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CLINICAL VIGNETTE

Two Cases of Long Term Control of Non-visceral Metastatic Melanoma Treated with Ipilimumab

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Case Report

A 32-year-old white male presented in 2006 with a Stage IIIB (T2 N1M0) melanoma of the left ankle with left groin metastases. He underwent wide excision of the ankle lesion as well as left inguinal lymph node dissection. He was treated with adjuvant high dose interferon. In 2009, he was found to have several in transit metastatic melanomas in the left inner popliteal region. He was placed on a clinical trial and was randomized to high dose interferon with complete resolution of the lesions. In 2011, he had a recurrence of several dermal lesions in the same distribution. He received ipilimumab and achieved a complete response to therapy within one month of completion of therapy. At dose two, he developed hypothyroidism and diarrhea, both of which were easily treated and did not delay subsequent dosages. He remains disease free two years later, after completion of 4 doses of ipilimumab therapy.

A 75-year-old white male presented with Stage III B (T unknown, N1, M0) metastatic melanoma in a right femoral node which was completely excised in 2009. In 2011, he had a nodal recurrence and in transit metastatic melanoma in both the femoral nodes and dermis of the right upper thigh. He was treated at that time with ipilimumab and achieved a complete response to therapy after the second dose of four that was given. He had no toxicity. He remains disease free two years later.

Discussion

Metastatic melanoma has been treated with some success with a variety of immunotherapies including interleukin -2 and interferon as well as targeted therapies for patients with V600E mutations in the BRAF gene. Chemotherapy with such agents as dacarbazine offers few meaningful responses. Rare complete responses associated with long term survival are reported with high dose interleukin- 2 therapy in highly selected patients. This treatment, however, must be administered in the intensive care unit and can result in multisystem toxicities including pulmonary edema and delirium. The range of objective response is 15-20% with 3-5% complete responses[1, 2]. In one study of patients with metastatic melanoma treated at the National Cancer Institute with high dose interleukin- 2 between 1985 and 1993, 44 % of all responders remained alive at a minimum of six years of follow up. Despite this encouraging data, high dose interleukin-2 protocols have significant toxicities including risk of death and prolonged hospitalization[3].

While interleukin-2 offers a small benefit to a carefully selected population, the need for immunotherapy that can be more broadly applied has been investigated. One such drug, ipilimumab, a monoclonal antibody, targets CTLA-4 among other immune check point inhibitors. By disabling CTLA-4, negative regulation of T cells is inhibited, therefore allowing T cell activation and enhanced immune response. This immune response is believed to break down tolerance to tumor associated antigens in the melanoma, making the melanoma more susceptible to the natural or enhanced anti tumor activity of the patient's T cells. Non tumor specific autoimmune reactions include colitis, hypothyroidism, neuropathy and rash. The drug is administered as four doses given every 3 weeks in an outpatient infusion center. Clinical trials with ipilimumab demonstrate overall survival advantage compared with some other therapies. A phase III trial combining ipilimumab with a gp 100 vaccine versus vaccine alone demonstrated approximately three and a half month overall survival advantage for the ipilimumab treated group. The objective response rate in the ipilimumab treated patients was 10.9 % with 60% of the patients in the ipilimumab alone group maintaining a response that lasted over 2 years[4]. Other pivotal phase III trials including ipilimumab with dacarbazine versus dacarbazine alone demonstrated a similar finding of

survival advantage of the ipilimumab treated patients[5].

As with Interleukin-2, while only a few patients achieve complete response with ipilimumab therapy, such responses are often of significant duration. Prieto, et al reported in 2012 that in three studies conducted at the National Institutes of Health, between 6-17% of patients achieved a complete response. Many had a delayed response, with fifteen patients who achieved complete response continued disease free at 54 to 99 plus months[6].

Clinical duration of response in the two patients described here is similar to those reported by Prieto[6]. Both patients received their therapy as an outpatient given as four one-hour infusions. Toxicity was easily managed and did not require hospitalization. The first patient remains disease free at 27 months and the second at 25 months.

As reported with interleukin 2, immunotherapy appears to lead to long term responses in a small number of patients, with ipilimumab increasing access to these therapies through easier administration and toxicity management.

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