Novel Melanoma Therapies and Their Side Effects

Noelani González, MD; Désirée Ratner, MD

PRACTICE **POINTS**

- Immune checkpoint inhibitors can cause immune-related adverse events (irAEs), which most commonly involve the skin but also involve the gastrointestinal, hepatic, endocrine, and neurologic systems.
- These irAEs can be treated with corticosteroids, tumor necrosis factor α antagonists, and mycophenolate mofetil.

In the last few years, melanoma treatment has been revolutionized by the development of immune checkpoint–blocking antibodies or immune checkpoint inhibitors including ipilimumab, vemurafenib, dabrafenib, trametinib, nivolumab, and pembrolizumab. Although they have shown promising results, they also have caused multiple adverse events (AEs), particularly immune-related AEs (irAEs). Specialists should be familiar with these AEs.

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In the last few years, melanoma treatment has been revolutionized by the development of immune checkpoint–blocking antibodies or immune checkpoint inhibitors. These drugs act through receptor or ligand blockades at certain points along the immunologic cascade to enhance the immune system's ability to fight malignancies.[1] In 2011, the US Food and Drug Administration approved ipilimumab, an inhibitor of cytotoxic T-lymphocyte antigen 4 (CTLA-4), for treatment of patients with unresectable or metastatic melanoma. Other immune-modulating agents followed thereafter. Vemurafenib and dabrafenib, 2 selective BRAF inhibitors, were approved in 2011 and 2013, respectively, and trametinib, a mitogen-activated extracellular signal-regulated kinase 1 (MEK1) and MEK2 blocker, was approved in 2013. These agents are being used to treat patients with activating *BRAF* or *NRAS* mutations.[2,3] Nivolumab and pembrolizumab, which target programmed death receptor-1 (PD-1) and programmed death ligand 1 (PD-L1), respectively, were approved in 2014. Furthermore, phase 2 and 3 trials are ongoing for patients with unresectable stage III or IV melanomas harboring activating c-KIT mutations, which are rare and usually are found in acral or mucosal melanomas. The multikinase inhibitors imatinib, sunitinib, dasatinib, and nilotinib are being used in clinical trials for this purpose and are not yet approved.[4]

Although immune checkpoint inhibitors have shown promising results, they lack direct activity against malignant cells. The nonspecific enhanced immune system response promoted by these drugs has been shown to cause multiple adverse events (AEs). A subset of these side effects has been termed *immune-related AEs* (irAEs), which occur secondary to reduced tolerance to antigens previously recognized as self-antigens, leading to immune-related side effects.[5] The majority of these AEs involve the skin and are mild to moderate in severity; however, other organ systems (eg, gastrointestinal, hepatic, endocrine, and neurologic systems) also may be affected. Most of the toxicities have been successfully treated with immunosuppressive agents such as corticosteroids, tumor necrosis factor α antagonists, and mycophenolate mofetil.[6]

Dermatologic Side Effects

The most common AEs associated with immune checkpoint inhibitors are cutaneous reactions, which

Both from the Icahn School of Medicine at Mount Sinai, New York, New York. Dr. Ratner also is from Mount Sinai Beth Israel, New York, New York.

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Correspondence: Désirée Ratner, MD, Mount Sinai Beth Israel, 325 W 15th St, New York, NY 10011 (dratner@chpnet.org).

commonly present after 2 to 3 weeks of treatment.[7] Approximately 50% of patients receiving ipilimumab (CTLA-4 inhibitor) will experience cutaneous reactions, including erythematous, reticulated, or maculopapular rashes.[8] Vitiligo and Sweet syndrome also have been observed.[9,10]

Antibodies against PD-1 and PD-L1 have been associated with oral mucositis and dry mouth.[11] Most patients treated with BRAF, MEK, and KIT inhibitors also experience dermatologic AEs. Rashes caused by BRAF inhibitors commonly are maculopapular to verrucous and hyperkeratotic. Keratoacanthomas, squamous cell carcinomas, and other hyperkeratotic lesions such as verruca vulgaris, actinic keratoses, and milia have been reported, usually in sun-exposed areas.[4,12,13] Other types of keratotic lesions have been observed, such as areolar hyperkeratosis with vemurafenib (BRAF inhibitor).[14] Photosensitivity, panniculitis (eg, erythema nodosum), and mild alopecia also have been reported.[15] Radiosensitization and radiation recall also have been reported in patients treated with BRAF inhibitors.[16-19] Cutaneous reactions observed with MEK inhibitors are acneiform to papulopustular and appear in seborrheic areas such as the face and chest.[4] In contrast to BRAF inhibitors, increased rates of squamous cell carcinomas and keratoacanthomas have not been reported with MEK inhibitors. Severe cutaneous effects such as toxic epidermal necrolysis and Stevens-Johnson syndrome may occur, and although rare, treatment should be discontinued in these cases.

Gastrointestinal Tract Side Effects

Gastrointestinal (GI) tract side effects commonly result from treatment with immunomodulators, usually occurring after 6 to 7 weeks.[7] Most patients will experience mild to moderate GI adverse effects (eg, diarrhea), but a few patients have had episodes of colitis, some of which have been fatal.[20] Diarrhea and other GI effects are more common in patients treated with ipilimumab, occurring in approximately 30% of patients,[20] in comparison to 1% to 2% of those treated with PD-1 and PD-L1 inhibitors.[11,21]

Liver abnormalities and asymptomatic elevations in liver enzymes can occur with KIT, BRAF, CTLA-4, and PD-L1 inhibitors.[11,20-23] More serious abnormalities such as symptomatic hepatitis and fever are mostly seen with CTLA-4 inhibitors.

Endocrinologic Side Effects

Immune-related AEs also can affect the pituitary, adrenal, and thyroid glands. These events occur after an average of 9 weeks and usually consist of nausea, headache, and/or fatigue.[7] Hypophysitis and hypothyroidism are the most common endocrinopathies reported based on characteristic laboratory or radiographic findings and are observed most often with CTLA-4 inhibitors, though they also have been reported with PD-1/PD-L1 blockers.[24,25] Ipilimumab-induced thyrotoxicosis also has been reported, though it is far less common than hypothyroidism.[26]

Other Side Effects

Other irAEs that are less common include neurologic side effects ranging from Bell palsy[27] and Guillain-Barré syndrome[20] to paresthesia, as well as pancreatitis,[28] ophthalmologic reactions,[29-33] nephritis,[34,35] and hematologic side effects.[36-38] One distinctive AE is lung toxicity, which has been reported with PD-1 inhibitors and presents as cough, dyspnea, or pneumonitis early in treatment.[21]

It is unclear whether immunomodulating agents exacerbate autoimmune diseases. Patients with autoimmune diseases were not included in the clinical trials but reportedly have been treated with ipilimumab without exacerbations. Nevertheless, there has been a report of worsening multiple sclerosis in a melanoma patient treated with ipilimumab.[39]

Conclusion

Immunomodulators have dramatically improved the survival and care of patients with unresectable melanomas. Because of their mechanism of action, they have the capability to produce substantial toxicity. Although most AEs are mild, lethal side effects can ensue. Therefore, all specialists treating patients with melanoma should be familiar with these side effects and their treatment options, as survival rates and survival times will be increasing over the next few years. Rapid AE identification and treatment can improve patient outcomes and optimize the therapeutic potential of these medications. Because immune checkpoint inhibitors are fairly new, further studies are needed to assess irAEs and the long-term impact in patients treated with immunomodulators.

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