Creating Clarity in Metastatic Melanoma: Optimizing Treatment and Improving Outcomes

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Abstract

Checkpoint inhibitors and oncolytic vaccine therapy have transformed the management of metastatic melanoma. This article presents the diagnosis and treatment landscape for metastatic melanoma, including clinicopathologic features of the disease, approved and emerging therapeutics, and strategies for integrating contemporary standard-of-care management practices.

In less than a decade, metastatic melanoma has transformed from a dreaded diagnosis to one of oncology's biggest success stories. In 2011, overall survival for patients with metastatic melanoma was approximately 8 months with chemotherapy (Korn et al., 2008). In contrast, recent data of dual checkpoint inhibition with ipilimumab plus nivolumab have shown median overall survival was not reached at 5 years (Ugurel et al., 2017). Advances with immunotherapy and targeted therapy have dramatically changed the prognosis of patients diagnosed with melanoma. As miraculous as these outcomes may be, however, these novel agents are frequently associated with severe adverse events that require early recognition and management. Furthermore, given the complexity of treatment decisions, collaboration and communication within a multidisciplinary, interprofessional team is imperative.

These topics were discussed at JADPRO Live 2019 by Amanda M. Viereck, PA-C, a medical oncology Physician Assistant at Fox Chase Cancer Center, and Anthony J. Olszanski, MD, RPh, Director of the Phase 1 Developmental Therapeutics Program, Director of the Medical Oncology Melanoma Program, and Vice Chair of the Department of Hematology/Oncology at Fox Chase Cancer Center, in Philadelphia, Pennsylvania.

PATHOLOGIC FEATURES AND IMMUNOTHERAPY POTENTIAL

Ms. Viereck emphasized the importance of using the pathology report to assess patient risk factors. Lymph node involvement is a very important

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factor in determining how aggressive the cancer is, said Ms. Viereck, who noted that the presence of any positive nodes is considered high risk. The presence of ulceration, or the loss of epidermal tissue overlying the melanoma tissue, also poses a greater risk for metastatic disease than tumors that do not show ulceration. A depth of invasion of 0.8 mm or greater is also considered "high risk," as well as any noted lymphovascular invasion. Features associated with better prognoses include regression of tumor tissue and the presence of tumor-infiltrating lymphocytes, which signal that the body's immune system is starting to fight against the cancer cells, Ms. Viereck noted.

As Dr. Olszanski explained, based on data from the MSLT2 trials published in 2017 (Faries et al., 2017), standard of care for patients with microscopic positive lymph nodes changed from complete lymph node dissection to observation with ultrasound of the affected area. Although there was no significant difference in overall survival between cohorts, lymphedema in the surgical arm remains a real risk for patients undergoing complete lymph node dissection, and this can be avoided with observation.

For patients with newly diagnosed stage 4 melanoma, current data support combination therapy with both anti–CTLA-4 (ipilimumab) and anti–PD-1 (nivolumab) compared with single-agent immunotherapy in an unselected population, said Dr. Olszanski. While the response rate is approximately 40% with nivolumab alone, the addition of ipilimumab has demonstrated a response rate of 58% (Wolchok et al., 2017). However, in PD-L1–positive patients, Dr. Olszanski added, a single-agent PD-1 inhibitor may retain efficacy and decrease adverse events.

"5-year overall survival data demonstrate that 52% of patients receiving combination therapy are alive," said Dr. Olszanski, who emphasized that median survival has still not been reached. "Given the duration of these responses, we are now starting to ask ourselves whether a cure is possible, which is truly remarkable" (Figure 1).

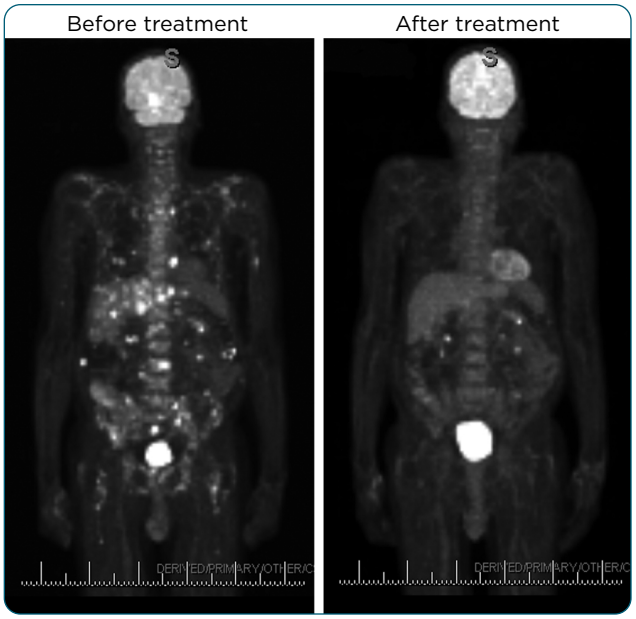

Figure 1. Checkpoint efficacy. Image courtesy of Anthony Olszanski, Fox Chase Cancer Center.

MANAGING TOXICITY

Despite these remarkable outcomes, however, Ms. Viereck noted that immunotherapy can be a "wild card" when it comes to toxicity. Although some symptoms are more common than others, because these agents are stimulating the immune system, they can affect nearly "anything, at anytime," and for a variety of reasons. Thus, vigilance is required from both providers and patients.

After only three doses of dual-agent immunotherapy, for example, one patient experienced symptoms of nausea, vomiting, gastroesophageal reflux disease symptoms, weight loss, early satiety, and anorexia. An emergency endoscopy showed severe active gastritis and duodenitis, which are consistent with immune checkpoint inhibitor therapy. In fact, there was so much inflammation, said Ms. Viereck, that the patient was unable to absorb oral steroids. The patient ultimately was admitted to the hospital where she received high-dose IV steroids. Her symptoms ultimately resolved before resuming treatment with single-agent nivolumab 4 weeks later.

