CLINICAL VIGNETTE

Optimism in the Face of Advanced Melanoma

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A 28-year-old female presented to primary care with a two-month history of a progressively painful, and swollen left-sided neck mass. She also reported an associated unintentional ten-pound weight loss and night sweats. She was otherwise healthy with no significant past medical history, surgical history, or relevant family history. She worked in the front office of a medical practice, was married with a young daughter.

On exam, she was found to have a firm and fixed 4 cm by 6 cm mass involving the left supraclavicular and sternocleidomastoid region, with overlying dark pigmentation and skin ulceration. The remainder of her exam was unremarkable. Routine labs showed normal complete blood count (CBC), complete metabolic panel (CMP), and lactic acid dehydrogenase. She underwent fine needle aspiration of the left neck mass, revealing a poorly differentiated malignant neoplasm, not otherwise classified. Open biopsy, revealed melanoma, positive for S100, HMG45, and SOX10 and negative for BRAF and PDL1 (0% expression). Staging imaging with PET-CT confirmed a 6.5 cm soft tissue left cervical neck mass with SUV max of 16.7. No additional FDG avid lesions were identified. Brain MRI was negative for metastatic involvement. She underwent complete dermatologic, ophthalmologic, and gynecologic exams, which were negative for a potential primary site of melanoma.

The patient was diagnosed with oligometastatic malignant melanoma with unknown primary. She was evaluated for surgery with otolaryngology, but her disease was deemed unresectable due to the size and location of melanoma involvement. This decision was validated in a second opinion consultation. Thus, she initiated systemic treatment with combination anti-CTLA-4 with anti-PD1 immunotherapy, ipilimumab and nivolumab. She received two cycles of therapy without complication. Following her third cycle, she presented to her local emergency department with nausea, vomiting, headache, fever, and chills. Her vital signs included a temperature of 39.4º F, heart rate 140 bpm, blood pressure 107/62, with normal respirations and oxygen saturation. Thorough lab investigation revealed a normal CBC and CMP. Her TSH was low at 0.01 with a high free T3 of 5.2 and high free T4 of 1.8. She was diagnosed with thyrotoxicosis secondary to immunotherapy and was initiated on propranolol and methimazole. She was discharged on hospital-day 4 with outpatient endocrinology follow up.

Within one week of discharge, she underwent her fourth and final cycle of combination immunotherapy. Two days later, she presented again to the emergency department with nausea, vomiting, and fever. Vitals signs included a temperature of 39.2º F, heart rate 130 bmp, blood pressure 90/56, with normal respirations and oxygen saturation. Both her complete blood count and basic metabolic panel were normal. Lactic acid was normal at 1.0. TSH was low at 0.01, and her free T4 had normalized to 1.28. Liver function tests were not drawn. On hospital day 4, she was found to have abnormal liver function tests including AST 61, ALT 102, alk phos 86, and T bili of 1.1. On hospital day 6, her AST measured 122, ALT 260, alk phos 346, and T bili 1.7. Hepatitis serologies were negative. She was diagnosed with grade 2 immune checkpoint inhibitor related hepatotoxicity and initiated prednisone at a dose of 1mg/kg. Immunotherapy was held. Four weeks later, her liver function tests had normalized and she slowly tapered off prednisone over the next 8 weeks. In shared-decision making with her medical oncologist, she decided to pursue a re-challenge of immunotherapy with the monotherapy agent nivolumab. After one treatment, she developed grade 1 hepatotoxicity and subsequently permanently discontinued nivolumab. Response assessment with PET-CT after discontinuation showed a complete response, marked by no evidence of disease.

The American Cancer Society estimates that nearly 1.9 million new cases of cancer will be diagnosed in 2021. Of those, melanoma of the skin ranks as the fifth most common cancer among both males and females.[1] However, cancer-related deaths are declining, with 2.2% drop in cancer related deaths from 2016 to 2017 representing the largest one-year drop in cancer mortality ever recorded. This was largely driven by improvements in lung cancer and melanoma mortality,[2] felt to be due in part to the advent and use of checkpoint inhibitor immunotherapy.

Combination immunotherapy for patients with advanced melanoma with ipilimumab and nivolumab has resulted in the longest survival rates to date. This combination was shown in the phase III CheckMate 067 trial to confer improved five-year overall survival rates when compared to either nivolumab monotherapy or ipilimumab monotherapy (52% in combination arm versus 44% and 26% respectively). However, the discontinuation rate was 39% in the combination arm versus only 12-16% in the monotherapy arms.[3] The toxicity profile of immune checkpoint inhibitor therapy is distinct from conventional anti-cancer therapy. Immune-related adverse events (irAEs) tend to

be relatively delayed-onset and inflammatory or autoimmune in nature and range from mild to life threatening. High-grade irAEs occur at a rate of 60% for combination immunotherapy versus 10-20% for monotherapy.[3]

Close consultation with disease specific subspecialties is encouraged for management of immunotherapy related toxicity. Select irAEs, including endocrinopathies, can often be treated while continuing immunotherapy. For neurologic, cardiac, or grade 3 and 4 irAEs, methylprednisolone or prednisone 1-2mg/kg/day is recommended followed by a prolonged taper (over 4-8 weeks) to prevent recurrence. While immunotherapy re-challenge can be considered on a case by case basis, the clinician must exercise caution with close follow up. Permanent discontinuation is warranted for severe irAEs. If the toxicity returns upon re-challenge, that class of immunotherapy should be permanently discontinued.

Data from a retrospective pooled analysis of patients with advanced melanoma treated with ipilimumab and nivolumab combination therapy showed treatment discontinuation due to adverse events does not seem to compromise treatment outcome. This analysis included 407 patients, 176 of which discontinued treatment due to adverse events. Progression free survival, overall survival, and overall response rates were similar in patients who discontinued treatment because of adverse events to those who continued on therapy.[4] Caution should be taken in the interpretation of these findings, given that this analysis was retrospective. However, this suggests that patients may continue to derive benefit from combination immunotherapy even after treatment is stopped due to immune related adverse events.

Happily, the patient described in this clinical vignette is now nearly two years out from the time of her diagnosis and repeat response assessments with PET-CT continue to show a complete response to treatment. In an update provided by Jedd D Wolchock, MD, PhD, FASCO at this year's ASCO annual meeting, nearly half the patients who received ipilimumab and nivolumab in the CheckMate 067 trial are reportedly alive at a median of 6.5 years after treatment.[5] This represents the longest follow-up result from a clinical trial of combination immunotherapy, and a new landmark in survival rates for patients with advanced melanoma treated with immune checkpoint inhibitors. This patient's experience and updated survival data provide significant optimism for patients diagnosed with advanced melanoma in the modern era of checkpoint inhibition immunotherapy.

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