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Case Report
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Metastatic Melanoma Responding to Combination Chemotherapy and Immunotherapy after Progression on Ipilimumab and Nivolumab Immunotherapy

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Abstract

We report the case of a patient with stage IV M1c melanoma that developed symptomatic disease progression after treatment with combination immunotherapy (ipilimumab with nivolumab). The patient was subsequently treated with nab-paclitaxel chemotherapy and pembrolizumab and had a rapid and dramatic clinical response. The case illustrates that clinical responses are possible after progression on combination immunotherapy.

Keywords: Metastatic melanoma; Nab-paclitaxel; Pembrolizumab; Ipilimumab; Nivolumab; Resistance

Introduction

The World Health Organization (WHO) estimates that the annual world-wide incidence of cutaneous melanoma is 132,000 cases per year[1]. Outcomes for patients with stage IV melanoma have historically been poor. In the 7th edition of the AJCC guidelines, the median survival for stage IV was ~8 months and the five year survival rate was <10% [1]. However, treatments and outcomes for these patients are rapidly changing.

The first agent approved by the United States Food and Drug Administration (FDA) for the treatment with stage IV melanoma was the cytotoxic chemotherapy dacarbazine (DTIC) [2]. Dacarbazine achieves clinical responses in 5-10% of patients, most of which are short-lived. The immunotherapy high dose interleukin-2 (HD IL-2) was approved for stage IV melanoma in 1998. While response rates remained low (~15%), patients that achieve complete responses (CR) frequently achieve long-term surival (i.e. > 10 years) [3]. Unfortunately, the CR rate for HD IL-2 therapy is only ~6%, and the treatment-related mortality is 1-2%. From 1998 to 2011 there were no new agents approved for patients with stage IV melanoma. However, from 2011 to 2016 five targeted therapy and 4 immunotherapy regimens have been approved by the FDA [4-14]. Targeted therapies are currently approved only for patients with $BRAF^{V600}$ mutations, which are detected in 40-50% of cutaneous melanomas. In contrast, immunotherapies may induce response regardless of genetic abnormalities. The approved immunotherapies include the anti-CTLA-4 antibody ipilimumab (FDA approval, 2011); the anti-PD-1 antibodies nivolumab (2014) and pembrolizumab (2014); and the combination regimen of ipiliumab and nivolumab (2015). In the recent Checkmate 067 study, treatment with ipilimumab monotherapy, nivolumab monotherapy, and ipilimumab + nivolumab combination therapy achieved objective responses in 19%, 44%, and 58% of treament-naive metastatic melanoma patients [9]. Additional reports have demonstrated that ipilimumab + nivolumab can achieve very rapid clinical benefit in patients, and can achieve durable disease control even in patients with high serum lactate dehydrogenase (LDH) levels, a known negative prognostic factor in stage IV melanoma [15,16].

These results have transformed first-line treatment of patients with metastatic melanoma. However, there is very little known about the efficacy of systemic therapies in patients who have progressed on immunotherapy, particularly after combination immunotherapy with ipilimumab and nivolumab. Here we describe the case of a metastatic melanoma patient with a wild-type *BRAF* gene that developed symptomatic progression after treatment with ipilimumab + nivolumab.

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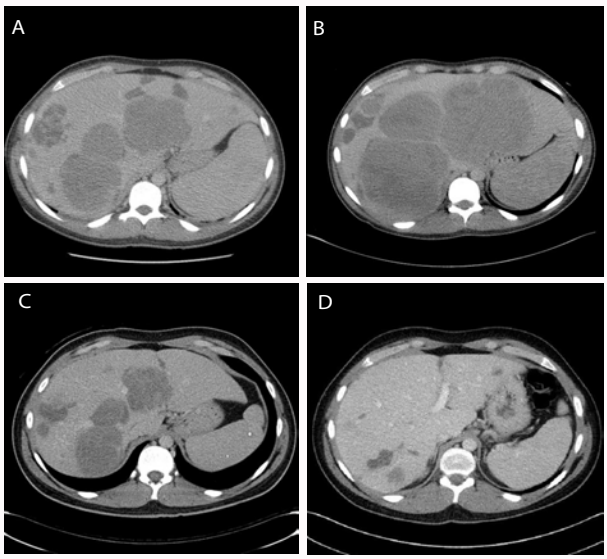

