Ital J Gender-Specific Med 2022; 8(1): 55-58

Consideration of sex and gender aspects in oncology: rationale, current status, and perspectives

Berna C Özdemir[1,2], Anna Dorothea Wagner[3]

[1]Department of Medical Oncology, Bern University Hospital and University of Bern, Switzerland, [2]International Cancer Prevention Institute, Epalinges, Switzerland, [3]Department of Oncology, Lausanne University Hospital (CHUV) and University of Lausanne (UNIL), Switzerland

Received 22 September 2021; accepted 25 November 2021

Summary. Although an individual's sex is one of the most important factors influencing cancer risk and response to treatment, it is usually not considered in decision making in oncology. The concept of a sexual dimorphism of cancer, referring to differences in tumor biology between non-sex related cancers arising in men and women is supported by increasing evidence in various cancer types.[1]
Women present in general higher toxicity rates for multiple anticancer drugs. One factor known to affect drug metabolism, and likely to explain – at least in part – the observed sex differences in pharmacokinetics, is fat-free body mass. The fat-free body constitutes about 80% of a man's total body mass and only 65% of a woman's total body mass, yet this difference is not taken into account when dosing chemotherapy according to body-surface area.
Given its clinical relevance, the European Society for Medical Oncology (ESMO) decided to address this topic and set up a Gender Medicine Task Force. The missions of this task force are to raise awareness of the presence of potential sex differences in biology and treatment outcomes of non-sex related cancers and to assess the impact of gender on access, quality of life and long-term consequences of cancer therapies.

Keywords. Sex differences, gender, cancer, chemotherapy, toxicity.

Introduction

Molecular profiling of tumors, the development of immunotherapy, and targeted therapies have transformed the practice of oncology in recent years and allowed for significant progress. However, while the special situation of both elderly and younger patients has attracted some attention in the past, other host factors, such as the patients' sex, have not been considered. At present, despite accumulating evidence that the individual's sex is one of the most important factors influencing cancer risk and response to treatment, it is usually not taken into account in clinical decision making in oncology.[1,2]

Why do sex and gender matter in oncology?

1. Impact on tumor biology

Globally, and independent of ethnicity and age, women have a reduced risk and better outcome than men in a wide range of cancer types, such as those of colon, lung, liver, head and neck, esophagus, and skin.[3-6] The reasons for this female survival advantage are not well understood, and not sufficiently explained by gender differences in exposure to environmental or workplace chemicals and carcinogens, diet, exercise and risk behaviors such as tobacco and alcohol consumption,[7,8] suggesting the presence of protective biological factors in women. 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.[9] The multitude of effects of sex hormones on non-sex related cancers has been discussed in Clochiatti et al, 2016.[10] Together, hormones and chromosomes influence both local and systemic determinants of carcinogenesis.[9] The concept of a sexual dimorphism in cancer, referring to differences in tumor biology between non-sex-related cancers arising in men and in women, was introduced in 2016[10] and is supported by rapidly accumulating evidence[11-13] in a wide range of tumor types.

Melanoma is only one prime example for the illustration of sex and gender-related differences in disease susceptibility and outcome. In general, men have a lower awareness of skin cancer and are less likely to self-detect melanomas compared to women, resulting in a diagnostic delay.[9] Therefore, melanoma in men is often diagnosed when thicker, at an older age, and at a higher disease stage.[14,15] In addition, according to data from over 11,000 melanoma patients included in the Munich Cancer Registry, women have not only smaller lesions, but they are located mostly on the lower extremities, while the larger lesions in men are located primarily on the trunk,[15] reflecting differences in behavior and clothing choices.

Across all ages, men have 15-30% poorer survival rates[16] in both locally advanced[17] and metastatic melanoma.[16] This survival gap is present across different prognostic subgroups and persists even after adjusting for possible confounding factors, such as tumor thickness and localization. In addition, women have a low-

er risk of disease progression and a lower susceptibility for lymph node and visceral metastases.[15] Preclinical studies suggest that sex hormone levels and receptor expression might play a role in the development of melanoma as well as other non-sex related cancers, such as lung adenocarcinoma, bladder and colorectal cancer.[18-20] Other examples of sex differences in cancer biology are the distribution of molecular subtypes in gastroesophageal cancers[13] and the better outcome of women with lung cancer.[21]

2. *Impact on treatment response*

Sex differences in the pharmacology of anticancer drugs have been described for a number of agents. A recently conducted literature survey identified sex differences in the pharmacokinetics of anticancer drugs of about 20% in around 20% of population pharmacokinetic studies, with a higher exposure in women.[9] Of note, this difference is generally smaller than the usually large reported interpatient variability (20-40% coefficient of variation) in drug concentrations. Importantly, among 256 studies screened, only 80 reported sex as a tested co-variate.[22] 5-fluoruracil (5-FU) is a cytotoxic agent used in various chemotherapy regimens for different cancer types, in particular in gastrointestinal tumors. It is a prominent example of a drug with a significantly higher clearance in men.[23] The resulting higher plasma levels in women have been observed by different authors and are independent of age.[23,24]

