Full Spectrum: Efficacy and Toxicity of Immunotherapy in Metastatic Melanoma

Matthew Zibelman, MD, and Anthony J. Olszanski, MD

Abstract

Metastatic melanoma is a devastating disease that has been increasing in incidence and until relatively recently had few effective treatment options. With the approval in 2011 of ipilimumab, a monoclonal antibody against cytotoxic T-lymphocyte associated protein 4 (CTLA-4), however, that has begun to change. Ipilimumab is an immune checkpoint inhibitor, a type of immunotherapy that can down-regulate inhibitory signals affecting T-cell activation to unleash more dramatic anti-tumoral responses and offer the possibility of deep and durable remissions in up to 20% of patients. Use of this and similar agents can lead to characteristic and varied immune-related adverse events (irAEs); however, experience has shown that these can be managed with patient education, early recognition, and judicious use of systemic steroids. Newer immune checkpoint inhibitors such as those that block PD-1 or PDL-1 have shown impressive results in early studies. Most recently, pembrolizumab, an anti-PD-1 antibody, was approved by the FDA for the treatment of patients with melanoma after progression on a CTLA-4 inhibitor and, if clinically relevant, a BRAF inhibitor. This supplement presents the case of a 60-year-old man with an enlarging right neck mass who was found to have disseminated metastatic melanoma. He was started on treatment with the CTLA-4 inhibitor ipilimumab (3 mg/kg intravenous). After the third dose, the patient developed grade 3 uveitis/retinitis and immune-mediated nephritis requiring hospitalization and systemic corticosteroids. Both conditions were considered irAEs secondary to ipilimumab. The patient recovered completely from all toxicities but did not receive further doses of ipilimumab. Nonetheless, the patient experienced a complete radiographic response and at time of writing was 19 months from diagnosis without evidence of disease. (J Natl Compr Canc Netw 2014;12(Suppl 2):S1–S5)

Case Report

A 60-year-old man presented for evaluation of a progressively enlarging right-sided neck mass. The patient reported that he had first noticed the mass about 6 months previously as a small, painless “lump.” The patient denied pain, dysphagia, or dyspnea. He reported no significant weight loss, fevers, or chills, and had not noticed any other masses or unusual skin lesions. He did report mild fatigue. A brief trial of antibiotics was prescribed by a primary care physician but did not have an effect. On his presentation to medical oncology, physical examination revealed a 6 to 7 cm fixed right neck mass with a small, centrally located hyperpigmented area without ulceration. Two smaller, firm but mobile nodules could be palpated just inferior to the dominant mass. No other significant findings were noted on physical examination, and the patient’s ECOG performance status was 0. Past medical history was significant for localized prostate cancer treated with primary radiation therapy to his prostate completed 2 years previously. He also carried diagnoses of hypertension, atrial fibrillation, and nonischemic cardiomyopathy, all well controlled with medications. He had a 14 pack-year smoking history, quitting more than 10 years before presentation. He admitted to consuming 6 to 8 alcoholic beverages per week. He had no significant family history of malignancy. He was employed as a pharmaceutical salesman and denied toxic exposures.

A needle biopsy of the right neck mass was consistent with metastatic melanoma. Molecular testing for BRAF and c-KIT mutational analyses were ordered but not immediately available. No primary lesions were ascertained on a full-body skin examination. Complete staging was performed with a whole-body PET/CT and brain MRI. The PET/CT scan showed bulky right cervi-
Immediately to the hospital for treatment with high-dose systemic corticosteroids. Laboratory evaluation on admission displayed acute kidney injury with a serum creatinine of 2.44 mg/dL, approximately 4 times higher than his baseline. He was diagnosed with immune-related uveitis/retinitis and nephritis, both secondary to ipilimumab. The patient remained hospitalized for 5 days. Renal function returned to baseline, and his energy level improved. He noted steady visual improvement, to grade 1 at discharge.

