus session which took place at the workshop and included input from the faculty and participants. Findings have been synthesised in consensus recommendations including an action plan to better understand and address these differences.

Background

From 1997 to 2000, among ten drugs which were withdrawn from the US market due to unexpected severe side effects, eight demonstrated greater toxicity in women [10]. According to the National Institutes of Health (NIH) “the current overreliance on male subjects in preclinical research can obscure key findings related to sex that could guide the planning and

development of clinical studies". Consequently, an initiative to guarantee the equal inclusion of male and female cells, biological samples or experimental animals in basic research has been launched [11]. According to the European Commission "integrating gender/sex analysis in research and innovation content helps to improve the scientific quality and societal relevance of the produced knowledge, technology and/or innovation". Resources providing advice on the integration of the gender dimension into research and how it can spark creativity as well as foster new knowledge have been created by the ongoing H2020 Advisory Group for Gender [12] for the European Union (EU) and by the EU/US "Gendered Innovations" project started at Stanford University (https://genderedinnovations.stanford.edu).

Sex differences in tumor biology

The two main differences between male and female cells in the human body are their sex chromosomes and the level of sexual hormones to which they are exposed. The interplay between sex chromosomes and hormones influences both local determinants of carcinogenesis, such as cancer initiating cells and components of the tumour microenvironment, and systemic ones, such as cell metabolism and the immune system [13]. In contrast to reproductive organs, limited data exist on the effects of sex hormones and their receptors [including estrogen receptor α (ERα), ERβ and the androgen receptor (AR)] on carcinogenesis in non-reproductive organs. Down-modulation or loss-of-function mutations of NOTCH1 are associated with dysfunctional squamous cell differentiation and development of squamous cell carcinoma (SCC) in skin and internal organs. ERβ was shown to directly control NOTCH1 expression in differentiation and is often impaired in SCC of various organs. In

addition, there are significant differences in gene expression signatures of head and neck and lung SCC in men versus women, pointing to a possible molecular basis for disease differences between the sexes [14]. Indeed, a comprehensive molecular characterization of various tumour types identified extensive sex-biased gene expression signatures and an important number of clinically targetable genes with sex bias [15]. The mutation pattern and load in many tumour types also shows large sex differences, with some cases of sex-selective gene inactivation [16]. Inactivation of the X chromosome seems to confer some protection against carcinogenesis in women given that mutations in oncogenes or tumor suppressor genes located on the X chromosome are dominant in males [17]. Moreover, about 25% of the X genes escape inactivation and are expressed from both alleles, so that their expression is generally higher in women[18] . As such, biallelic expression of “escape from X-inactivation tumor-suppressor” (EXITS) genes may explain some of the reduced cancer incidence in women [19].

Furthermore, the aging-associated increase of cancer risk is related to stromal fibroblast senescence and concomitant cancer associated fibroblast (CAF) activation. Experimental data show that not only epithelial cells but also CAFs are under sex hormone control, with variable results depending on the tissue [20] [21]. In mouse models, AR loss in dermal fibroblasts enhances tumorigenicity of SCC and melanoma cells [22], and AR expression is downregulated in dermal fibroblasts underlying premalignant skin cancer lesions as well as in CAFs from different skin cancer types [22]. Therefore, sex differences in the biology of non-sex related cancers likely contribute to their differences in incidence and outcome [23, 24] and this highlights the need to better understand the effect of sex-related genetic and hormonal factors on carcinogenesis in non-reproductive tissues.

