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Mini-Review

Sex and Gender Differences in Anticancer Treatment Toxicity: A Call for Revisiting Drug Dosing in Oncology

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Abstract

The practice of oncology has dramatically changed in the last decade with the introduction of molecular tumor profiling into routine tumor diagnostics and the extraordinary progress in immunotherapies. However, there remains an unmet need to explore personalized dosing strategies that take into account the patient's sex and gender to optimize the balance between efficacy and toxicity for each individual patient. In this mini-review, we summarize the evidence on sex and gender differences in toxicity of anticancer therapies and present data on dose reduction and dose discontinuation rates for selected chemotherapies and targeted therapies. Finally, we propose the investigation of body composition (specifically fat-free muscle mass) as a viable approach for personalized treatment dosage.

Key Words: sex differences, gender differences, body composition, fat-free muscle mass, targeted therapies

Abbreviations: 5-FU, 5-fluorouracil; ADR, adverse drug reaction; AE, adverse event; BSA, body surface area; FFM, fat-free body mass; MTD, maximum tolerable dose; TKI, tyrosine kinase inhibitor.

In the last decade, the practice of oncology has profoundly changed with the introduction of molecular tumor profiling in routine tumor diagnostics and the extraordinary progress in immunotherapies. Yet, largely missing in treatment decisions is the integration of a patient's sex and gender as a critical modulator of their cancer risk and potential treatment outcomes. Despite the significant progress in treatment options for most cancer types, there remains an unmet need to explore personalized dosing strategies that take into account the patient's sex and gender to subsequently optimize the balance between efficacy and toxicity for each individual patient.

In this mini-review, we discuss the evidence pertaining to observed sex differences in the toxicity of anticancer therapies, present data on dose reduction and dose discontinuation rates for selected drugs, and propose the investigation of body composition–based drug dosing as a viable approach to personalize cytotoxic agents and targeted therapies. To obtain information for this mini-review, we performed a literature search on PubMed in January 2022 using the terms "sex differences," "gender," "cancer," and "drug toxicity" and also manually searched the reference lists of several publications of interest.

Sex vs Gender

The terms "sex" and "gender" are often used interchangeably in scientific literature (1), although this can be misleading as there are important distinctions between the terms. Sex refers to a person as female and male based on their biological features assigned by their gonads and sex chromosomes. As such, sex-related differences are the result of the interplay between genetic, hormonal, and physiological traits. Gender, on the other hand, is based on a person's cultural self-identification as a woman or man and also encapsulates how that person may be perceived by society given their presentation (1). Gender-based differences arise in part from environmental factors related to the sociocultural roles of women and men. Often these biological and environmental factors are entangled and interact with each other. In this mini-review, we use the terms "female," "woman," and "women" to refer to people who were assigned female sex at birth and socially self-identify as women. Likewise, we use the terms "male," "man," and "men" to refer to people who were assigned male sex at birth and socially self-identify as men. We acknowledge that there are likely important gender-based differences in anticancer treatment toxicity among transgender people that should be further examined in future work as it is beyond the scope of this mini-review.

Women Have a Higher Risk of Experiencing Adverse Drug Reactions

A patient's sex is a key modulator of drug responses (2, 3), which is expected given the important biological differences

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between women and men that can affect many aspects of treatment. Multiple analyses from different countries have shown that women have a 1.5- to 2-fold greater risk for developing adverse drug reactions (ADRs) across all drug classes and are significantly more likely to be hospitalized because of ADRs than men (4, 5). This increased ADR risk among women may be related to the fact that many Phase I and Phase II clinical drug trials are conducted predominately among men (6, 7) and the optimal drug dosings that are subsequently derived from these trials are likely not generalizable to women. These underexamined sex differences in drug dosing can have serious implications. Of the 10 drugs withdrawn from the US market between 1997 and 2000, 80% were found to represent a greater health risk for women than for men and 37% of the FDA-approved drugs between 2000 and 2002 were found to have sex differences in pharmacokinetics, efficacy, or adverse events (AE) (8). However, no recommendation on sex-based dose adaptation was made (9), possibly based on the erroneous assumption that these differences are not clinically relevant.

