



Analysis of the association between adverse events and outcome in patients receiving a programmed death protein-1 or programmed death ligand-1 antibody

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Since their discovery, new immunotherapies have demonstrated their ability to induce durable tumor responses, which have significantly improved long-term survival in patients with different types of metastatic disease. Among the most effective strategies of cancer immunotherapy, the use of monoclonal antibodies against inhibitory immune checkpoint molecules affecting T-cell activation, such as protein death-1 (PD-1) and protein death ligand-1 (PD-L1), represents one of the main investigation areas in cancer research today (1).

Despite the significant benefit that checkpoint inhibitors have represented for metastatic patients, these therapies can promote the activation of autoreactive T-cells resulting in profound inflammatory and unique immune-related adverse events which may be life-threatening and can cause a reduction of the optimal medication dose or treatment discontinuation (2). Although these complications may represent an important impediment for the success of checkpoint blocking therapies, there is a need to understand if the development of autoimmune adverse events may be related with the activation of the immune system and subsequent patient outcome.

In their recent article, Maher *et al.* evaluate the relationship between the development of adverse events and patient outcome, in terms of response and overall survival,

among 1,747 patients with metastatic or locally advanced urothelial cancer who received an anti-PE-1/PD-L1 inhibitor in seven clinical trials that led to product approval by the FDA (3). Provided that systemic corticosteroids could cause immunosuppression and interfere the immune response, they also ask if the use of these substances would affect the duration response.

The authors find that patients who respond to PD-1/PD-L1 blocking antibodies are more likely to report a related adverse event of special interest (AESI) or related immune-mediated adverse event (imAE) regardless the duration of treatment. They also find that the use of systemic corticosteroids neither appear to affect the chances of developing a response nor duration of response.

As the authors observe, both the duration of observation for AESIs/imAEs and the ability of clinicians involved in cancer patients care to correctly identify which adverse events are actually caused by the use of PD-1/PD-L1 inhibitors represent limiting factors for this type of study which justify the need to develop clinical guides and updated training that allow for the correct definition and management of AESIs/imAEs related to the corresponding drug.

The authors also highlight the existence of significant differences in the percentage of responding patients with a related AESI/imAE, which leaves an open-ended question

of whether related AESIs that occur before response and other factors, such as AESI grade, may be predictive of patient outcome, which could have important clinical implications. In this respect, it is necessary to highlight the importance of setting the limits in which adverse events must lead to treatment discontinuation. Accordingly, the development of biomarker panels that allow for patient selection and predict patient response should also be considered, as well as the study of all the different variables that could affect the intensity of related AESIs/imAE, such as drug administration sequence or delay.

Suggested improvements could include the need to improve current understanding of the relationship between systemic immune activation and clinical response to immune therapies in order to develop novel strategies for both patients who are intolerant or refractory to steroids as well as for patients presenting life-threatening adverse events. Basic studies in this area are already showing promising results about the potential value of non-conventional treatments to mitigate AESIs/imAE (4).

Despite the limitations described in the study, provided the large population of patients and the number of trials, their conclusions result convincing and would be useful in clinical practice for patients affected by metastatic or locally advanced urothelial cancer treated with PD-1 or PD-L1 inhibitors.

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Footnote

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