Integrating Sex as a Biological Variable in Early-Phase Cancer Trials: A Literature Review & Recommendations

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Background & Aim

Sex significantly modulates cancer development, progression, and treatment response, yet its consideration as a biological variable in clinical trials remains limited.

Early-phase (phase 1 and 2) clinical trials evaluate the safety, preliminary efficacy and optimal dosage of new cancer therapies, and provide foundational data that guides subsequent research phases. However, failure to incorporate sex-based analysis at these initial stages impedes the advancement of personalised medicine, potentially resulting in inaccurate dosing, toxicity underestimation, and missed opportunities to uncover sex-specific therapeutic effects.

Aim: *to recommend methodological updates that incorporate sex differences towards enhancing the efficacy and safety of cancer therapies for both sexes.*

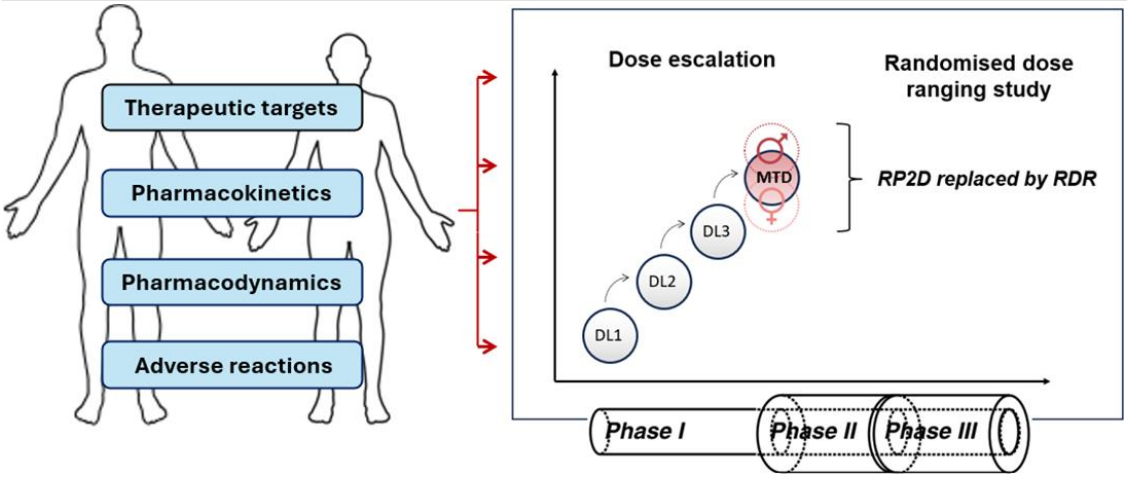
Methods

1. A systematic search was conducted in the Ovid Medline and Embase databases to identify studies elucidating the causes of sex differences in cancer treatment response. This search specifically targeted areas of pharmacokinetics (PK), pharmacodynamics, adverse reactions, and the current practices in sex-based analysis and reporting within early-phase clinical trials.

2. The review further explored the impact of existing research guidelines on the design of early-phase clinical trials, aiming to understand the integration of sex as a biological variable in research practices.

3. Informed by the comprehensive review and analysis, this study proceeded to develop recommendations aimed at enhancing the integration of sex as a biological variable in the design and methodology of early-phase clinical trials

Results



A Dose of Insight!

- **$30.1 billion:** the annual cost of adverse drug reactions in US[1]
- **2.5 times**: the heightened risk faced by women in experiencing severe adverse reactions[2]
- **10-15%:** the percentage of early-phase trials terminated due to inadequate PK profiles[3]

Figure 1. Sex modulates the endpoints of phase I cancer clinical trials, which determine a single maximum tolerated dose (MTD) to inform the recommended phase 2 dose (RP2D); an approach predicated on the assumption that "one dose fits all".

1. Optimising the dose-finding paradigm

- Trials should aim to build a more comprehensive foundation for dosing decisions to allow appropriate adjustments based on patient charactersitcs, including sex.
- Instead of a single RP2D, phase 1 trials should aim to establish a recommended dose range (RDR) based on the total available data (Figure 1)
- The search for an optimal dose(s) could extend into well powered randomised dose-ranigng trials in phases 2 & 3.

2. Fat-free body mass as a novel dosing parameter

- Sex differneces in body composition can infuence drug metabolism
- Fat-free mass (FFM) is a better estimate of metabolically active body mass, and incorporates a sex coefficient to better reflect differences in drug clearnace
- FFM measured by a single abdominal CT scan of the L4-L5 spine is economically feasible and has demonstrated utility as a novel dosing parameter in several recent studies[4]

3. Sex-based variables in physiologically-based pharmacokinetic modelling

- Computational PBPK modelling can incorporate sex-specific parameters, such as absorption values, and enzyme and transporter coefficients to refine predictions about drug response between the sexes
- This may reduce attrition and early-closure due to poor pharmacokinetics
- Regulatory bodies encourage PBPK modelling, but development of sex-specific models are hindered by the qualitative nature of current sex difference data

4. Subgroup analysis & sex-disaggregated reporting

- Skepticism remains that sex-specific analysis is impractical in phase 1 trials, which are not powered for definitive hypothesis testing
- Exploratory subgroup analysis, interpreted with caution, can suggest hypotheses for future studies, and prioritising confidence intervals over p-values improves result validity
- Improved regulatory measures, including incentives for quantitative sex-disaggregated reporting and collaboration with industry stakeholders to close these gap

Conclusion

Integrating sex as a biological variable in early drug development is crucial for refining cancer treatment for both sexes, enhancing efficacy, safety, and health equity. Acknowledging sex differences from the outset is not only scientifically sound but ethically necessary.

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