Immune checkpoint inhibitor therapy

A double-edged sword?

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Cancer and autoimmunity can be viewed as differing consequences of deranged immune responses. The overexpression of certain molecules could result in development of cancer (failure of the immune system to control tumor cell growth), whereas oversuppression of the same molecules could lead to autoimmunity (failure of the immune system to regulate autoreactive responses). Hence, finely balanced immune surveillance against cancer and autoimmunity is critical.

Immune checkpoints are cell surface proteins that play a key role in maintaining self-tolerance, preventing autoimmunity, and modulating the duration and amplitude of immune responses in order to protect tissues from excessive inflammatory reactions.[1] Several immune checkpoint molecules have been identified that either activate or inhibit immune responses. Two inhibitory molecules, which have been characterized and translated from bench to bedside, are cytotoxic lymphocyte-associated protein 4 (CTLA-4) and programmed cell death-1 protein (PD-1).[2]

Tumor cells are able to escape from immunologic destruction through several mechanisms, including the exploitation of certain immune checkpoint pathways, particularly against T cells specific for tumor antigens.[1–3] As a consequence, blockade of negative immune checkpoint molecules, which can unleash antitumor immunity, has become a promising therapeutic approach against cancer. Indeed, monoclonal antibodies that block the inhibitory immune checkpoints CTLA-4 and PD-1 have, of late, proved effective even in patients with advanced cancer and opened a new era of cancer immunotherapy; however, clinical benefit is limited to certain subsets of patients and only a minority achieves the promise of long-term survival.[2,3]

Despite clinical benefit, immune checkpoint inhibitors can lead to imbalances in immunologic tolerance that may result in exaggerated uncontrolled immune responses, as inflammatory or autoimmune disorders targeting different organs and tissues.[4] There have been several reports of neurologic diseases, including immune-mediated polyneuropathies, Guillain-Barré syndrome, myasthenia gravis, posterior reversible encephalopathy syndrome, aseptic meningitis, enteric neuropathy, transverse myelitis, and immune-mediated encephalitis, in patients treated with immune checkpoint inhibitors.[5] As the clinical applications of immune checkpoint inhibitors are burgeoning, it is essential to recognize and treat these adverse events, as early treatment increases the odds of a complete recovery.

In this issue of *Neurology*®, Suzuki et al.[6] evaluated the frequency and clinical features of myasthenia gravis (MG), following treatment with immune checkpoint inhibitors, using a 2-year safety database of 10,277 patients with cancer who had received monotherapy with either nivolumab (a monoclonal antibody targeting PD-1) or ipilimumab (a monoclonal antibody against CTLA-4). The authors identified 12 MG cases (0.12%) among 9,869 patients with cancer treated with nivolumab, but none among 408 patients treated with ipilimumab.

This study provides useful information about nivolumab-related MG, although it is not conclusive about ipilimumab-related MG because of a relatively low number of patients treated with this agent in the database. First, nivolumab-related MG occurred early after treatment (the shortest interval from the first treatment to MG onset was only 6 days), while most other complications, such as hepatotoxicity, endocrinopathies, or colitis, are usually reported after 4 to 8 cycles of nivolumab treatment.[7] Second, nivolumab-related MG often showed a progressive and severe clinical course with frequent involvement of bulbar muscles and frequent need for respiratory support. Many patients needed assisted ventilation (mean duration of 54 days) and 2 persons died. Third, myositis or myocarditis with marked elevation of serum creatine kinase levels were frequently associated with MG in this cohort. This finding is surprising when considering that the co-occurrence of myositis with idiopathic MG is uncommon. Fourth, the vast majority of patients with myositis or myocarditis rapidly progressed to respiratory crisis and, on the whole,

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the associated muscle inflammatory disease seems to have contributed to patients' clinical symptoms, as the authors acknowledged.

It is also worth noting that a patient with colon cancer treated with an inappropriately low dose (0.3 mg/kg) of nivolumab developed severe MG and myositis, requiring respiratory support and emergency treatment. This finding, together with early occurrence, suggests that immune-related neurologic complications can occur regardless of dose and duration of nivolumab treatment.

Immunotherapy is an encouraging approach to cancer treatment, and immune checkpoint inhibitors have been approved for a variety of tumors. The safety profile of these agents is specifically linked to their effects on immune surveillance. Immune-mediated neurologic diseases are rare adverse events, as this study proves for MG. However, physicians must be aware of potential neurologic complications, because of their often severe and rapidly progressive course that requires prompt diagnosis and aggressive treatment. It would be helpful to identify prospectively patients at risk of developing immune-related adverse events with immune checkpoint therapies. In this respect, the occurrence of MG after treatment with ipilimumab is interesting, as polymorphisms in CTLA-4 locus have been associated with the disease.[8] Another crucial question is whether immune-related adverse events occur at a higher rate in patients with underlying autoimmune diseases. The observation that 2 of 12 patients with nivolumab-related MG had preexisting autoimmune disorders may be relevant, but future studies are needed to address this question.

Immune checkpoint inhibitors have a dramatic therapeutic effect. A better understanding of their interaction with the immune system will hopefully improve their benefit-to-risk ratio and will inform us how to make better use of these powerful agents.

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