Ipilimumab: A New Era in Metastatic Melanoma Management

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The development of ipilimumab (Yervoy) and its approval by the US Food and Drug Administration (FDA) in March 2011 have opened a new era in the treatment and management of patients with metastatic melanoma. The continued innovation in cancer drug development has been focused on a different mechanism of action that engages the patient's own immune system in attacking malignancy in contrast to the more traditional myelosuppressive drugs that have been used in the past half century to kill rapidly dividing cancer cells.

The hallmark of successful therapy for melanoma has always been surgical excision. Although curative, this method does not necessarily reduce the likelihood of recurrence. To minimize this potentially lethal risk, interferon therapy has historically been instituted, administered as 1 month of induction therapy, followed by 11 months of injections; however, this is an intense regimen for patients, who therefore benefit from a multidisciplinary approach to treatment that can include pharmacy management of symptoms. Even then, the disease can recur and progress. As a result, biimmunotherapy, a rudimentary type of immunotherapy, was developed in the late 1990s. Like interferon therapy, however, biimmunotherapy is intense and necessitates hospital services, sometimes including the intensive care unit.

Despite these efforts, melanoma all too often still claims a large number of lives. Although the cure rate is high for patients whose disease is detected early and surgically resected, the 5-year survival rate is fairly low for those with disease that has metastasized—less than 15% according to the 2010 data from the American Cancer Society. In the United States alone, just under 70,000 new cases of melanoma were diagnosed in 2010, and 8700 deaths occurred, mostly from advanced or metastatic disease.

For some time now, researchers have focused on the development of immune stimulants and vaccines designed to enlist a patient’s immune system to attack cancer cells, culminating with the March 25, 2011, FDA approval of ipilimumab—the first T-cell-mediated therapy for unresectable or metastatic melanoma. This drug is a monoclonal antibody that binds CTLA-4 (cytotoxic T-lymphocyte antigen 4), thereby blocking its interaction with the ligands CD80/CD86. This appears to result in T-cell overproduction, which in turn stimulates an activated immune response.

My professional experience with 5 patients provides a unique perspective for those who have not yet treated any patient with this novel medication. My center is a multidisciplinary center involved in a robust clinical trials program that includes active pharmacist participation in symptom management. In one of these trials, 3 of our patients were treated with ipilimumab before the FDA approval of the drug; in addition, 1 patient was in the expanded access program created by Bristol-Myers Squibb (BMS), while awaiting final FDA approval for the drug, and 1 patient had just begun to receive it on April 11, 2011, the day ipilimumab became commercially available.

Our experience with these 5 patients shows that the drug indeed has a novel mechanism of action and it quite simply “revs up” the immune system, and then stands back. There have been many previous attempts to develop vaccines and other products to stimulate the immune system in patients with melanoma by killing the melanoma-affected cells, but ipilimumab is the first product to receive FDA approval.

Although the activity of ipilimumab is impressive, it is also associated with a wide range of potential toxicities, which can manifest in almost any system in the body, including gastrointestinal, liver, skin, neurologic, and endocrine toxicities that are highlighted in the risk evaluation and mitigation strategy (REMS) for this agent. There is currently no way to predict the focus of any of the immune system’s responses.

What is predictable is the response to ipilimumab therapy, which is associated with a 34% risk of death. Unlike traditional chemotherapy, the goal with ipilimumab is not to deliver as much drug as possible but rather to stimulate the immune system properly—only 4 doses maximum can be given, according to the FDA approval. Also noteworthy is the agent’s cost, which has captured much media attention. The price is in the same range as the prostate cancer drug sipuleucel-T (Provenge). Both drugs have a limited number of cycles (3 administrations for sipuleucel-T and 4 for ipilimumab).

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Iiplimumab will be distributed only through the wholesaler McKesson and the distributor Oncology Supply.

Because ipilimumab is approved with a REMS program, BMS has designed a comprehensive plan that employs sales and medical science liaisons in coordinated teams to ensure clinicians are properly educated about the risks and benefits of the drug. The REMS program also includes a medication guide for patients. At its center is a wallet card that a patient carries to alert any potential urgent care and emergency department physicians to the possibility of immune-related toxicity and the resultant need for steroids. The copious and early use of steroids has been found to ameliorate many toxicity-related problems, because the toxic effects in this case are not from myelosuppressive chemotherapy but rather from stimulated T lymphocytes.

In addition, BMS has initiated a surveillance and peer-to-peer education program in which medical service liaisons will contact clinicians within a very tight window of a few days after receiving a new order for ipilimumab, to provide educational services and follow-up.

As the Pharmacy Practice Editor of the Journal of Hematology Oncology Pharmacy, I urge those not experienced with this novel agent to accept any offer of education or assistance regarding its use. Despite the associated risks involved, this new therapy offers benefits beyond the standard myelosuppressive agents or monoclonal antibody drugs that we have become accustomed to in the past decade and a half, when these therapies proliferated on the oncology scene.

It is certainly not my wish to deter clinicians from using this drug, but it does involve many occasions for errors, including the aggressive use of corticosteroids as the primary response to almost any toxicity— which is counterintuitive for many clinicians. Getting the appropriate education about the use of this drug is therefore crucial for preventing adverse outcomes and potentially denying other patients the opportunity for this therapeutic option. Although cost has become a major issue, nothing costs as much as a therapy that is not used successfully or safely.

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The FDA has been criticized for having approved the fewest number of new drugs in decades, but the approval of ipilimumab offers a novel agent with promising therapeutic outcomes in an area of oncology that has had few worthwhile choices.

Author Disclosure Statement
Dr Tyler is on the Speakers’ Bureau of Bristol-Myers Squibb and Eisai Pharmaceuticals.

References