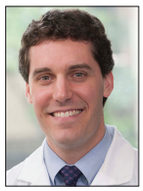
ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

Section Editor: Mark J. Ratain, MD

Toxicities of Checkpoint Inhibitors: Causes and Management



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H&O What are some of the approved checkpoint inhibitors?

MP The US Food and Drug Administration (FDA)-approved checkpoint inhibitors fall into 2 broad categories: the cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) inhibitors and the programmed death (PD-1)/programmed death ligand 1 (PD-L1) inhibitors. The CTLA-4 inhibitor ipilimumab (Yervoy, Bristol-Myers Squibb) is approved by the FDA as monotherapy for metastatic melanoma. The PD-1/PD-L1 blockers include pembrolizumab (Keytruda, Merck), nivolumab (Opdivo, Bristol-Myers Squibb), atezolizumab (Tecentriq, Genentech), durvalumab (Imfinzi, AstraZeneca) and avelumab (Bavencio, EMD Serono/Pfizer).

These agents are approved for a variety of malignancies, which currently include lung cancer (pembrolizumab, nivolumab, atezolizumab, and durvalumab), melanoma (pembrolizumab and nivolumab), bladder cancer (atezolizumab, durvalumab, and avelumab), kidney cancer (nivolumab), and Merkel cell carcinoma (avelumab).

H&O What is the mechanism of action for checkpoint inhibitors?

MP Checkpoint inhibitors disable a normal regulation step of the immune system. The immune system is tightly regulated, so that it acts when it should and stops when it should. In the setting of cancer, there is a theory that the immune system stops too often. Checkpoint inhibitors remove the stop signals on the immune system, allowing it to act more aggressively against the cancer.

H&O Is there a central cause of the adverse events associated with checkpoint inhibitors?

MP It is believed that removing the stop signals in the immune response increases the aggression of this response. When the immune system is less regulated in this way, it is more apt to attack normal healthy tissue, which leads to adverse events.

H&O What are the most common adverse events?

MP Inflammatory reactions involving the skin and the gastrointestinal tract are among the most common adverse events seen with checkpoint inhibitors. Moderate to severe side effects occur in approximately 10% to 20% of patients treated with PD-1 or PD-L1 drugs, in approximately 30% of patients treated with ipilimumab, and in approximately 50% to 60% of patients treated with ipilimumab in combination with a PD-1–type drug.

H&O How are these adverse events managed?

MP The first treatment for skin reactions is usually topical corticosteroids. For significant gastrointestinal side effects, management usually consists of an oral corticosteroid. Depending on the severity and the patient's response to oral corticosteroids, additional immunosuppressants can be used for the skin, gastrointestinal system, or most other types of side effects.

H&O Does the use of immunosuppression to treat side effects from immunotherapy impact efficacy or prognosis?

MP Most studies have suggested that using immunosuppression to treat side effects does not impair treatment efficacy. The one exception concerns hypophysitis, which is pituitary inflammation. A study in patients treated with corticosteroids for pituitary inflammation suggested that higher doses were linked to inferior outcomes compared with lower doses. No other studies have found a similar correlation, but research is ongoing.

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H&O Are there any other less-common adverse events of note?

MP There are some rare but potentially severe and/or permanent toxicities, which are worth mentioning to patients. Patients can develop insulin-dependent diabetes, which is believed to be caused by an inflammatory reaction within the pancreas. Another potential adverse event is serious inflammation of the heart and lungs. This rare event (<1%) can be fatal.

H&O Are there certain patient populations at higher risk for adverse events from checkpoint inhibitors?

MP It is not known why adverse events occur in some patients treated with checkpoint inhibitors but not others. It is therefore difficult to determine an individual patient's risk profile. There is the potential for a higher risk of adverse events among patients who have baseline autoimmune disorders, such as rheumatoid arthritis or inflammatory bowel disease. These patients should still be considered candidates for immunotherapy with immune checkpoint inhibitors, but the choice should be made in multidisciplinary collaboration with their other physicians and with careful consideration of alternative treatment options.

H&O Do adverse events differ when checkpoint inhibitors are used in combination with other therapies?

MP Adverse event profiles differ when immune checkpoint inhibitors are combined with other agents. The adverse events differ depending on the combinatorial partner. For example, the combination of CTLA-4–blocking antibodies and PD-1–blocking antibodies will cause more side effects overall because the immune response is being enhanced in 2 different, complementary ways. Studies combining checkpoint inhibitors with chemotherapy show that several chemotherapy-type toxicities can arise. It is important to consider all of the drugs in the cocktail when administering immunotherapy with other types of cancer drugs.

H&O How do the adverse events of checkpoint inhibitors differ from those seen with chemotherapy?

MP The adverse events associated with chemotherapy are immunosuppressive, whereas those associated with immunotherapy are immunostimulatory. In most cases, the adverse events seen with chemotherapy manifest in a classic, temporal way. After administration of chemotherapy, the patient may be tired for a few days. Predictably, 7 to 14 days after treatment, the patient's blood counts will decrease owing to bone-marrow suppression. With immunotherapy, the timing of adverse events is less predictable. However, they usually occur within the first few months of treatment.

H&O What do you tell your patients about adverse events when you are initiating treatment with checkpoint inhibitors?

MP I explain that the goal of therapy is to turn on their immune response to help fight their cancer. Sometimes, however, the immune response becomes too strong and tries to fight not only the cancer, but also the normal healthy body tissue. When that occurs, patients may experience side effects, and it may be necessary to dial back the immune response with the use of tailored immunosuppression, which is usually temporary. The degree of immunosuppression is tailored based on the nature and severity of the side effects. For example, mild-to-moderate side effects may require only a short course of oral corticosteroids. Severe liver inflammation, however, may require many weeks of corticosteroids and possibly additional immunosuppression, such as with mycophenolate mofetil. Immunosuppression to treat an ongoing side effect can quickly restore the patient's quality of life.

H&O How do you monitor patients for toxicities during treatment with checkpoint inhibitors?

MP When a patient of mine is starting immunotherapy,

I first describe the side effect profile. At each subsequent visit, which usually occurs approximately every 3 weeks, we evaluate any symptoms that might have arisen. Additionally, we perform blood tests to assess asymptomatic toxicities, such as inflammatory hepatitis. We review the patient's symptoms at each visit before the next dose of immunotherapy.

H&O Do you think that future checkpoint inhibitors might have different toxicity profiles?

MP Absolutely. The goal with immunotherapy approaches is to continue the anticancer effects of the immune boost without the toxicity. I am hopeful that as we learn more about how the immune response mechanistically interacts with the cancer, it will be possible to develop newer immune checkpoint inhibitors, and newer immunotherapies in general, that preserve an immune response against cancer without damaging healthy tissue. I expect that over time, there will be different side effect profiles for different checkpoint inhibitors, just as the profiles differ between the CTLA-4 antibodies and the PD-1/PD-L1 antibodies. With each new class of immune checkpoint inhibitors, there may be overlapping or perhaps distinct toxicities that will need to be considered when monitoring the patient.

Disclosure

Dr Postow has received consulting fees from 2015 to the present from BMS, Merck, Array BioPharma, Novartis, Incyte, NewLink Genetics, and Aduro. He has received honoraria from BMS and Merck, and institutional support from BMS, Rgenix, Infinity, Merck, Array BioPharma, and Novartis.

Suggested Readings

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Postow MA, Sidlow R, Hellmann MD, et al. Immune-related adverse events associated with immune checkpoint blockade. *N Engl J Med*. 2018;378(2):158-168.

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