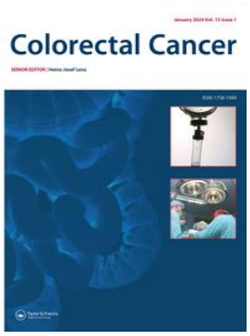

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EDITORIAL

Sex differences in the treatment of gastrointestinal cancers with anti-cancer drugs

1. Introduction

The importance of sex and gender in oncology is becoming increasingly recognised; however, they remain an undervalued issue in the era of precision oncology. A patient's sex is rarely considered in clinical decision making for patients with gastrointestinal (GI) cancers despite increasing evidence that an individual's sex is one of the most important factors influencing disease risk and response to treatment. There are now numerous studies in the treatment of GI cancers showing that women are more susceptible to the toxicity of many different types of drugs.

In this editorial, our focus will be biological 'sex' and not 'gender' and terminology will reflect this. Sex refers to the biology of living things, i.e., as male or female according to reproductive organs or functions based on the chromosomal complement. Gender, on the other hand, refers to sociocultural attributes, behaviours or personal identification. Both are important in the treatments of cancer; although the focus of this editorial is on sex differences, it is worth noting that gender differences are of relevance when striving to improve outcomes and an area where there is a dearth of evidence.

2. The significance of sex differences in treatment effects

At large, females are prescribed more drugs than males; they require increased access to health care services but suffer from more adverse drug reactions (ADRs) and are hospitalised more often due to ADRs compared to men [1,2]. Within colorectal cancer chemotherapy treatment, this trend is increasingly well documented.

Numerous studies have reported sex-specific differences exist in patients receiving fluorouracil (5FU), an essential component of systemic anti-cancer therapy (SACT) regimens in the adjuvant and palliative settings for colorectal cancer. The toxicities of 5FU in male and female patients has been studied extensively and included several different types of toxicity, the maximum toxicity grading, and the incidence of severe toxicities. These toxicities include hematologic toxicities such as leukopenia, neutropoenia, and thrombocytopaenia, and self-reported toxicities such as stomatitis, diarrhoea, nausea, vomiting, or hand-foot syndrome. A meta-analysis of North Central Cancer Treatment Group cancer control trials concluded that women receiving 5FU-based chemotherapy regimens experienced haematological and non-haematological toxicities more frequently, and with more severity than men for four of the six studied toxicities (stomatitis, leukopenia, alopecia, and diarrhoea) [3]. Similarly, another study reported women receiving 5FU experienced more toxicities, with greater average toxicity grade, and incidence of severe toxicities than men [4].

Other chemotherapeutic agents with significant sex differences in pharmacokinetics include paclitaxel, a taxane used to treat numerous types of cancers, including gastric cancer. A review examining sex-discrepancies and discussing sex-dependent mechanisms of action and clinical outcomes reported paclitaxel-induced toxicities are more prevalent in women compared to men [5]. Existing paradigms of sexual dimorphisms in cancer point to the role of sex-specific immune modulation as a factor in treatment-induced toxicities and overall survival.

Severe adverse effects can have significant impact on patients' quality of life and compliance with treatment. A retrospective, cohort study across four hospitals in England investigating the association of biological sex with the incidence of chemotherapy treatment delays in patients with colorectal cancer reported that

women were more likely to have a treatment delay compared to male patients [6]. The findings of this study are concordant with existing literature conducted in other countries, such as the United States of America [7].

Treatment delays can result in reductions in dose intensity, a measure linked to treatment outcomes in colorectal cancer. A systematic review reported that a four-week delay in treatment has been associated with a 13% increased risk of death for patients with colorectal cancer receiving adjuvant systemic treatment [8]. However, according to population studies, survival rates are similar between the two sexes. For example, the EUROCARE-4 study reported that women had a 2.2% survival advantage over men for cancer deaths due to bowel and rectal cancer in Europe [9]. The updated EUROCARE-5 found negligible difference in CRC survival rates between men and women [10]. This difference may be due to differences in tumour biology

3. Pharmacodynamic and pharmacokinetic considerations for differing toxicities in men and women

Many cytotoxic agents present a significant dose-response relationship and their dose-intensity correlates with response rates and survival. A number of studies with various chemotherapy regimens have described a positive correlation between female sex, higher response rates, and longer survival. In addition to the dose and independent of sex, chemotherapy-related toxicity is usually correlated with clinical outcomes [11].

