G-DEFINER

Gender difference in side effects of immunotherapy: a possible clue to optimise cancer treatment

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Clinical Oncology, Biology, Biostatistics, Bioinformatics

Overview

In patients with cancer, the increasing use of immunotherapic treatments is associated with immune-related adverse events (irAEs) caused by non-specific activation of the immune system. IrAEs usually develop within the first few weeks to 6 months after treatment initiation; however, they can also present after cessation of immunotherapic treatment. Sex influences the adaptive immunity, and may influence irAEs types, frequency and severity. Accumulating evidences support the existence of sex-driven differences in immune responses as potential factors contributing to disease outcome and response to therapy. Together with genetic and biological differences, the roots of irAEs inequalities between female and male patients could also be linked to psycho-social and behavioral determinants.

This is a multicenter observational prospective clinical study aimed at investigating the inequalities between female (F) and male (M) cancer patients in the development of irAEs associated with immunotherapy treatment. The evaluation of the differences in terms of irAEs incidence concerning biological aspects will be integrated by the exploration of their gender dimension.

Project Outcomes

The value of this project is in identifying predictive factors of immune-related adverse events (irAEs), and discovering whether these factors are different according to biology (sex) and gender-related characteristics. This is of great value for cancer patients who are being treated with immunotherapeutics. A key challenge in modern oncology is to match patients with the particular targeted drug most likely to improve their outcome, whilst not being associated with serious adverse treatment events. This project will test our hypothesis that sex and gender related factors play a role in a patient's response to IO's and the occurrence of immune related adverse events. The study results, being obtained in a "real world" (outside experimental clinical trial setting) context, will be more easily translated in a ready to use irAEs timely diagnosis and personalization of treatment approaches. The results of our study will also provide actionable knowledge in the following areas:

a. Translating our findings towards better clinical practice, by determining which patients are likely to suffer from immune related adverse events when they receive immunotherapeutics.

b. Accelerating the translation of biomedical research results towards clinical validation by using our model in future studies to inform selection of patients for specific targeted anti-cancer therapies.

c. Reducing costs in the healthcare system: It is estimated that the EU spent €51 billion on cancer-related healthcare in 2009. The results of this study will result in potential cost savings for the Health Service Executive and Governments as we will identify a specific cohort of patients likely to respond to these treatments. This will reduce the cost burden on both patients and healthcare providers.

Team members

	Woman	Man	Other
Gender balance in the whole consortium	17 (68%)	8 (32%)	0 (0%)
Presence of women as lead researchers/PIs	3 (75%)	1 (25%)	0 (0%)
Gender Experts in the team	1 (100%)	0 (0%)	0 (0%)
Subsequent team members trained	1 (100%)	0 (0%)	0 (0%)

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Contribution to the achievement of UN Sustainable Development Goals (SDGs)

One of the goals of the new global Sustainable Development is to set a world with equitable and universal access to health care and social protection. It is well known that the response to therapies or their adverse events can differ between female and male patients. Some physiological parameters are different in men and women and affect the absorption of drugs, their mechanism of action, and the subsequent elimination of drugs. Despite these differences, all medical practice today codified by Evidence Based Medicine and by Guidelines is based on evidence obtained from large trials conducted almost exclusively on one sex, mainly male. Thus, biomedical knowledge and practices are pretty far from being equitable and gender neutral.

This research can contribute to understanding the mechanisms associated to the difference in the incidence of immune-related adverse events in female and male cancer patients treated with immunoterapic agents. This could identify personalised treatment for patients who will undergo treatment with immunotherapeutics, for instance adjusting the dosage of drugs according to the individual risk of developing immune related adverse events. The research falls under the umbrella of “gender medicine” (which, according to the WHO indication, is defined as the study of the influence of biological (defined by sex) and socio-economic and cultural (defined by gender) differences on the state of health and disease of each person), and can contribute to the achievement of equitable medical treatment.

Differences/inequalities between women and men highlighted by the project

We have highlighted that there were differences in irAE outcome between women and men in favour of the latter, associated to differences in quality of life at baseline and even after one immunotherapy cycle, and in intersectional variables, but not any difference/inequality in other aspects (such as, for instance, their oncologic treatment).

The results obtained so far highlight the importance of focusing on intersectional variables and quality of life measures to i) discover irAEs inequalities between female and male patients; ii) discover more frail subgroups to be monitored more strictly (e.g. anxious/fearful); iii) characterize patients at higher irAEs risk: in order to allow timely diagnosis and personalization of irAEs treatment approaches and reduce ICI interruptions (especially for female patients) and maximize ICI efficacy. This ultimately contributes to equitable medical treatment, ensuring that interventions are inclusive and effective for all individuals.

Positive impact of the project on gender equality/scientific evidence on gender in the field

Our clinical trial inclusion criteria and the study results ensured we recruited cancers which were represented in both male and female patients. G-DEFINER is expected to impact on scientific knowledge on sex and gender inequalities in the field of oncology, by highlighting sex and gender differences on the occurrence of immune-related adverse events. This, in turn, will have a positive impact on management of patients who will undergo treatment with immunotherapeutics, thus improving clinical practice and decision making in relation to the individualized anticipated toxicity profile.

Socio-economic impact; involvement of policy makers/civil society

Civil society organizations were not involved in G-DEFINER at the moment, because the immediate impact of the research will be on patient’s bedside. We expect to translate our findings towards better clinical practice, providing a pathway to identify those patients who will likely suffer from immune-related adverse events (irAEs), and develop signature which can be used as biomarker of irAEs. The information generated by G-DEFINER will be of especial importance to both clinicians and pharmaceutical companies, because it will allow them to identify a personalised treatment for patients who will undergo treatment with immunotherapeutics. Towards completion of our project, we will engage with pharmaceutical companies to discuss how future clinical trials can utilise our results.