As Ms. Viereck explained, rechallenging with anti–PD-1 monotherapy was still an option for this woman because she was young, had children, had an otherwise good response to treatment, and had limited therapeutic options. According to National Comprehensive Cancer Network (NCCN) Guidelines, permanent discontinuation of a given class of immunotherapy is typically warranted for severe immune-related adverse events induced by that class of agent, but recommendations for re-

challenge allow for clinical judgment depending on toxicity, grade level, and type of immunotherapy (Brahmer et al., 2018). Caution, clinical judgment, and discussion of risks vs. benefits with the patient are key when considering rechallenging with immunotherapy following significant toxicity, Ms. Viereck observed.

Following two additional doses, the patient complained of significant fatigue, headaches, mild nausea, and general malaise. Hypophysitis, inflammation of the pituitary gland and a primary cause of adrenal insufficiency, was diagnosed with a test of cortisol and adrenocorticotropic hormone (ACTH).

"Dermatitis and fatigue are a few of the most common side effects associated with immunotherapy, but immune-mediated side effects can occur across a wide range of organ systems," Ms. Viereck emphasized. "In this case, the endocrine system was affected; we need to have a heightened sensitivity for that possibility, as it is not always easily detected."

ONCOLYTIC VACCINE

In patients with autoimmune-related comorbidities, stimulating the immune system with immunotherapy may not be a viable option. One patient with ulcerative colitis, for example, required active immunosuppression and continued to have intermittent diarrhea and abdominal pain. Because anti–PD-1 or anti–CTLA-4 therapy could cause a flare of this significant comorbidity, talimogene laherparepvec (TVEC), an oncolytic vaccine, was chosen as therapy.

As Dr. Olszanski reported, a randomized phase III trial of 419 patients showed improved response rates with TVEC vs. granulocyte macrophage colony-stimulating factor (GM-CSF) along with a relatively mild side-effect profile: flu-like symptoms, fatigue, chills, fevers, and some pain at the injection site (Andtbacka et al., 2015). The durable response rate was 16% for TVEC vs. 2% for GM-CSF. However, the bigger story, said Dr. Olszanski, was that many of those patients had complete responses.

TVEC is an intratumoral or intranodal injection delivered once every 2 or 3 weeks. The use of TVEC requires special training and sufficient resources and thus is not widely available.

MULTIDISCIPLINARY REVIEW

Given the complexity of treatment decisions, Dr. Olszanski and Ms. Viereck also emphasized the importance of multidisciplinary review throughout the course of therapy. The tumor board is a critical step in the evolution of these patients, said Dr. Olszanski, who discussed the use of an isolated limb infusion for one patient with in-transit melanoma metastases.

"Isolated limb infusion is not FDA recommended, but it is on the NCCN Guidelines as an option for patients," said Dr. Olszanski, who described the surgical technique. "A tourniquet is placed over the top of the extremity, stopping the flow of blood to and from the limb, and catheters are inserted into an artery and a vein so that blood can be circulated through the limb in isolation. Chemotherapy is then infused into the limb via a catheter, allowed to dwell, and then removed."

Although this procedure yielded a promising initial response, said Dr. Olszanski, new lesions appeared on the same leg 8 months later. Additional discussions with the multidisciplinary team and patient followed, and targeted therapy with BRAF/MEK inhibitors was eventually initiated, leading to a response that is ongoing.

BRAF PLUS MEK INHIBITION

As Ms. Viereck reported, there are currently three FDA-approved regimens available for patients with *BRAF*-mutated melanoma. Although all of these are good options, the combination of dabrafenib (150 mg twice daily) and trametinib (2 mg a day) has a total daily pill load of five tablets, compared with 11 to 12 tablets for the other regimens.

"Having to take more tablets per day can be confusing for patients and can cause issues with adherence and timing, so the dabrafenib/trametinib combination is typically a reasonable choice for us," said Ms. Viereck, who also noted subtle differences in side effects.

"Dabrafenib plus trametinib is a great regimen, but it often comes with stubborn pyrexia, or fevers, in these patients," she continued. "You have to be vigilant with the treatment of pyrexia and know when to stop the drug when fever is too high."

In patients with metastatic melanoma, dabrafenib plus trametinib demonstrated an overall

response rate of 64% vs. 51% in patients receiving single-agent BRAF inhibition with vemurafenib (Robert et al., 2015). Duration of response was also better at about 14 months vs. 7 months, said Dr. Olszanski, who also noted that adverse events were "amazingly" lower with the combination vs. single-agent therapy.

"Most of the time, when we combine two different agents, we get a higher adverse event rate, but in this scenario, we actually get a lower adverse event rate," said Dr. Olszanski, who noted that data presented at the recent American Society of Clinical Oncology Annual Meeting showed a 5-year overall survival of 34% in the first-line setting.

"The data presented here today show just how fortunate we are to work in the health-care field at this moment in time," Dr. Olszanski concluded. "Ms. Viereck and I are so filled with hope because we can provide effective medicines to patients in a situation where we once had no improvement in survival. This is extremely gratifying for patients and health-care providers alike."

Disclosure

Dr. Olszanski has consulted for Alkermes, Array, Merck, EMD Serono, Novartis, and Pfizer. Ms. Viereck has no conflicts of interest to disclose. This symposium was supported by educational grants from Array BioPharma Inc., Bristol-Myers Squibb Company, and Merck Sharp & Dohme Corp.

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