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Sex differences in cancer chemotherapy effects, and why we need to reconsider BSA-based dosing of chemotherapy

Anna Dorothea Wagner

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Department of oncology, Division of medical oncology, Lausanne University Hospital (CHUV) and University of Lausanne (UNIL), Lausanne, Switzerland

Correspondence to
Dr. Anna Dorothea Wagner; Dorothea.Wagner@chuv.ch

> One sees only what one knows.
> Johann Wolfgang von Goethe

Thus we ignore what we don't know.

In oncology, it is traditionally assumed that men and women are equal. As a result, sex differences in treatment effects and the biology of non-sex-related cancers have largely been ignored in the last decades. However, the observation of increased chemotherapy toxicity in women is not new. Although overall insufficiently studied, available data from different types of tumours[1–4] clearly demonstrate that women are more susceptible to toxicity from various types of chemotherapy.

WHY DO DIFFERENCES IN TOXICITY EXIST?

Theoretically, sex differences in drug effects can be broken down into two categories:

1. Differences in pharmacokinetics: sex differences in pharmacokinetics have been reviewed elsewhere[5] and affect the different types of pharmacokinetic parameters, such as bioavailability, distribution, metabolism and excretion.[6] Examples for chemotherapeutic drugs with significant sex differences in pharmacokinetics are 5-fluouracil[7] and paclitaxel.[8] However, the impact of the patients' sex is most often not analysed, and/or subgroup analyses according to sex are not reported in pharmacokinetic studies and clinical trials. According to a recent literature survey of population pharmacokinetic studies of anticancer drugs,[9] among 256 studies identified, only 80 reported sex as a tested covariate.
2. Differences in pharmacodynamics: in addition to differences in drug metabolism, the sensitivity of both normal tissues and tumours in men and women may be different. Furthermore, the dose–response and dose-toxicity relationships may not necessarily be the same in both sexes.

SEX DIFFERENCES IN TREATMENT EFFECTS GO BEYOND DIFFERENCES IN TOXICITY

While differences in incidence and mortality of different types of cancers have initially been attributed to differences in exposure to risk factors, evidence from large epidemiologic studies clearly indicates significant sex differences in susceptibility and survival of non-sex-related cancers, which cannot be explained by differences in behaviour. Clocchiatti and colleagues introduced the term 'sexual dimorphism in cancer' to describe this observation.[10] In addition, sex-biassed gene-expression signatures have been described for multiple solid tumours.[11] Sex differences in host factors, especially the immune responses, differentially affect the susceptibility to many diseases, especially autoimmune diseases, but as well infectious diseases and non-reproductive cancers.[12]

WHY DO SEX DIFFERENCES MATTER IN ONCOLOGY?

Understanding sex differences in treatment effects is key for three major reasons:

First: The balance between efficacy and toxicity may be improved by the development of rationally designed, sex-specific dose modifications

The SEXIE-R- CHOP-14 trial (Optimization of rituximab for the treatment of DLBCL: increasing the dose for elderly male patients)[13] prospectively investigated different doses of rituximab in men and women with diffuse large B-cell lymphoma and demonstrated an improved progression-free survival by 32.5% (p=0.039), with a trend for a (30%) better overall survival in the experimental arm. It demonstrates the feasibility and is an example for the potential of rationally designed, sex-specific dose modifications to improve patient outcomes in oncology. Further studies with other classes of drugs with significant sex differences in pharmacokinetics are required. The current process

of drug development in oncology does not identify potentially different optimal doses for men and women. Cardiologists recently discovered that optimal doses of drugs to treat heart failure are not the same[14] in women as in men. We should learn from them.

