Patients' sex may impact efficacy of immunotherapy in cancer treatment

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Different immune responses between men and women, and potential interaction with hormones might impact how men and women benefit from immunotherapy drugs, authors propose.

A patient's sex might impact on the efficacy of immunotherapy in cancer treatment, according to a new meta-analysis of 20 randomised trials in over 11000 patients with advanced cancer published in *The Lancet Oncology*.

Cancer immunotherapy represents one of the most important advances in cancer treatment in the past decade. It is the standard treatment for some types of cancers, including melanoma and non-small-cell lung cancer, and trials are ongoing into its effectiveness in the treatment of other cancers. While the findings do not imply a change in treatment guidelines for men or women, the authors say they should prompt further research to understand the mechanisms at play in order to improve treatments for all patients.

Additionally, the under-representation of female patients in clinical trials is a widely recognised problem. Indeed, in half of the trials in this study, women comprised less than a third of the overall population, meaning that individual trials likely cannot reliably show the interaction between sex and treatment efficacy. The findings from the meta-analysis highlight the need for sex-specific analyses to avoid erroneously extending to women results that are obtained mainly in male patients, which may lead to poorer care, and potentially harm.

Previous studies have shown that men have an almost two-times higher risk of mortality from all cancers than women, likely as a result of behavioural and biological factors. In this study, the authors looked specifically at the differences in survival for patients treated with immunotherapy.

They combined data from 20 previously published randomised trials including 11351 patients who had received an immune checkpoint inhibitors (ipilimumab, tremelimumab, nivolumab, or pembrolizumab) for advanced or metastatic cancers. These included melanoma, renal cell carcinoma, urothelial cancer, head and neck cancer, and lung cancer. 3632 (32%) of 11351 patients had melanoma and 3482 (31%)
had non-small-cell lung cancer. Of those included in the analysis, 7646 (67%) were male and 3705 (33%) were female.

Overall, for both men and women, immunotherapy was more effective than the control, whether this was a placebo, or another type of cancer drug. But, there was a higher survival benefit for men compared to women, regardless of the type of cancer and the type of drug administered. On average, the relative survival gain was double the size for men compared to women. "An individual's prognosis will depend on multiple variables including type of cancer and the drugs used, and immunotherapies continue to be the standard treatment for several cancers, with survival often far better than other drugs. Treatment for women should not altered based on these findings, rather we need to understand more about the mechanisms to ensure that these novel treatments can be optimised for both men and women," explains author Dr. Fabio Conforti, European Institute of Oncology, Milan (Italy).

"Both sex and gender can potentially affect the strength of the body's immune response. On average, women mount stronger immune responses than do men, which results in more rapid clearance of pathogens, explaining the lower severity and prevalence of many infections in women, and their greater response to vaccination than men. On the other hand, women account for roughly 80% of all patients with systemic autoimmune diseases worldwide. Therefore, it's possible that differences in the immune system of women and men could be relevant to the natural course of chronic inflammatory conditions such as cancer, and potentially how they respond to drugs," adds Dr. Conforti.

The authors add that sex differences in the immune system at the cellular level have also been reported, likely as a result of complex interactions between genes, hormones, the environment, and microbiome composition. Immune checkpoint inhibitor (CTLA-4 and PD-1) pathways play an important part in tumour-induced immunosuppression, and animal studies have suggested that sex-hormones may modulate some of these pathway. Similarly, female and male mice show different responses to anti-PD-L1 monoclonal antibodies.

"Despite the available evidence on the potential role played by sex in influencing how drugs work, trials testing new therapies rarely take sex into account. Immune checkpoint inhibitors have revolutionised cancer treatment, showing higher efficacy than standard therapies in several cancers. As we seek to improve immunotherapy further by identifying predictive biomarkers of response, sex differences should be further investigated." says Dr. Conforti.

The authors note several limitations, including that the meta-analysis relies on published results rather than on individual patients' data. The authors also note that
EGFR-mutated non-small-cell lung cancers are less sensitive to immune checkpoint inhibitors than are EGFR wild-type non-small-cell lung cancer tumours, and are more common in female patients than in male patients. However, most (94%) non-small-cell lung cancers included in the meta-analysis were wild-type, indicating that sex-dependent differences in the efficacy of immune checkpoint inhibitors were not exclusively related to mutation status.

Writing in a linked Comment, Omar Abdel-Rahman, Ain Shams University (Egypt) and University of Calgary (Canada), cautions that the meta-analysis incorporates a diverse group of solid tumours: "... within each solid tumour, there are a multitude of baseline characteristics that might differ in their distribution between men and women, and these baseline characteristics have been reported to affect outcomes of patients treated with immune checkpoint inhibitors. Moreover, there are also lifestyle or behavioural characteristics that differ between men and women that might also have confounding effects... Although the Article by Conforti and colleagues is a thought-provoking and hypothesis-generating piece of work, caution needs to be exercised before jumping directly to radical conclusions and before changing the current standard of care among approved indications for immune checkpoint inhibitors. Female patients who are otherwise indicated for treatment with any immune checkpoint inhibitor should not be denied treatment solely on the basis of these findings. Further prospective studies that are disease-specific and that account thoroughly for potential confounders are needed before a final judgment can be made about the effect of the patient's sex on the efficacy of immune checkpoint inhibitors."


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