Various sex- (biological) and gender-related (psychosocial and societal) factors might contribute to the disproportionately higher ADR susceptibility among women than men. These include sex differences in pharmacokinetics and pharmacodynamics, gut microbiota composition (10, 11), sex-specific organizational (early life) and activational (peripubertal through adulthood) endogenous sex hormone exposure, sex differences in exogenous sex hormone supplementation (eg, oral contraceptives, menopausal hormone replacement therapies), higher rates of polypharmacy in women with a consequently greater risk of potential drug–drug interactions, and gender differences in the reporting or recall of ADRs (with women being more frequent reporters) (12). Importantly, sex differences in pharmacokinetics predict ADR across multiple classes of drugs, including antineoplastic agents (5).

Women present significantly higher blood drug concentrations and longer drug elimination times than men when administered the same drug dose. This is possibly related to the greater plasma volume, organ perfusion, and the approximately 10% higher body fat in women (13). Given the binding of drugs to erythrocytes, the lower hematocrit levels in women might also contribute to this excess drug toxicity (14). Sex differences in the expression levels of drug-metabolizing enzymes resulting from genetic polymorphisms (eg, cytochrome P450 isoforms; "pharmacogenetics") may also play a role (15). While data on differential expression of various CYP450 isoforms provide either conflicting results or do not indicate moderation by sex; the isoform CYP3A (which accounts for the metabolism of about 50% of drugs) has been reported to have a 25% higher activity in women (16). In contrast, the expression levels of the drug efflux pump P-gp encoded by the *MDR1* gene are higher in men and might partially explain the lower toxicity rate observed in men (17). Indeed, sex steroids were found to regulate P-gp expression and increase drug absorption through blocking of P-gp activity in the small intestine of rats (18). A comprehensive review of sex differences in pharmacokinetics and pharmacodynamics can be found in (3).

Several pharmacokinetic analyses have found that women have a lower elimination capacity for various anticancer drugs, including cytotoxic agents (ie, paclitaxel (19), 5-fluorouracil [5-FU] (20), doxorubicin (21)), tyrosine kinase inhibitors (ie, imatinib (22), sunitinib (23)), and monoclonal antibodies (ie, bevacizumab (24) and rituximab (25)), which results in higher plasma levels (Table 1). There are significant sex differences in renal function (which is taken into account in renal function calculators (48, 49)), with men having an average of 20% greater renal function than women (50). Despite these well documented sex-related differences, most analyses of anticancer drug elimination and distribution do not even include sex as a covariate. In a literature survey of 256 population studies on anticancer agents, only 80 reported that sex was included as a covariate in the analytic models (51).

Flat Doses and Doses Based on Body Surface Area Hamper Personalized Anticancer Treatment

A recent study of over 23 000 patients (38% women) in Phase II and III clinical trials found that female sex was associated with a higher risk of experiencing toxicity from anticancer therapies (52). Unger and colleagues analyzed individual patient data from 202 Phase II and III clinical trials testing systemic anticancer therapies and severe treatment-related AEs. Their findings indicated that women had 34% greater risk of severe toxicity than men (odds ratio [95% CI] 1.34 [1.27-1.42], $P < .001$). Moreover, this increased odds of AEs among women persisted across treatment type (chemotherapies, targeted therapies, immunotherapies), AE type (symptomatic or hematological), and treatment setting (advanced vs adjuvant) (52). Although it is possible that some of these AEs may be due to social gender differences in the reporting of symptomatic AEs, the higher odds of objective hematological toxicity clearly point to the presence of biological sex differences in pharmacokinetics and/or pharmacodynamics which modulate the patient's sensitivity toward adverse effects. The sex-specific toxicities likely result from both increased drug exposure through hormonal regulation of proteins involved in drug metabolism and via the direct effect of sex hormones on the drug target (13). Given the lack of a systematic collection of information on menopause status, the dose and type of hormonal contraception and the measurement of sex hormone levels in clinical trials, the magnitude of the hormonal effects remains unknown.

In addition, the individual genetic background/ethnicity as well as differences in gut microbiota diversity and composition and diet also potentially contribute to the observed sex differences (53). In fact, microbiome profiling in age- and diet-matched individuals indicates that the microbiota composition can be affected by gender in a body mass–dependent manner (54). Yet, given the complexity of the crosstalk between immune responses, microbiome, and sex hormones, dissecting the individual contribution of each of these factors is challenging (11).