Sex differences in the immune system and immune reactions

The immune system differs significantly between men and women [25], with differences modulated by:

1. Genetic mediators: sex chromosomes, micro-RNAs located on the X chromosome, escape from X-chromosome inactivation, and genetic polymorphisms

2. Hormonal mediators: estradiol, progesterone and androgens

3. Environmental mediators: nutrition and microbiota

4. Age and reproductive status

Generally, adult women mount stronger innate and adaptive immune responses, resulting in a faster clearance of pathogens and greater vaccine efficacy, but also contributing to their increased susceptibility to inflammatory and autoimmune diseases [25]. Given that the sex differences in the number and function of immune cells remain consistent across different species from fruit flies to humans, this seems to be an evolutionarily conserved trait [25], which may be partly explained by the localization of various genes and micro-RNAs to the X-chromosome [26] [27]. In addition, the *TLR7* gene, a member of the Toll-like receptor (TLR) gene family, which is fundamental for recognition of pathogens and activation of innate immune effectors, evades silencing by physiological X chromosome inactivation in immune cells in women [28]. Due to biallelism, this leads to enhanced *TLR7* expression and contributes to the higher risk of women developing autoimmune disorders. Sex hormones further modulate the interplay between genes and the immune response: progesterone has broad anti-inflammatory effects and androgens generally suppress immune cell activity, whereas estradiol enhances cell-

mediated and humoral immune responses (for review see [29]). Although some of the sex hormone dependent differences in immunity, such as pro-inflammatory responses, are most evident at puberty and wane later in life, differences in immune cell numbers and ratio (i.e. higher CD4 T cell counts and CD4/CD8 ratios in females) remain constant from birth to old age [25].

The impact of the microbiome on immunity and drug responses is becoming increasingly recognised [30, 31]. However, the relative contribution of the microbiome is difficult to define given that the microbiota composition can be influenced by sex in a body-mass dependent manner [32].

Sex hormones, in particular androgens, seem critical in shaping the gut microbiota composition. In mice, sex differences in gut microbiota appear with the onset of puberty and upon castration: the gut microbiota of a castrated male resembles that of a female [33]. Likewise, transfer of gut microbiota from males to females increases female testosterone levels and protects from autoimmunity [34], while the absence of gut microbiota diminishes sex specific gene expression and metabolism [35][30, 31].

Sex differences in body composition

Men and women differ with regard to their body composition. The overall percentage of metabolically active fat-free body mass (FFM) is significantly higher in men: in a man and a woman of equal weight and height, FFM accounts for 80% and 65% of the man's and woman's body mass, respectively [36]. Furthermore, the distribution of body fat varies, with men having

more visceral and women having more subcutaneous fat [37]. Compared to body surface area (BSA) or body mass index (BMI), FFM serves as a better estimate of the metabolically active body mass. Lean body weight can be estimated according to a formula published by Janmahasatian et al. [36]. To measure body composition in an individual patient, magnetic resonance imaging (MRI) is the gold standard. According to analyses performed with MRI, at a given BMI of 24 kg/m^2, the body fat content varies from 7.8 to 38.3 % in men and between 29.9 to 44.2 % in women [38]. An excellent and cheaper alternative to MRI is computed tomography (CT) of cross-sectional tissues in the lumbar area, which shows a strong correlation with whole body adipose tissue, muscle, and lean tissue mass. A single abdominal CT scan of the L4 region without contrast enhancement compares well with whole body MRI (r = 0.90 at the L4–L5 intervertebral space) [37]. While CT scans are more easily carried out and evaluated, MRI permits the *in vivo* quantification of the total adipose tissue and its subdepots, including ectopic fat, or fat deposited outside of the classical adipose areas [38]. Of interest, specific body composition according to sex not only impacts drug metabolism and toxicity, it is also a prognostic factor in clear cell renal carcinoma, where females with high visceral fat had a poorer overall survival than females with low and males with high or low visceral fat [39].

Sex differences in the pharmacology of anticancer drugs

One of the basic paradigms in clinical pharmacology is that drug effects are produced by the circulating concentration profile of a drug, rather than directly by the dose itself. As a consequence, variability in drug disposition may lead to suboptimal response, either lack of efficacy or increased toxicity. Nevertheless, most anticancer agents are administered at