The patient returned for follow-up 2.5 weeks after discharge. His vision continued to improve, but he had developed new symptoms marked by a pruritic, erythematous, folliculitis-like rash on his scalp associated with frank hair loss. However, his right-sided neck mass was now nearly flat and the left chest wall mass was no longer palpable. He was started on a topical steroid for the alopecia and scalp rash. Systemic steroids were slowly weaned over the course of 1 month. Due to his multiple immune-related adverse events (irAEs) requiring systemic steroids and hospital admission, the patient was informed that no further doses of ipilimumab would be administered. Over the next 8 weeks, his rash subsided and his hair grew back. His vision returned to pretreatment acuity. A PET/CT scan to evaluate for response revealed a very good partial response with hilar lymphadenopathy with a maximum standardized uptake value (SUV) of 67.6. The nodal involvement extended to the right upper shoulder. Additional areas of metastasis included a subcutaneous left chest wall implant, bilateral adrenal gland lesions, multiple mesenteric implants, and bony involvement of the left proximal femur. No brain lesions were identified. Laboratory testing was notable for a lactate dehydrogenase (LDH) of 758 U/L (normal range 313–618 U/L).

Due to his history of prostate cancer, the patient was not eligible for a clinical trial and he was started on treatment with the cytotoxic T–lymphocyte associated protein 4 (CTLA-4) inhibitor ipilimumab at 3 mg/kg. The patient tolerated the first cycle without any events, but on evaluation before his second dose, he noted growth of the right-sided neck mass with overlying skin changes. On examination, the mass appeared larger than 7 cm and extended from the subauricular area to the supravacular space with an enlarging, raised, central hyperpigmented lesion measuring 1.5 X 4 cm. The overlying skin appeared to be blistering but without ulceration or discharge. Additionally, a mass on his left chest wall was now palpable. The patient received his second dose of ipilimumab and was referred for radiation to the right neck mass.

The patient received a total of 20 Gy of radiation to the right neck mass over 5 fractions. He returned for evaluation and the third dose of ipilimumab and reported that the neck mass had continued to grow in size. He also reported visual changes, self-described as a halo around objects, which seemed to improve over the course of the day, along with worsening nearsighted vision. The patient believed these were ongoing chronic changes and that he needed new glasses. Physical examination revealed a 10-cm firm right neck mass. No conjunctival irritation or papilledema was noted. Extraocular movements and bilateral visual reflexes were intact and normal. Molecular testing results became available and demonstrated a V600K BRAF mutation (c.1798_1799GT>AA). The patient was referred to ophthalmology and the decision was made to proceed with the third dose of ipilimumab.

Two weeks later, the patient presented for a toxicity evaluation and was complaining of severe fatigue. Additionally, his vision was worsening, and he could only see shapes, without the ability to differentiate visual details. On examination, marked conjunctival irritation was seen. The patient was admitted immediately to the hospital for treatment with high-dose systemic corticosteroids. Laboratory evaluation on admission displayed acute kidney injury with a serum creatinine of 2.44 mg/dL, approximately 4 times higher than his baseline. He was diagnosed with immune-related uveitis/retinitis and nephritis, both secondary to ipilimumab. The patient remained hospitalized for 5 days. Renal function returned to baseline, and his energy level improved. He noted steady visual improvement, to grade 1 at discharge.

The patient returned for follow-up 2.5 weeks after discharge. His vision continued to improve, but he had developed new symptoms marked by a pruritic, erythematous, folliculitis-like rash on his scalp associated with frank hair loss. However, his right-sided neck mass was now nearly flat and the left chest wall mass was no longer palpable. He was started on a topical steroid for the alopecia and scalp rash. Systemic steroids were slowly weaned over the course of 1 month. Due to his multiple immune-related adverse events (irAEs) requiring systemic steroids and hospital admission, the patient was informed that no further doses of ipilimumab would be administered. Over the next 8 weeks, his rash subsided and his hair grew back. His vision returned to pretreatment acuity. A PET/CT scan to evaluate for response revealed a very good partial response with...
Immunotherapy in Metastatic Melanoma

A decrease in SUV and size in all measurable lesions (Figure 1). The patient continued to show disease regression and at time of writing was 19 months from the initial ipilimumab dose. He has experienced a complete response with no evidence of disease.