This difference results in a statistically significant and clinically relevant higher toxicity in women which has been documented in several large studies and pooled analyses in colorectal cancer.[25,26] However, the higher plasma levels and toxicity do not translate to a higher efficacy in women with colorectal cancer.[27] Therefore, in addition to differences in pharmacokinetics, differences in drug sensitivity need to be considered. Among other chemotherapies with significant sex differences in pharmacokinetics, which may be limited to certain tumor types or age groups, are temozolomide,[28] doxorubicine,[29] paclitaxel[30] and irinotecan.[31] Examples of other classes of drugs with sex differences in pharmacokinetics include tyrosine-kinase inhibitors (e.g., sunitinib)[32] and monoclonal antibodies (e.g., nivolumab[33] and rituximab). For all these drugs an about 20-30% lower clearance, with resulting higher plasma levels in women have been described.[9]

One important factor known to affect drug metabolism, and likely to explain – at least in part – the observed sex differences in pharmacokinetics, is fat-free body mass. Although the metabolically active, fat-free body mass constitutes about 80% of a man's total body mass, and only 65% of a woman's, this difference is not taken into account when dosing chemotherapy according to body-surface area.[22] Thus, if their body surface area happens to be identical, a man and a woman with a significantly different body composition and possibly differences in drug metabolism, receive the same dose of chemotherapy. Of note, estimation of an individual patients' body composition can easily be performed by a computed-tomography scan (CT) at lumbar vertebra 3 (L3).[34] Indeed, numerous studies, for example in patients treated with capecitabine[35] or sorafenib,[36] have confirmed the positive association between sarcopenia and toxicity of anticancer treatments. Thus, assessment of a patients' individual body composition by CT scan not only has significant potential to improve drug dosing but also provides valuable prognostic information. Moreover, the immune system is sexually dimorph, which may impact the response to immunotherapy.[37]

Finally, it needs to be emphasized that sex differences in cancer biology and drug effects are just the tip of the iceberg of this topic. Further basic research to understand the biological basis of sex differences in tumor biology is necessary and encouraged. In addition, there are many more aspects, whose discussion is impossible within the scope of this work, such as the potential impact of gender on access to treatment[38] and gender stereotypes on medical decisions and treatment allocation,[39,40] which can contribute to survival differences between men and women.

The ESMO Gender Medicine Task Force

Given its clinical relevance, the European Society for Medical Oncology (ESMO) decided to address this topic and organized a first workshop "Gender Medicine and Oncology" in 2018.[9] During this workshop, examples of available evidence of sex and gender differences in oncology, as well as possible strategies for investigating sex specific treatment strategies to improve the balance between efficacy and toxicity for men and women, were discussed. Following the success of this initial workshop, ESMO set up a Gender Medicine Task Force (https://www.esmo.org/about-esmo/organisational-structure/esmo-task-forces/esmo-gender-medicine-task-force).

The missions of this Task Force are to raise awareness of the presence of potential sex differences in biology and treatment outcomes of non-sex related cancers and to assess the impact of gender on access, quality of life and long-term consequences of cancer therapies. Furthermore, systematic reviews of sex differences in pharmacokinetics of anticancer drugs are among the ongoing projects of this task force, as well as the discussion of strategies to improve dosing of anticancer drugs based on host factors, such as body composition and sex.

One of the conclusions of the 1st ESMO Workshop was that "especially in cancers or subtypes of cancers 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".[9] This statement is revolutionary for the oncology community. Its consequence is that benefits and risks of any given anticancer treatment for a non-sex-related cancer need to be evaluated separately in men and in women. It will take some time until both the scientific community and regulatory authorities accept this message and until sex-specific treatment strategies are incorporated into standard of care in oncology. Yet, there is reason to be optimistic as the first steps are taken towards this goal and work in this field progresses. While there are currently significant disparities in the integration of sex and gender aspects into clinical practice in Europe, with Italy being a clear leader in the field having anchored the application and dissemination of gender-specific medicine in the National Health Service, the commitment of ESMO to this topic is a valuable opportunity to develop and disseminate educational material to its members and foster international collaborations.

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Key messages

- Globally, and independent of ethnicity and age, women have a reduced risk and better outcome than men in a wide range of cancer types.
- Women show lower clearance rates for multiple anticancer drugs and present higher toxicity rates.
- In current clinical practice, a man and a woman with a significantly different body composition and possibly differences in drug metabolism, receive the same dose of chemotherapy if they have the same body surface area.
- Especially for tumor types with significant differences in epidemiology, and for treatments with significant differences in pharmacokinetics, men and women with non-sex-related cancers should be considered as biologically distinct groups of patients, for whom specific treatment approaches merit consideration.
- Benefits and risks of any given anticancer treatment for a non-sex-related cancer need to be evaluated separately in men and in women.

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Author contribution statement: both Authors conceived this article and contributed equally to the work.

Conflict of interest statement: BCÖ has declared to receive institutional honaria for advisory boards and lectures from Merck, Roche, BMS, MSD and Ipsen, all outside the submitted work. ADW has declared to receive consulting fees or travel support from BMS, Pfizer, Merck, Servier, Lilly, Shire, Celgene, MSD, Bayer, Ipsen, Servier, and Sanofi, all outside the submitted work. She is the coordinating investigator of EORTC-trial 1203, which is supported by an educational grant from Roche to EORTC.

ADW declares no conflicts of interest.

Correspondence to:
Berna Özdemir
Melanoma and GU Cancers
Oncology Department
Bern University Hospital
email: berna.oezdemir@insel.ch