standard dosages according to body weight or BSA. The lack of accuracy of chemotherapy dosing according to BSA and the associated risk of underdosing was recognised over a decade ago [40]. While BSA predicts the drug clearance across individuals of various sizes and weights relatively well, it is limited by not taking into account the sex differences in FFM. In contrast, FFM or lean body weight, which incorporate a sex coefficient and thus better reflect sex differences in renal and metabolic clearance, were shown to be the best predictors of drug clearance [36, 41]. In addition to differences in metabolism and excretion of commonly used drugs, sex differences also exist in drug absorption and distribution, with women having a larger distribution volume of lipophilic drugs, whereas men have a larger distribution volume of water-soluble drugs. Men tend to have, on average and for similar genotypes, increased CYP1A2, CYP2D6, and CYP2E1 activity, resulting in increased metabolism of the drug substrates of these enzymes, which is of particular relevance for psychotropic drugs with regard to CYP2D6. Women show higher CYP3A4 activity, which is the most abundant cytochrome isoenzyme and is integral in metabolising the majority of drugs [42]. Phase II metabolism of drugs by the UDP-glucuronosyltransferase (UGT), the sulfotransferases, and the N-acetyl transferases, such as 6-mercaptupurine, paracetamol, and oxazepam, is increased in men [43]. Furthermore, renal function reveals significant sex differences and is, on average, about 20% greater in men [44]. This is taken into account in renal function calculators [45, 46]. A literature survey was conducted for this workshop to identify if, and to what magnitude, the patients' sex influences the pharmacokinetics of chemotherapeutic drugs. Among 256 population studies screened, only 80 reported sex as a tested covariate on drug elimination and distribution. Of these, 23 found a statistically significant impact on pharmacokinetics. In an additional 18

studies focusing on drugs excreted by the kidneys, the influence of sex was integrated in the estimator of renal function. No sex differences in drug exposure were observed in 57 studies. Table 2 summarizes the findings of this review. In drugs with a significant difference in pharmacokinetics, the exposure was about 15-25% higher in women. This difference is generally smaller than the usually large reported interpatient variability (20-40% coefficient of variation) in drug concentrations.

5-fluorouracil (5-FU) is a prominent example of a drug with a substantial inter-individual variability in clearance resulting in large differences in patient exposure and a significant impact of the patients' sex, with an approximately 26% higher exposure in women [47]. In addition, pathway-associated gene polymorphisms (e.g. DPD), age, and organ function have been associated with the variability of 5-FU clearance. Current dosing based on BSA reaches the target concentration of 20 to 30 mgh/L in only about 25% of patients, leaving the majority underexposed [48]. The observation of a higher proportion of women reaching therapeutic concentrations of 5-FU is independent of anthropometric factors [47], such as body weight or BSA [48]. Temozolomide is another example of a drug with a significantly higher clearance in men: in a study of 35 glioma patients, the clearance was 19% higher in men [49]. In contrast to most anticancer agents, the clearance of temozolomide shows a very small degree of inter-individual variability as it involves essentially non-enzymatic degradation. Sex differences in pharmacokinetics have also been noted for monoclonal antibodies, e.g. panitumumab or bevacizumab, with the clearance being reduced by roughly 20% in women [50, 51] and for some tyrosine kinase inhibitors (TKIs), such as sunitinib and imatinib [52, 53]. For other molecules, the absence of acknowledged sex differences in pharmacokinetics may be the

consequence of either insufficient investigation or lack of statistical power in available studies rather than true non-existence. In addition to sex differences affecting drug exposure, sex-related pharmacodynamic differences, which modulate the patients' sensitivity towards adverse effects, may also exist. In conclusion, sex disparities affect the pharmacokinetic profile of a large number of anticancer drugs, and are responsible of about 20% overexposure in women after administration of standard dosages according to mg/m^2, mg/kg or BSA. Given their clinical impact, consideration of either the patients' sex, or other parameters that take into account its impact on body composition, such as FFM, is considered as a promising approach to individualise treatments and improve the balance between efficacy and toxicity of systemic treatments in oncology.