Figure 1: Radiographic response to nab-paclitaxel with pembrolizumab. Representative images of liver metastases (A) after 4th treatment with ipilimumab with nivolumab, (B) after 3rd treatment with nivolumab, (C) after 4th treatment with nab-paclitaxel and pembrolizumab, and (D) after 10th treatment with nab-paclitaxel and pembrolizumab.

Case Presentation

The patient presented at age 11 with a pigmented lesion of the left ear. A shave biopsy revealed melanoma in situ. A subsequent wide local excision revealed no residual disease. At age 27 the patient presented to an emergency room with complaints of fatigue, night sweats, and weight loss of 1 month duration. Diagnostic testing identified elevated liver enzymes and MRI of the abdomen demonstrated innumerable masses in the liver, with 50-75% replacement of normal liver tissue. CT scans revealed subcarinal adenopathy, liver metastases, an enlarged lymph node in the mesenteric root, and in the left pelvic sidewall, and rectal wall thickening near the anorectal verge with associated perirectal lymphadenopathy. MRI of the brain showed no abnormalities. A biopsy of a liver mass confirmed metastatic melanoma. Molecular testing on the biopsy detected no mutations in the *BRAF, NRAS,* or *c-KIT* genes, and immunohistochemistry failed to identify expression of PD-L1 protein by the tumor cells. Colonoscopy revealed a 5 cm by 8 cm discolored rectal mass with an ulcerated center; rectal brushings confirmed the diagnosis of metastatic melanoma.

The patient started treatment with the combination immunotherapy regimen ipilimumab (3 mg/kg) and nivolumab (1 mg/kg) six weeks after initial presentation. At the start of treatment, the serum LDH level was approximately 6 times greater than the upper limit of normal (ULN). The patient's symptoms improved significantly after the first cycle of treatment and the second cycle was given as scheduled three weeks later. The patient subsequently developed symptoms of mild colitis, which resolved with oral budesonide therapy. Standard blood testing demonstrated normal serum AST, ALT, and LDH levels prior to the third cycle. After the fourth cycle, the patient developed grade 2 hepatitis with elevated transaminases, along with fevers and night sweats. The patient was started on oral prednisone therapy for presumed autoimmune hepatitis, with rapid resolution of symptoms and transaminitis. Restaging studies demonstrated progressive disease. The patient was weaned off steroids, and then started single-agent nivolumab (3 mg/kg every 2 weeks). After 3 cycles of maintenance nivolumab, the patient noted increasing fatigue, night sweats, and abdominal distention. Serum LDH was ~18x the ULN, the serum AST ~2x the ULN, and the patient was anemic (serum hemoglobin of 7.9 g/dl). CT demonstrated marked increase in the size of hepatic and rectal metastases, as well as worsening lymphadenopathy in the axilla, abdomen, and inguinal regions (Figure 1). The patient was screened for multiple clinical trials, but did not meet inclusion criteria. The decision was made to treat the patient with nab-paclitaxel (260 mg/m^2) and pembrolizumab (2 mg/kg) given every three weeks. The first treatment was administered one month after the last dose of nivolumab, and the patient reported symptomatic improvement after just a few days. Three weeks later laboratory testing demonstrated normalization of transaminases and an 85% reduction in LDH. CT scans performed 3 weeks later showed ~40% reduction in size of the target liver metastases along with improvement of the other masses.

The patient has now completed 11 cycles (8 months) of nab-paclitaxel with pembrolizumab treatments. The only side effect the patient has experienced is grade 1 neuropathy. Testing after cycle 10 demonstrated normal liver enzymes, near-normal serum LDH, and continued objective response by RECIST criteria (Figure 1).