Despite the abovementioned sex differences and the basic paradigm of clinical pharmacology that drug effects are generated from the circulating concentration profile of a drug rather than directly by the dose itself, dosage recommendations for anticancer drugs are not sex specific and most agents are administered either as flat doses (eg, tyrosine kinase inhibitors and some antibodies) or according to body weight (eg, some antibodies such as bevacizumab and ipilimumab) or body surface area (BSA; eg, cytotoxic agents). The recommended chemotherapy doses are meant to represent the dosages with the best therapeutic window showing the highest

Table 1. Sex-moderated elimination capacity, toxicity, and efficacy of various anticancer drugs

Drug/Regimen	Pharmacokinetics		Toxicity		Efficacy	
	Male	Female	Male	Female	Male	Female
5-Fluorouracil	Higher clearance (26)					
5-FU + LV (27)				Higher		
5-FU + XX (6 NGCCT trials) (28)				Higher		
Adjuvant FOLFIRI (PETACC-3) (29)				Higher		
Adjuvant FOLFOX/CAPOX/FOLFIRI (ACCENT database) (30)				Higher		
First line FOLFIRI/FOLFOX (ARCAD database) (31)				Higher		No difference in OS, PFS
First-line FOLFIRINOX (prospective trial) (32)				Higher		Higher OS
First-line FOLFIRI + bevacizumab/FOLFOX + bevacizumab/ FOLFOXIRI + bevacizumab (TRIBE trials) (33)				Higher		No difference in ORR, PFS
First-line FOLFOX + bevacizumab (SOFT trial) (34)				Higher		No difference in OS, PFS
Capecitabine						
Adjuvant capecitabine (BILCAP trial) (35)				Higher	Higher OS	
Paclitaxel	20% higher elimination (19)					
First-line paclitaxel + carboplatin (36)				Higher		Higher PFS
Oxaliplatin						
First-line S-1 + oxaliplatin (G-SOX trial) (37)				Higher		No difference in OS, PFS
First-line (?) S-1 + oxaliplatin + bevacizumab (SOFT trial) (34)				Higher		No difference in OS, PFS
Cisplatin						
Cisplatin-based therapy (prospective) (38)				Higher		
First-line ECF, ECX, EOF, EOX (4 UKNCRI trials) (39)				Higher		Higher OS
First-line S-1 + cisplatin (G-SOX trial) (37)						No difference in OS, PFS
First-line cisplatin-based therapy (ECOG 1594 trial) (40)				Higher		Higher OS and PFS
Doxorubicin	Higher clearance (21)			Higher (41-44)		
Irinotecan						
First-line FOLFIRI + bevacizumab (XELAVIRI trial) (45)			No difference		Higher OS and ORR	
Temozolomide						
Retrospective data (46)						Higher ORR
Adjuvant temozolomide (repository data) (47)						Higher OS

Abbreviations: ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

efficacy at the maximum tolerable dose (MTD). However, drug dose has been demonstrated to have a positive correlation with drug-related toxicity in Phase I trials (55). This phenomenon may be occurring given that the recommended anticancer drug dosages are often developed from clinical trial data among predominately male study populations and may have limited generalizability. Considering that women are consistently underrepresented in all phases of drug testing in clinical trials (6, 7), the MTD may actually be lower in women. As such, the administration of current standard doses may lead to increased blood drug concentrations and toxicity in women. Indeed, higher toxicity rates for most of the commonly applied cytotoxic agents have been reported among women than among men (Table 1). In addition, there is an increasing population of old, obese, or underweight cancer patients who are often undertreated because of arbitrary reductions of the calculated doses based on body weight or BSA and the use of an idealized body weight or capping of the total dose, although it was shown that BSA-based dosing is safe for obese patients (56, 57). However, obese patients can be sarcopenic and at risk of excess toxicity. Until the impact of sarcopenia and other measures of body composition on optimal antineoplastic dosing has been addressed, clinical guidelines recommend using the full, approved doses of anticancer treatments for obese adults with cancer (58, 59).

Interestingly, although obesity is a risk factor for cancer and treatment toxicity, recent analyses suggest that some degree of obesity (body mass index >30 kg/m^2) might be protective, with obese cancer patients showing better responses to treatment than lean patients, in particular for immune checkpoint inhibitors and targeted therapies (60, 61). This phenomenon is termed the "obesity paradox" and has been reported for different cancer types. Visceral adipose tissue is in fact considered an endocrine organ, responsible for secreting various factors which regulate innate and adaptive immunity, hematopoiesis, and angiogenesis (62).