Sex and gender differences in epidemiology, biology, and treatment outcomes of melanoma, gastrointestinal cancers, and lymphoma

Melanoma

Melanoma is a particularly illustrative example of the differential impact of both sex and gender in a non-sex-related disease. Men are less likely to self-detect melanomas, make fewer visits to health care providers, have a lower awareness of skin cancer risk and, therefore, are less likely to engage in preventive behaviour than women. All these factors result in a diagnostic delay. Thus, melanomas in men are likely to be diagnosed when thicker, at an older age, and at a higher AJCC stage [54] [55]. Indeed, according to data from 11,774 melanoma patients diagnosed between 1978 and 2007 and included in the Munich cancer registry, women had smaller lesions located mostly on the lower extremities, while men more often had larger

lesions (2.01 to 4.0 cm) located primarily on the trunk (12.0 versus 9.3%, *P*< 0.001) [55]. Therefore, differences in preventive behaviour and clothing choices impact the presentation of melanoma at diagnosis. In addition, melanoma-specific survival after diagnosis was higher in women, with events occurring in 14.5% of men versus 9.1% of women, and lymph node metastasis occurring in less than half as many women (553 women versus 1,331 men, adjusted HR 0.80; 95% CI 0.66-0.96) [55]. In a pooled analysis of 2,734 patients included in 5 randomised trials, sex emerged as an independent prognostic indicator for survival. In stage III, overall survival (OS) (HR 0.81, 95% CI 0.72-0.91; *P* < 0.001), disease specific survival (DSS) (HR 0.85, 95% CI 0.76-0.95; *P* < 0.01), and relapse-free survival (RFS) (HR 0.86, 95% CI 0.77-0.95; *P* < 0.01) all favoured women. The comparison held for stage IV regarding OS (HR 0.82, 95% CI 0.72-0.93; *P* <. 01), DSS (HR 0.81, 95% CI 0.72-0.92; *P* < 0.01), and progression-free survival (PFS) (HR 0.79, 95% CI 0.70-0.88; *P* < 0.001) [56]. While behavior explains, at least partly, differences in incidence and distribution, the survival difference remained significant after adjusting for virtually all known prognostic indicators, including age, Breslow thickness, Clark level of invasion, body site, histological subtype, and newly emerged prognostic factors, such as ulceration, sentinel lymph node status, and mitotic rate [56]. Thus, "a biologic sex trait seems to profoundly influence melanoma progression and survival" [56]. The clinical observation of a more rapid progression to stage III melanoma in men is in line with the observation that male mice develop more liver metastases after injection of melanoma cells [57]. The reasons for the greater aggressiveness of melanoma in men are not entirely clear: estrogens have been studied extensively, but there is no strong evidence that pregnancy, oral contraceptives, or hormonal replacement therapy influences melanoma survival [54, 58-60]. Sex differences in treatment

outcomes for immunotherapy have been addressed in two meta-analyses based on aggregate data, which however pooled results across indications and treatments and therefore do not allow any definitive conclusions [61, 62]. Available data on the toxicity of immune checkpoint inhibitors does not suggest any sex differences [63].

Gastrointestinal cancers

According to data from the Netherlands Cancer Registry, past behaviour, for example smoking in pancreatic cancer, explains only in part the generally higher incidence of gastrointestinal (GI) cancers in men. While the overall cancer incidence in the Netherlands is rising, especially in women, the relative contribution of GI cancers remained stable between 1989 and 2015. A striking gender gap exists for oesophageal cancer of the lower third, where the incidence (European Standardised Rate) in men has increased between the periods 1990-1995 and 2012-2017 from 5.8 to 12.1 per 100.000 inhabitants, as compared to 1.3 and 2.5 per 100.000 in women. Of interest, this dramatically rising incidence concerns only adenocarcinomas. A striking male predominace of in the incidence of esophageal adenocarcinoma is observed in different populations [64, 65] with the greatest excess risk in the US, where the male-female incidence ratio is as high as 9:1. In fact, hormonal factors, such as higher levels of anti-inflammatory estrogens, which delay or prevent gastro-esophageal reflux disease (GERD) [66], and also androgen concentrations [67, 68] may play a role, but the reasons for this male predominance are not fully understood [64, 65]. Furthermore, differences in fat distribution might contribute to the persistent inflammation associated with GERD and the development of