Discussion

This case highlights the full spectrum of clinical responses that are possible with the new generation of immunotherapies in metastatic melanoma—from rapidly developing and unpredictable irAEs to impressive and durable disease regressions. Melanoma incidence has been increasing in the United States. It is currently the fifth most commonly diagnosed cancer overall but the most common cancer diagnosed in patients between the ages of 25 and 29.1,2 Ipilimumab has heralded a new era in immunotherapy, offering patients new hope.

Until the FDA approved ipilimumab in 2011, the treatment for metastatic melanoma was limited and offered modest benefit for most patients, while prognosis remained uniformly dismal. At that time, the only systemic FDA-approved therapies for metastatic melanoma were the alkylating agent dacarbazine and high-dose interleukin-2 (HD IL-2). The oral prodrug temozolomide offered an off-label alternative. Other chemotherapeutic modalities had been investigated, but no chemotherapy has improved overall survival for metastatic melanoma.

Alternatively, HD IL-2 was the original immunotherapy for metastatic melanoma.3 Publications in the 1950s illustrated cases of spontaneous primary melanoma regression, suggesting an immune-related phenomenon.4,5 IL-2 was known to play a role in enhancing the body’s innate immune response, but Rosenberg et al6 were the first to show evidence that induced tumor regressions were possible. In subsequent phase II melanoma trials, HD IL-2 showed modest response rates, from 6% to 16%, but the duration of response could exceed 10 years in select patients.7,9 Based on these data, HD IL-2 was FDA-approved for treatment of metastatic melanoma in 1998. However, tempering the excitement was the fact that HD IL-2 use was fraught with potential treatment-related toxicity, including capillary leak syndrome, multiorgan failure, and death.10 Thus, its use has been limited by strict patient selection and to experienced, high-volume centers.

Continued research since the HD IL-2 experience has focused on a more-specific immunotherapy approach, one method of which involves immune checkpoint inhibition (Figure 2). Immune checkpoints are inhibitory pathways regulated via T-cells that serve to control the duration and magnitude of the immune response to a recognized antigen. When the immunosurveillance machinery identifies a malignant cell, it triggers a cytokine cascade designed to activate antitumoral immunity. However, increased tumor cell expression of proteins that hijack these inhibitory immune checkpoint pathways on T-cells dampens the antitumor response and equates to a method of evading detection to thwart immune destruction.11,12 CTLA-4 is an inhibitory receptor located exclusively on T-cells, and it regulates the early stages of T-cell activation.

CTLA-4 marks the first immune checkpoint to be successfully targeted, leading to approval of the first CTLA-4 inhibitor, ipilimumab.12 Ipilimumab is a fully human monoclonal antibody against CTLA-4 that was approved for treatment of patients with metastatic melanoma based on evidence of an overall survival (OS) benefit in 2 randomized phase III trials (MDX010-20 and CA184-024).13,14 The MDX010-20 trial was a 3-arm study that randomized patients with previously treated metastatic melanoma to receive ipilimumab alone at 3 mg/kg, ipilimumab at the same dose plus the melanoma peptide
vaccine gp100, or gp100 alone. Both ipilimumab-containing arms showed improved OS compared with gp100 alone (P<.001).13 The CA184-024 trial was a first-line study comparing ipilimumab at 10 mg/kg plus dacarbazine versus dacarbazine plus placebo. The addition of ipilimumab improved OS from 9.1 to 11.2 months (P<.001).14 Notably, there was not an ipilimumab-alone arm on this trial, potentially calling into question a role for ipilimumab as a single agent in the first-line treatment of patients with metastatic melanoma. However, the drug was approved for use as a single agent in this setting.

