HHS Public Access

Author manuscript

Lancet Oncol. Author manuscript; available in PMC 2020 February 05.

Published in final edited form as:

Lancet Oncol. 2018 August ; 19(8): e377. doi:10.1016/S1470-2045(18)30517-5.

Sex as a predictor of response to cancer immunotherapy

Brian Claggett,
Division of Cardiovascular Medicine, Brigham and Women's Hospital, Boston, MA, USA

Lu Tian,
Department of Biomedical Data Science, Stanford University School of Medicine, Palo Alto, CA, USA

Zachary R McCaw,
Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, MA 02115, USA

Masahiro Takeuchi,
Department of Clinical Medicine (Biostatistics), Kitasato University School of Pharmacy, Tokyo, Japan

Lee-Jen Wei
Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, MA 02115, USA

Fabio Conforti and colleagues did a meta-analysis[1] to assess heterogeneity in efficacy of immune checkpoint inhibitors between men and women. The primary outcome was overall survival. The authors included 20 randomised controlled trials in their meta-analysis, in which the hazard ratio (HR) was used to quantify the treatment effect for each study and sex. A random-effects model was used to obtain a pooled HR for the overall treatment effect for each sex. Therefore, the 20 individual HRs were assumed to be a random sample from a hypothetical, super-population (ie, HRs from all current and future comparative trials of this type of intervention in similar patient populations) with a log-normal distribution. The pooled HR was 0·72 (95% CI 0·65–0·79) for men and 0·86 (0·79–0·93) for women, in favour of immune checkpoint inhibitors. The overall survival benefit from immunotherapy was significantly higher for men than women. However, it is not clear how to interpret this difference clinically.

The use of HRs to assess overall treatment effect has several limitations. First, this type of immunotherapy often has a delayed treatment effect, indicating that a HR is not an adequate summary measure of treatment benefit and is difficult to interpret clinically.[2–4] Second, if the assumption of log-normally distributed study-level HRs is not valid, the random-effects estimate might not be valid. Third, the assumption that the selected studies represent a random sample from a super-population of studies is not well-defined or easily understood.[5] Even if each study-specific HR is an appropriate summary measure, the pooled HR should not be interpreted as the HR for any specific patient population. Moreover, it is not obvious how to justify whether this super-population of HRs would be applicable to patient

wei@hsph.harvard.edu.

We declare no competing interests.

populations that are included in future studies. In a future study of a similar population, the true study-level treatment effect might differ substantially from the pooled estimate since the pooled estimate is an average across all theoretically possible study-level treatment effects.

The first fundamental principle in a comparative clinical study is to define the patient population of interest, then to identify a population-level summary measure for quantifying the treatment effect, and finally to collect data that enables inferences to be made about the treatment effect in that population. It is not appropriate to rely on a single, clinically uninterpretable, averaged treatment effect, estimated via meta-analysis, for decision making in any specific population, especially when the treatment effects might vary substantially across different target populations. An approach that combines treatment effects across heterogenous study populations, which does not require strong modelling assumptions, might be more appropriate.[5]

References

1. Conforti F, Pala L, Bagnardi V, et al. Cancer immunotherapy efficacy and patients' sex: a systematic review and meta-analysis. Lancet Oncol 2018; 19: 737–46. [PubMed: 29778737]
2. Uno H, Claggett B, Tian L, et al. Moving beyond the hazard ratio in quantifying the between-group difference in survival analysis. J Clin Oncol 2014; 32: 2380–85. [PubMed: 24982461]
3. Pak K, Uno H, Kim DH, et al. Interpretability of cancer clinical trial results using restricted mean survival time as an alternative to the hazard ratio. JAMA Oncol 2017; 3: 1692–96. [PubMed: 28975263]
4. Alexander BM, Schoenfeld JD, Trippa L. Hazards of hazard ratios-deviations from model assumptions in immunotherapy. N Engl J Med 2018; 378: 1158–59. [PubMed: 29562148]
5. Hasegaw T, Claggett B, Tian L, Solomon SD, Pfeffer MA, Wei LJ. The myth of making inferences for an overall treatment efficacy with data from multiple comparative studies via meta-analysis. Stat Biosci 2017; 9: 284–97.