Barrett's oesophagus [69]. Other examples of sex differences in the biology of GI cancers are as follows: in colorectal cancer a higher percentage of tumours with the Consensus molecular subtype-1 (CMS-1) [70] is found in women and the risk of developing peritoneal carcinomatosis is greater in women in gastric cancers, molecular subtypes are not distributed with the same frequency between men and women [71], with a higher rate of microsatellite instability occurring in women [72]; sporadic early-onset non-hereditary diffuse gastric cancer is more frequent in women and has a distinct mutational profile [73]. In addition, a statistically significant and clinically relevant higher toxicity of 5-FU based chemotherapy has been reported in different indications [74-76]. In an analysis of the adjusted association between haematological grade III/IV adverse events and sex in > 28.000 patients, the OR (95% CI) for neutropenia associated with 5-FU was 1.55 (1.37-1.76), for FOLFOX 1.55 (1.25-1.91), for FOLFIRI 2.01 (1.66-2.43), for single-agent capecitabine 4.07 (1.84-8.00), and for CAPOX 1.45 (1.06-1.99), with women being at higher risk. In addition, nausea, vomiting, stomatitis, and diarrhoea were more frequently observed in women for most regimens and these observations were statistically significant and clinically relevant. In metastatic colon cancer, a close relationship between plasma levels, toxicity, and efficacy following 5-FU therapy has been established [48]. Individual 5-FU dose-adjustment based on pharmacokinetic monitoring has resulted in a significantly improved objective response rate (18.3 vs. 33.6%, P = 0.0004) in a randomized phase III-study [77]. The higher clearance of 5-FU in men [47] likely explains the higher toxicity of 5-FU in women. This hypothesis is further supported by a prospective study (n=683 patients) [78] which addressed the contributions of genetic and non-genetic factors in 5-FU-related severe toxicity. Again, in addition to genotype, mode of 5-FU administration and modulation by

folinic acid, female sex was found by multivariate analysis to be an independent risk factor for severe 5-FU-toxicity. Among patients with grade 3/4 toxicity, a significantly higher percentage with the DPDYD*2A variant were men. Thus, the toxicity of 5-FU in women was independent of the DPYD genotype and explained by other nongenetic factors. Furthermore, the example of 5-FU in colon cancer clearly demonstrates that sex differences in toxicity do not impact all effects equally: while neutropenia differs significantly between the sexes, no sex difference in the incidence of thrombocytopenia has been observed [79]. Thus, apart from pharmacokinetics, pharmacodynamic factors may also play a role in both toxicity and efficacy. In general, the question of why some (e.g. neutropenia), but not other toxicities (e.g. thrombocytopenia) occur more frequently in men than in women may theoretically be explained as follows:

a. If significant sex differences in pharmacokinetics are present: these differences may have varying impact on different organs or cell lines (independent of the patients' sex'), or by a sex-dependent difference in drug sensitivity (which modulates the pharmacokinetic effect).

b. If significant sex differences in pharmacokinetics are absent: occurrence of toxicities may be due to differences in drug sensitivity between men and women.

It should also be noted that many chemotherapy drugs and regimens are associated with higher rates of neutropenia than of thrombocytopenia. 5-FU is an example of such a drug. This differential effect may be caused by various factors, such as a more rapid turnover of neutrophils as compared to thrombocytes, with a resulting greater sensitivity of myeloid progenitor cells as compared to megakaryocytes. However, in the absence of valid data on sex differences in pharmacokinetics for the majority of drugs, the relative contribution of potential

differences in pharmacodynamics and pharmacokinetics is difficult to separate. Potential variations in tumour biology are another reason why pharmacokinetic differences are unlikely to explain all differences in treatment outcomes. The recently presented analysis of the XELAVIRI-trial [80] provides an example of sex differences in treatment outcomes, which cannot be explained by differences in pharmacokinetics. This randomized trial (n=421) [81] comparing upfront versus sequential addition of irinotecan to the combination of a fluoropyrimidine and bevacizumab in colorectal cancer demonstrated a significantly higher response rate in men (58.3 versus 33.6%, $P < 0.01$) compared to women (43.1 versus 42.7%, $P > 0.9$) treated upfront with the irinotecan-based combination, which translated to a significant survival benefit for men, but a tendency for inferior survival in women.

