Determining predictive factors for immune-checkpoint toxicity

Cancer Immunology and Immunotherapy: Response to Letter to Editors

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Dear Editors,

We read with interest the correspondence from Dr Hansen and colleagues (Hansen et al Cancer Immunol Immunother 2016) with regards to their case of immune checkpoint-induced insulin-dependent diabetes mellitus. Especially noteworthy was that the diabetes in their case resolved after cessation of pembrolizumab. Their management paralleled ours in that insulin was initiated and no steroids were given. Our patient continued pembrolizumab beyond the onset of her diabetes (after cycle 3) and in total she received 17 cycles of treatment, until disease progression. No other immune-related toxicities were observed. [1] She remained insulin-dependent until her death in March this year with stable insulin requirements.

Given immune checkpoint inhibitors are increasingly used across several different tumour types and some of the associated toxicities can have long-term implications, there is an argument for early identification of those patients who may be predisposed to developing certain side effects. This would enable more careful screening, especially for conditions such as diabetes where acute complications such as ketoacidosis may be life-threatening. Pre-emptive treatments, once identified, may also be activated.

Human Leukocyte Antigen (HLA) typing holds promise as a means to identify those with

vulnerabilities to autoimmune diseases such as rheumatoid arthritis, diabetes and coeliac disease in the general population. HLA is a system of genes that encodes the proteins responsible for antigen presentation to various immune cells, including cytotoxic T-lymphocytes (CTLs). Looking for a predisposing HLA type for the development of autoimmune conditions is not a routine test. HLA type has been associated with various autoimmune diseases by means of complex, multilocus effects.[2] Our patient had the autoimmune diabetes high-risk genotype DRB1*04, DQB1*0302 (HLA A2 DR4 DQ8), which is associated with developing Type 1 diabetes in childhood. Whether the patient reported by Dr Hansen and colleagues also had a similar high-risk genotype would be interesting to know, especially given the insulin-dependence was only short-term in their case. This would strengthen evidence for a link between a predisposing HLA genotype and the development of an autoimmune condition triggered by treatment with a checkpoint inhibitor.

Other biomarkers for autoimmune toxicity, or indeed resistance to such toxicity, are being pursued. Gut microbioma and its association with anti-CTLA4-induced colitis is one such example.[3] In a cohort of 34 patients, the intestinal microbiota was studied before and after development of gut inflammation due to ipilimumab. In this cohort, enrichment of members of the Bacteroidetes phylum was demonstrated in the colitis-resistant patients (24 of 34 patients). These bacteria may stimulate the differentiation of T-regulatory cells, leading to reduced inflammation. Whether deliberate acquisition of greater numbers of commensal Bacteroidetes species prior to treatment may be of benefit is yet to be explored. In theory, this approach may provide local protection without compromising immune function at other sites. Further investigation is warranted.

There is also the counter-argument that knowledge of vulnerability to a certain toxicity may just increase anxiety, without changing management. Generally speaking, immune-related adverse events should be identified and managed promptly. When faced with a chance of prolonged remission in the context of stage IV melanoma for instance, development of a manageable autoimmune disorder may seem a small price to pay. Implications may be lifelong, however, and quality of life can be significantly impacted. As development of biomarkers enables more tailored treatment selection and as our therapeutic repertoire gains precision, knowing patients' vulnerabilities to certain toxicities will become more relevant. Thus, research in this area should be supported.

In addition, having clinicians willing to share their experiences of unusual and challenging cases is important to help optimise the care of patients suffering from rare toxicities of immune checkpoint inhibitors. This is especially relevant since an increasing number of patients are being treated worldwide with these agents and therefore infrequent autoimmune toxicities will become more prevalent.

Disclosures

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