Second: Due to potential differences in tumour biology, the magnitude of the treatment benefit may be different in men and women

One example of a recent study with significant differences in treatment efficacy between men and women is the BILCAP (Capecitabine compared with observation in resected biliary tract cancer) study, in which adjuvant treatment with capecitabine after curatively resected biliary cancer was compared with observation alone.[15] The subgroup analysis of this trial demonstrated a HR of 0.93 (0.64–1.35) in women and 0.7 (0.50–0.99) in men. Certainly, the result of the subgroup analysis in women is limited by its small sample size and may be false. This trial was neither designed nor powered to detect a treatment benefit in women. A subgroup analysis is not a sufficient argument to withhold a potentially effective treatment for women with biliary cancer. However, these results should raise doubts about the efficacy of capecitabine as adjuvant treatment in women with biliary cancer as they may as well reflect true biological differences in sensitivity of this type of cancer to capecitabine. Further research and trials specifically addressing this question are necessary to confirm or infirm the efficacy of adjuvant capecitabine for biliary cancer in women. Since we understand the concept of a sexual dimorphism in cancer,[10] we can no longer conclude from the observation of a certain treatment benefit in men that this benefit will be the same in women.

Third: Understanding of the biological basis of sex differences in tumour biology might allow for the development of sex-specific drugs with greater efficacy

The recent ESMO workshop concluded that 'especially in diseases 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] Another example for a disease with a significant difference in tumour biology between men and women is melanoma: a pooled analysis of 2734 patients included in five randomised trials reported in 2013[16] clearly described a significantly better survival (HR 0.81, 95% CI 0.72 to 0.91, p<0.001) in stage III and stage IV (HR 0.82, 95% CI 0.72 to 0.93, p<0.001). The authors conclude that 'a biologic sex trait seems to profoundly influence melanoma progression and survival'. Further research is necessary to identify and understand such biological differences.

Finally, when thinking about the individualisation of systemic treatments in oncology, we have to keep in mind that the patients' sex is only one of different host factors, which deserves consideration: a patients' body composition is an example of another one. Body surface area (BSA)-based dosing of chemotherapy has been introduced in the 1950s and remained the default approach since then. Its inaccuracy has already been discussed nearly 25 years ago,[17 18] and more recently by Bins *et al*,[19] where paclitaxel is taken as an example to illustrate both the lack of correlation between clearance and BSA, and the impact of the patients' sex. BSA-based dosing of chemotherapy ignores both the sex differences in fat-free body mass and the large individual variations of body composition, which can easily and precisely be assessed by CT scanning.[9] In an editorial published in 1998,[20] Ratain asked if BSA-based dosing of chemotherapy is 'science, myth or habit?' and concluded that myth and habit have gotten in the way of science. Alternatives to chemotherapy dosing according to BSA, such as toxicity-based dosing, genotype-based dosing or therapeutic drug monitoring (TDM) have been developed. However, the complexities of TDM make its universal use impractical,[17] genotype-based dosing is possible only for a limited number of drugs and in a limited number of settings, but information about the patients' host factors, such as sex, age and body composition, as well as treatment-related toxicity, is available wherever oncology is practiced.

We are now in 2020 and should put greater efforts in the investigation of alternatives to BSA-based dosing of chemotherapy. Rationally designed concepts for chemotherapy dosing, developed on the basis of the understanding of a drugs' pharmacokinetics, which integrate information about the relation between host factors, such as sex, age and body composition and drug clearance, as well as genotypes wherever possible, need further development. Furthermore, dose adjustment according to toxicity should not be limited to reductions in presence of toxicity. The potential of uptitration of chemotherapy doses in absence of toxicity in eligible patients to increase treatment efficacy deserves further investigation. Ideally, composite models, which take these different parameters according to their specific relevance for a given drug into account, should be developed. The clinical benefit of such new concepts in terms of reduction of toxicity and improvement of efficacy needs confirmation in randomised clinical trials.

Finally, body composition matters not only for chemotherapy dosing, but might also affect the results of immunotherapy.[21] By individualising cancer treatments on the basis of tumour characteristics we made significant progress. We have understood the importance of the microenvironment and are exploring the role of the microbiome. We should now continue and explore the impact of host factors, such as sex and body composition, as well as their interactions with tumour biology and treatment effects, to further individualise the administration of anticancer treatments.

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ORCID iD

Anna Dorothea Wagner http://orcid.org/0000-0003-4728-7013

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