Lymphoma

Lymphoma offers several examples of sex specific outcomes, where male sex is nearly always a poor prognostic factor [82]. In Hodgkin lymphoma (HL), diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, T-cell non-Hodgkin lymphoma (T-NHL) and, to a lesser extent, Mantle cell lymphoma, adult men have a poorer prognosis and survival that is exacerbated by increasing age [83]. Despite a limited understanding of the underlying reasons, female hormonal status likely plays a role. The female advantage begins with puberty, increases until menopause, and then declines [84, 85]. In experimental models ERβ activation inhibits lymphoma growth, vascularization and dissemination [86]. Furthermore, differences in drug metabolism, with impact on toxicity and efficacy, are likely: sex differences in the haematologic toxicity of chemotherapy for HL have been reviewed elsewhere [87]. Low acute haematological toxicity,

which is significantly more frequent in men (44 vs 19%, $P < 0.00001$), predicts disease recurrence, and male sex is an independent negative prognostic factor in HL [82, 88] . The question of whether either increasing the chemotherapy doses in men not presenting any toxicity after the first cycle or upfront calculation of chemotherapy doses according to fat-free body mass instead of BSA may improve their prognosis is currently open. Data from prepubertal children receiving treatment according to the paediatric BFM NHL protocol [89] and DLBCL patients in the 2016 German Childhood Cancer Registry [90] underline the current paradigm that the female survival advantage in lymphoma requires the hormonal changes of puberty. On a molecular level, analysis of DLBCL global transcriptome data from the Cancer Genome Atlas associated female sex with decreased interferon signalling, cell cycle, and PD-1 signalling [91]. A Swedish study demonstrated a particularly pronounced survival improvement following the introduction of rituximab as standard lymphoma therapy in elderly women [92], which was explained by reduced clearance with resulting longer exposure times of rituximab [93] [94]. Consequently, the SEXIE-R-CHOP-14 trial investigated whether increasing the dose of rituximab for elderly men (61-80 years of age) with DLBCL to 500 mg/m^2 while treating women with the standard dose of 375 mg/m^2 could improve their outcome. In this academic trial, which was prematurely closed due to insufficient funding, PFS was increased by 32.5% ($P = 0.039$), with a trend (30%) for better OS ($P = 0.076$) [95] in men treated with the increased rituximab dose, demonstrating the feasibility and potential benefit of sex-specific dose adaptations (Figure 1).

Methodological challenges

Methodological hurdles concerning analyses of trials in oncology start with the adequate representation of men and women, which should correspond to the distribution of the incidence of the type of cancer studied. In general, women were adequately represented in clinical registration trials [96]. However, this may not be the case for certain types of cancer [97]. In randomised clinical trials, sex should be a standard stratification factor, also noting it is a good stratification candidate since each group corresponds to a large fraction of the total sample size. Subgroup analyses of efficacy, treatment exposure, safety, and risk benefit ratio according to sex are required by the FDA for any submission dossier. Possible prognostic and predictive effects, as well as competing risks like deaths from other causes, which may occur at different frequencies, need to be explored [98]. The need for adequate reporting of results by sex in publications should be reemphasized. Testing for sex differences in safety studies is challenging due to the multiplicity of tests leading to an increase of false positive results. To pre-specify testing of certain selected adverse events by sex is considered as important and may help in the better interpretation of safety results. Reporting of the number and types of analyses conducted and whether they were pre-specified is important to allow the reader to judge the strength of the evidence. Discussions of the results of subgroup analyses should also address issues such as whether the study was sufficiently powered to detect minimal important differences, the plausibility of the findings, their biological rationale, and reproducibility. In patient-level analyses, sex should be used as an independent variable in multivariable Cox models. A significant interaction indicates a differential effect. Meta-analyses of individual patient data, with the examination of overall interactions, are the preferred option to better understand treatment results by sex. However, registry data could also provide further

important information. The question of what constitutes a clinically meaningful difference in toxicity and/or efficacy needs further definition. Importantly, incidence, severity, and duration of toxicities need consideration in this context. In conclusion, while sex differences in outcomes of clinical trials in oncology need interpretation with the same caution as any subgroup analysis, they may reflect real differences in cancer biology or treatment effects. This is especially relevant in diseases or disease subgroups with significant differences in epidemiology or outcomes, or for drugs with significant differences in pharmacokinetics, where men and women with non sex-related cancers should be considered as biologically distinct groups of patients, and for whom specific treatment approaches merit consideration and further investigation (Table 1).