Calculations based on BSA do not provide an accurate optimal therapeutic window for both sexes because this approach does not take into account sex differences in body composition and pharmacokinetics. As a comparison of 25 BSA formulas has shown, the BSA value may differ by 0.5 m^2 depending on the formula used for the calculation (63). Additionally, the Du Bois and Du Bois formula for the BSA calculation was developed solely from the data derived from 9 male individuals (64) and may be a less effective measurement tool among females. Similarly, according to 3 BSA bands (ie, 1.7 m^2, 1.7-1.9 m^2, ≥1.9 m^2) the dosing of the cytotoxic drugs cisplatin, docetaxel, paclitaxel, doxorubicin, irinotecan, and topotecan yielded comparable target area of the curve values as dosing according to the calculated individual BSA, highlighting the inexactitude of the BSA method (65).

Alternative chemotherapy dosing strategies have been studied (ie, dose-dense regimens and toxicity- or response-guided regimens) and are successfully incorporated in the management of hematological malignancies (66, 67). In contrast, pharmacokinetically guided dose adaptation (therapeutic drug monitoring) or genotyping for drug-metabolizing enzymes with known genetic polymorphisms have not been adopted for routine clinical use. This is due to several factors, most importantly due to the lack of an established therapeutic range for the majority of cytotoxic drugs, the scarcity of genetic studies characterizing the expression of specific enzyme variants, and the insufficient progress that has been made in investigating the factors responsible for sex-related pharmacokinetic differences (68).

Compared with cytotoxic agents, the impact of sex on the type, frequency, and severity of the toxicity from tyrosine kinase inhibitors (TKIs) is largely unknown for many recently approved targeted therapies (69). Depending on the targeted signaling pathway (eg, EGFR, ALK, VEGFR, BRAF), TKIs show highly variable dose reduction (4-70%) and discontinuation rates for toxicity (6-24%, Table 2). According to a meta-analysis of Phase I trials of TKIs, treatment with intermediate doses (40-80% of the MTD) is associated with better survival than lower or higher doses (81). For instance, subgroup analysis by age in the METEOR trial investigating the TKI cabozantinib in renal cell carcinoma showed that patients aged 65-74 years and 75 years or older had an average daily median dose of 41 mg and 33 mg, respectively, compared with the recommended standard dose of 60 mg daily. However, their response rate (21% vs 19%, respectively) was very similar to that of the total trial population receiving cabozantinib (17%) (82).

Fat-free Muscle Mass Could Become a Novel Parameter for Drug Dosing in Oncology

The high toxicity rate of anticancer treatments has a negative impact on the quality of life of cancer patients, and strategies to diminish AEs without affecting efficacy need to be explored. One possible strategy to decrease toxicity rates could be personalized dosing according to the body composition of the patient.

Drug metabolism is affected by body composition, specifically the metabolically active fat-free body mass (FFM). A single abdominal computed tomography scan without contrast enhancement of the L3-L4 region is sufficient to measure the FFM and body composition in an individual patient, as it shows a strong correlation with whole body adipose tissue, muscle, and lean tissue mass (83). The FFM is significantly higher in men; in a man and a woman of equal weight and height, the FFM accounts for 80% and 65% of the man's and woman's body mass, respectively (84). The FFM also decreases with increasing age (85), highlighting potentially significant differences in drug metabolism by age (younger vs older patients) in addition to sex (male vs female patients).

In a meta-analysis of 28 studies including over 6000 metastatic renal cell carcinoma patients, low muscle mass was associated with a significantly higher toxicity rate of the TKIs sunitinib and sorafenib and a higher mortality rate (86). In a retrospective analysis of 107 children, a higher skeletal muscle density at diagnosis was associated with lower odds of severe hematological toxicity of chemotherapies (87). Also, a prospective trial with 60 colon cancer patients receiving adjuvant 5-FU treatment found that 20 mg 5-FU/kg lean body mass was the threshold for developing overall toxicity, which shows the potential utility of body composition as a dosing parameter (88). Given this evidence, dosing of chemotherapies and targeted therapies based on the FFM would take into consideration important patient characteristics, such as sex, age, and body composition. This proposed approach to anticancer drug dosages could lead to a valuable improvement in the quality of life of cancer patients, including protecting them from unnecessary toxicity without compromising the efficacy of their treatment.