It is well documented that there is an underrepresentation of women in pre-clinical, clinical, and post marketing research. The pre-clinical work may not seem of significance but it is important to note that in fact, every nucleated cell has a sex containing sex chromosomes (in its simplest form, XX in females or XY in males [12]. It is understood that there are distinct differences in cell lines, however, the majority of pharmaceutical research is undertaken in cell lines which are male [13]. Notably, Caco-2 cells which are derived from colorectal adenocarcinoma and utilized for studying intestinal permeability of drugs are male. Therefore, existing research on drug availability in this disease is biased against women.

There are also significant physiological differences between men and women, such as body fat, body water volume, plasma volume, organ blood flow, and body weight. However, these parameters are often overlooked in the drug development process and can consequently result in differing response to medicines [14]. As a principle, sex differences in drug effects are attributable to either differences in pharmacodynamics or pharmacokinetics, the latter comprising drug absorption, distribution, metabolism, and elimination [14].

Pharmacokinetic and pharmacodynamic differences between the sexes have been studied extensively; however, the impact of the patients' sex on toxicity is most often not analysed, and/or subgroup analyses according to sex are not reported in pharmacokinetic studies and clinical trials [14]. A recent literature survey of population pharmacokinetic studies of SACT reported that of 256 studies identified, only 80 reported sex as a tested covariate [15]. The greater incidence of 5FU-associated ADRs in women have been hypothesized to be the result of decreased rate of clearance and elimination of 5FU and differences in body composition (e.g., fat mass, volume of distribution) [16]. Following administration, 5FU is distributed in the tissue with fat-free body mass being the greater predictor of its pharmacokinetic profile; men generally have greater fat-free mass compared to women who tend to have a higher percentage of body fat. Therefore, traditional anthropometric measurements such as BSA which does not account for individual variations in body composition can result in significant under- or over-dosing in men and women [15]. A population pharmacokinetic study assessing the impact of patient anthropometrics on the pharmacokinetics of 5FU infusion reported most men who received a standard dose (as determined by BSA) of 5FU had sub-therapeutic plasma levels of 5FU [17].

Renal function, another key factor in the pharmacokinetic profile of medicines, has also been reported to differ widely between sexes [18]. However, unlike BSA, this has typically been accounted for in the various formulas used in estimating glomerular filtration rates (eGFR) such as Cockcroft and Gault. This is of particular relevance to chemotherapy agents that are renally cleared, such as cisplatin.

4. Future avenues of research

There is growing evidence highlighting the significance of sex differences in the treatment of colorectal cancer, and the wider field of oncology. In particular the role of oestrogen is poorly understood, but known to be a protective factor, with prognosis for women differing depending on whether they are pre- or post-menopausal [19]. Exploration of the mechanisms of hormonal influence and how these impact treatment effects are critical

to optimizing treatments for women. Traditionally, SACT dosing has utilized BSA, however, this fails to account for pharmacokinetic and pharmacodynamic differences between the sexes. Numerous studies have highlighted the profound impact of overdosing SACT which can lead to higher incidence of ADRs which affect patients' quality of life, response to treatment, and overall survival. Future research should focus on optimising treatment dosing for women and greater emphasis on sex and gender diversity in clinical trials to improve equity, representation, and health outcomes for women.

Authors contributions

Kari Leung: Investigation, Writing – Original draft preparation. ***Dr Anna Dorothea Wagner***: Review and editing. ***David Shorthouse***: Writing – Review and editing. ***Simon Jenkinson***: Writing – Review and editing. ***Pinkie Chambers***: Conceptualization, supervision, writing – review and editing.

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