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Figure 1:

Sex and gender differences may influence cancer treatment outcomes in different ways. All effects are modulated by age.

1. Major open questions and challenges

- To investigate systematically sex disparities in cancer incidence and outcomes. Where sex disparities in either epidemiology or treatment outcomes are identified, further research is necessary to understand their biological basis, and evaluate if sex-specific treatment modifications might improve outcomes. Importantly, wherever possible, sex disparities should be investigated in different age groups. Potential interactions between sex and age need to be considered and understood.
- To review in depth the published literature on sex differences in pharmacokinetics of all types of anticancer drugs. Where gaps in the published literature are identified and/ or methodology or patient numbers are insufficient, and for drugs currently used in clinical practice, further research is necessary.
- BSA-based dosing for chemotherapy needs to be reevaluated. For drugs with established sex differences in pharmacokinetics and a clinically relevant impact on treatment efficacy and/or toxicity, interventional clinical trials evaluating alternative approaches for dose determination and adjustments, for example according to fat-free body mass (either calculated according to [28] or determined by CT [29]), or according to sex- and BSA, are necessary. The magnitude of the difference in drug disposition, dose-response relationship, and inter-individual variability of drug clearance all need consideration in the definition of strategies for dose modification according to sex need to be tested in clinical trials.

- Sex differences may not only be limited to drug treatment: Differences in anatomy and/ or tumour biology may also affect outcomes of surgery, radiotherapy, or combined modality treatments and need further investigation.

2. How should these challenges be addressed?

- Considering frequency and severity of adverse events of anticancer treatments, large meta-analyses on the basis of individual patient data are the best approach to understand how sex and age modulate their effects.
- A uniform methodology for data collection, which defines the major parameters likely to affect the impact of the patients' sex and gender on treatment outcomes in oncology, needs to be developed. The EORTC Elderly Minimal Dataset designed to harmonize data collection within geriatric oncology studies could be used as an example.

3. Points to be considered in the analysis, interpretation and reporting of clinical trial results:

- Data should be reported according to sex in clinical trials, and potential sex differences need consideration in their design and analysis. Such differences may concern baseline condition and prognosis, treatment efficacy, as well as incidence, type, and severity of toxicities.
- Planned and administered dose intensities, dose reductions and treatment interruptions due to toxicity and serious adverse events according to sex and age need consideration and reporting in publications.

4. Implications for drug development and clinical research?

- Cell and animal studies need a balanced inclusion of samples and animals of both sexes as appropriate for the question studied [9]. Clinical trials of all phases need to ensure that the number of men and women enrolled is proportionate to the incidence of the cancer type. Sex should become a standard stratification factor in Phase III studies. General concepts for integrating sex in basic and clinical research in other disciplines have been published [88, 89].
- While results of early phase trials should be screened for signals suggestive of sex differences in efficacy and/ or toxicity, late phase trials need to disaggregate results by sex and age and report both individually and make raw data available.
- The evaluation of potential pharmacokinetic differences between men and women is particularly important during early drug development, in pharmacokinetic trials and for dose determination. Once a drug has demonstrated its efficacy, the question of potential differences in efficacy and toxicity, their pharmacokinetic or other biological basis, and if a dose modification according to sex could improve the balance between efficacy and toxicity, should be addressed.
- Analyses of biomarkers and molecular tumour profiles should be disaggregated by sex and age, especially in diseases with sex differences in epidemiology or outcomes. Such analyses may help to understand sex disparities in tumour biology.