Table 2. Dose reduction and discontinuation rates for selected anticancer drugs

Drug classification, *trial name* (indication)	n	Starting dose	Grade 3-4 AEs	Dose reduction rate	Discontinuation rate (for toxicity)	ORR	Sex moderation	
							Male	Female
ALK inhibitors								
ALEX, Phase III (ALK-positive NSCLC; First line treatment [1L]) (70)	303							
Alectinib vs		600 mg bid	41%	16%	11%	83%	45%	55%
Crizotinib		600 mg bid	50%	21%	13%	76%	42%	58%
BRAF + MEK inhibitors								
COMBI-d, Phase III (BRAF V600- positive melanoma, 1L) (71)	423							
Dabrafenib + placebo vs		150 mg bid	30%	NR	7%	53%	54%	46%
Dabrafenib + trametinib		150 mg bid + 2mg qd	32%		11%	69%	53%	47%
COLUMBUS, Phase III (BRAF V600-positive melanoma, 1L) (72)	577							
Encorafenib + binimetinib vs		450 mg qd + 45 mg bid	34%	48%	6%	63%	60%	40%
Encorafenib vs		300 mg qd	34%	70%	10%	51%	56%	44%
Vemurafenib		960 bid	37%	61%	14%	40%	58%	42%
EGFR inhibitors								
LUX-Lung 3, Phase III (EGFR mutant NSCLC; 1L) (73)								
Afatinib vs chemotherapy	345	40 mg qd	49%	NR	8%	56%	36%	63%
EURTAC, Phase III (EGFR mutant NSCLC; 1L) (74)								
Erlotinib vs chemotherapy	174	150 mg qd	45%	21%	13%	58%	33%	67%
FLAURA, Phase III (EGFR mutant NSCLC; 1L) (75)	556							
Osimertinib vs		80 mg qd	34%	4%	13%	80%	36%	63%
Erlotinib/Gefitinib		140 mg qd/250 mg qd	45%	5%	18%	76%	38%	62%
VEGFR inhibitors								
SELECT, Phase III (thyroid cancer; 1L) (76)	261	24 mg qd						
Lenvatinib vs placebo		24 mg qd	76%	68%	14%	69%	48%	52%
REFLECT, Phase III (HCC; 1L)	954							
Lenvatinib vs		12 mg qd for ≥60 kg or 8 mg qd for <60 kg	57%	37%	9%	24%	85%	15%
Sorafenib		400 mg bid	49%	38%	7%	9%	84%	16%
COMPARZ, Phase III (RCC; 1L) (77)	1110							
Pazopanib vs		800 mg qd	74%	44%	24%	31%	71%	29%
Sunitinib		50 mg qd, 4 weeks on/2 weeks off	74%	51%	20%	25%	75%	25%
METEOR, Phase III (RCC; Second or further line treatment [2L]) (78)	658							
Cabozantinib vs		60 mg qd	68%	60%	9%	21%	77%	23%
Everolimus		10 mg qd	58%	25%	10%	5%	74%	26%
PARP inhibitors								
PROfound, Phase III (mCRPC with BRCA1, BRCA2, ATM mutation, ≥2L) (79)	387							
Olaparib		300 mg bid	51%	22%	18%	33%	100%	0%
SOLO-3, Phase 3 (ovarian cancer with BRCA mutation, ≥Third or further line treatment [3L]) (80)								
Olaparib vs chemotherapy	266	300 mg bid	50%	27%	7%	72%	0%	100%

Abbreviations: AEs, adverse events; bid, twice a day; n, patient sample size; NSCLC, non–small cell lung cancer; HCC, hepatocellular carcinoma; RCC, renal cell carcinoma; mCRPC, metastatic castration resistant prostate cancer; NR, not reported; ORR, overall response rate; qd, every day.

Conclusions

Compared with the progress made in drug development, the optimization of drug dosing lags significantly behind in the field of oncology. Given the different body composition of women and men, the administration of recommended drug doses established from studies with predominantly male populations may lead to increased blood drug concentrations and toxicity in female patients. In the era of precision medicine, a patient's biological sex and gender needs to be taken into account for treatment decisions. As such, the representation of women needs to be increased in clinical trials, and trials should be designed to allow meaningful subgroup analysis by sex for both drug response and drug toxicity. Prospective studies testing the dosing of cytotoxic agents and targeted therapies according to the FFM could represent a viable alternative to the current BSA-based or fixed dosing, and significantly improve the balance between the toxicity and efficacy of anticancer therapies.

Disclosures

C.L.G. and C.E.D.S. declared to have nothing to disclose B.C.Ö. declared receiving institutional honoraria for lectures and advisory boards from BMS, MSD, Merck, Ipsen, Roche, Novartis, and Pfizer and a contribution to registration fees for conferences from Janssen.

Data Availability Statement

Not applicable.

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