Discussion

The care of patients with metastatic melanoma has been revolutionized by the development of increasingly effective therapies. The recent approval of ipilimumab and nivolumab has provided a powerful new therapeutic option for stage IV melanoma patients. While this therapy achieves clinical responses in 55-60% of patients, there is a clear unmet need to identify effective treatments for patients that are resistant to this combination. Current National Comprehensive Cancer Network (NCCN) Guidelines for the treatment of patients with metastatic melanoma recommend the use of a different class of therapy in the second-line setting [17]. For patients with a *BRAF^{V600}* mutation that progress on ipilimumab and nivolumab, there are multiple effective targeted therapy options. However, there are currently no targeted therapies that are approved for patients without a *BRAF^{V600}* mutation. While clinical trials are a good option, often patients are not able to participate in such trials due to a variety of factors.

Treatment with cytotoxic chemotherapy is a potential second-line treatment option. However, many oncologists are reluctant to use chemotherapy in metastatic melanoma patients due to the low activity of dacarbazine (DTIC), which to date remains the only cytotoxic agent FDA approved for stage IV melanoma. Alternative NCCN-recommended options include single-agent paclitaxel, the combination of paclitaxel with carboplatin, and nab-paclitaxel. A recently reported phase III trial in 529 stage IV melanoma patients with serum LDH less than 2-times the ULN demonstrated that nab-paclitaxel achieved clinical responses in 15% of patients and resulted in a significant improvement in progression-free survival (PFS) (median 4.8 versus 2.5 months, hazard ratio (HR) 0.792, p=0.044) compared to DTIC [18]. Notably, nab-paclitaxel is prepared as a solvent-free formulation which does not require steroids, which are generally required for paclitaxel. This trial included very few patients with previous immunotherapy treatment (6%). The patient in this case report achieved a rapid and dramatic clinical response with combined treatment using nab-paclitaxel and pembrolizumab after progression on ipilimumab and nivolumab. Although the kinetics of the observed clinical response are consistent with the activity of

a cytotoxic agent in this patient, we cannot exclude the possibility that pembrolizumab contributed to this response. However, there is no published data demonstrating a difference in activity for pembrolizumab versus nivolumab, or that pembrolizumab has benefit after progression on nivolumab. There is also no data demonstrating benefit for combining cytotoxic chemotherapy with immunotherapy. It is also possible that the previous exposure to immunotherapy may have contributed to the response, as the potential for prolonged effects of immunotherapy are supported by the observation of delayed autoimmune toxicity from these agents even several months after they are discontinued, particularly with ipilimumab [19]. Despite this possibility, in the KEYNOTE-002 trial for metastatic melanoma patients that had progressed on ipilimumab treatment, the response rate for patients treated with a variety of chemotherapies (DTIC, temozolomide, paclitaxel, carboplatin, or paclitaxel with carboplatin) was only 4% [20]. The activity of nab-paclitaxel has not been evaluated systematically in metastatic melanoma patients previously treated with immunotherapy, nor has any chemotherapy after progression on anti-PD-1 (+/- anti-CTLA-4) treatment. In summary, this case reports illustrates that cytotoxic chemotherapy may produce significant clinical benefit with acceptable side effects in patients that have progressed on combination immunotherapy, even in the setting of active symptoms and elevated LDH levels. This report supports the rationale to consider such treatments in appropriately selected patients. Further, in order to inform clinical decision-making, we believe that there is need to systematically evaluate cytotoxic chemotherapies in patients previously treated with anti-PD-1 (+/- anti-CTLA-4), and potentially to compare the effects with and without continued immunotherapy. Such trials would be particularly relevant for patients without a *BRAF*^{V600} mutation and/or that are excluded from immunotherapy trials due to prior toxicities.

Foot Note: [1]World Health Organization (WHO), http://www.who.int/uv/faq/skincancer/en/index1.html, accessed December 1, 2016.

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