Although the survival benefits and response rates (RRs) with ipilimumab were modest (10.9% overall RR in the ipilimumab-alone group in MDX010-20), some patients experienced durable disease control.15,16 In the MDX010-20 second-line study, 18% of the patients who received ipilimumab survived beyond 2 years, compared with only 5% receiving gp100 alone.12,13 Before ipilimumab, the median survival of patients with metastatic melanoma was less than 1 year.17 However, autoimmune-like reactions can occur, from inflammatory states such as dermatitis, enterocolitis, or pneumonitis to less common toxicities such as hypophysitis and uveitis. These reactions have been fatal in some cases. The frequency of grade 3 or 4 irAEs in the ipilimumab-containing arms of the MDX010-120 and CA184-024 phase III studies were 11.6% and 38.1%, respectively. Seven of the irAEs in the MDX010-20 trial led to death; none in CA184-024 were fatal.13,14

As physicians have become more experienced with this agent, however, improved clinical monitoring and prompt, algorithm-based initiation of appropriate treatment (generally steroids followed by tumor necrosis factor inhibitors when needed) have appreciably approved the drug’s safety.18 For example, in the patient discussed in this report, prompt administration of high-dose steroids on diagnosis of uveitis/retinitis and immune-mediated nephritis prevented permanent vision loss and renal failure.

However, an ongoing controversy regards the optimal sequencing of treatment for patients with BRAF-mutated metastatic melanoma. Single agent BRAF inhibitors such as vemurafenib and dabrafenib yield RRs of 48% to 54%, with disease control rates greater than 90%; however, median progression-free survival (PFS) is less than 6 months.19–21 Dual BRAF and MEK inhibition with dabrafenib and tramekinib improves RRs to 76% and median PFS to 9.4 months, but few responses prove to be durable.21 Consensus opinion has led to a therapeutic dogma suggesting that patients with BRAF mutations with high-volume, symptomatic disease should start on BRAF inhibitors for disease control, followed by immunotherapy. Unfortunately, currently available data comparing outcomes of immunotherapy before or after BRAF inhibitors are limited and much of what is available is retrospective. The largest available retrospective study analyzed data for 274 patients at 5 cancer centers who had received any type of immunotherapy before or after a BRAF inhibitor, although only 32 patients received immunotherapy initially (10 patients received ipilimumab).22 Although no difference was seen in PFS or OS based on the order of sequencing, a nonsignificant trend towards improved OS was seen when immunotherapy was given first. Interestingly, treatment with ipilimumab after a BRAF inhibitor was associated with no tumor responses and a poor outcome overall. Whether this result reflects patient selection in this retrospective study or a true change in tumor biology requires further randomized studies.

After decades of little to no advancement in the treatment of metastatic melanoma, the new era of immunotherapy ushered in by the approval of ipilimumab has ignited a firestorm of hope and excitement. The programmed death-1 (PD-1) pathway is another immune checkpoint that works later in the T-cell activation timeline and limits autoimmunity.12 Promising early-phase studies have exhibited even higher RRs as a single agent with similar durability to ipilimumab.23–26 Most recently, pembrolizumab, a PD-1 inhibitor, was approved by the FDA in the second or later-line therapeutic space, based on phase I trial results.25,26 Furthermore, results from a phase III trial of the PD-1 inhibitor, nivolumab, were reported at ESMO 2014. In the CheckMate-037 study, nivolumab was given in the second or later-line setting and revealed an impressive overall response rate of 32%, compared with 11% for patients treated with chemotherapy. Importantly, anti PD-1–induced responses appear to be durable, with the median duration of response not reached. Data for OS are not yet mature. Combining ipilimumab with the PD-1 inhibitor nivolumab in a proof-of-concept phase I study in patients with advanced metastatic melanoma yielded even better clinical responses, with a 40%