5. What should be included in the curriculum for medical oncologists?

▪ Medical oncologists need to be aware of sex differences in pharmacokinetics, as well as the potential impact of the patients' sex on tumour biology [81].
6. Implications for clinical practice:
▪ Prior to the definition of any recommendations for clinical practice, interventional clinical trials investigating the need and demonstrating the benefit of sex-specific treatment strategies or dose modifications are recommended. ▪ If significant sex differences in toxicity or outcomes are identified, patients need to be informed about these differences

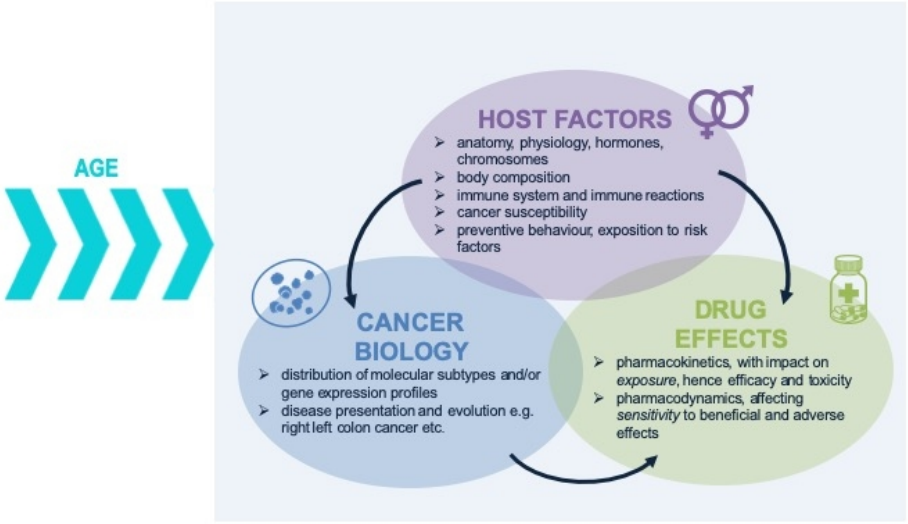
Table 1. Consensus statements

Class / Drug, Name	Indication	n (Men)/(Women)	Variability on CL (CV%)	Relative change in women vs men	
Angiogenesis Inhibitors					
Aflibercept [99]	Advanced solid tumors	767/739	31%	Clfu Vfu	- 16% - 19%
Bevacizumab [50, 100]	Gastric cancer ; solid tumors	1101/949	26%	CL	- 14% to - 27%
Antineoplastic Agents : Antimetabolites					
5-fluorouracil [47, 101] and metabolite	GI malignancies ; metastatic colorectal cancer	74 /42	22-40%	CL CLmet	- 14% to - 27% - 18%
Myeloablative Agents					
Busulfan [102]	Marrow transplantation	904/689	22%	V	+ 7%
Antineoplastic Agent : Alkylating agents					
Temozolomide [49, 103]	Glioma, glioblastoma, melanoma	303/177	5-10%	CL	- 19 to 27%
Mephalan [104]	Advanced malignancies	22/42	45%	CL	- 19%
Trabectedin [105]	PD study	232/467	51%	V Keo	- 17% + 22%
Antineoplastic Agents : Alkaloids					
Paclitaxel [106, 107]	Solid tumors	159/160		CL	- 30%

				Vmax	+14%
Irinotecan (SN38) [108-110]	Solid tumors, glioblastoma	67/58	47%	CL	- 30% to 38%
Antineoplastic Agent : Antibodies					
Rituximab [111]	Lymphoma	16/13	19%	CL	- 21%

Table 2: Anticancer agents with relevant differences in clearance between men and women.

CL: total clearance**;** CLfu: clearance of the unbound fraction**;** V: volume of distribution**;** Vfu: volume of distribution of the unbound fraction**;** V max: maximal metabolization rate**;** CLmet: metabolic clearance (i.e. the part of the total clearance corresponding to metabolism)**;** CLren: renal clearance (i.e. the part of the total clearance corresponding to excretion); CL = CLmet + CLren**;** Keo: equilibration constant between central and effect compartments. CV%: interindividual variability of the total clearance



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