Delayed response in ipilimumab therapy

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Metastatic melanoma is a deadly disease with a 5-year survival rate lower than 20%.[1] In 2011, ipilimumab, a fully humanized antibody that binds to cytotoxic T-lymphocyte–associated antigen 4 (CTLA4) was approved by the US Food and Drug Administration based on improved survival in a pivotal trial.[2] CTLA4 is a molecule on cytotoxic T-lymphocytes that plays a critical role in attenuating immune responses. Ipilimumab blocks the binding of B7, the ligand of CTLA4, thereby blocking the activation of CTLA4 and sustaining antitumor immune responses. The time course to response can be variable with immunotherapeutics. We report on a patient who experienced a considerable delay before responding to ipilimumab.

Case presentation

A 27-year-old man with metastatic melanoma was initially treated with 11 cycles of paclitaxel plus carboplatin, but demonstrated progressive disease. In June 2010, he was found to have a mass that had eroded into his descending colon and a mass in the occipital region of the scalp (Figure). The abdominal mass was resected and he was started on ipilimumab in August 2010 on the expanded-access protocol. After the second dose of ipilimumab in September 2010, he developed grade 3 diarrhea and was admit-

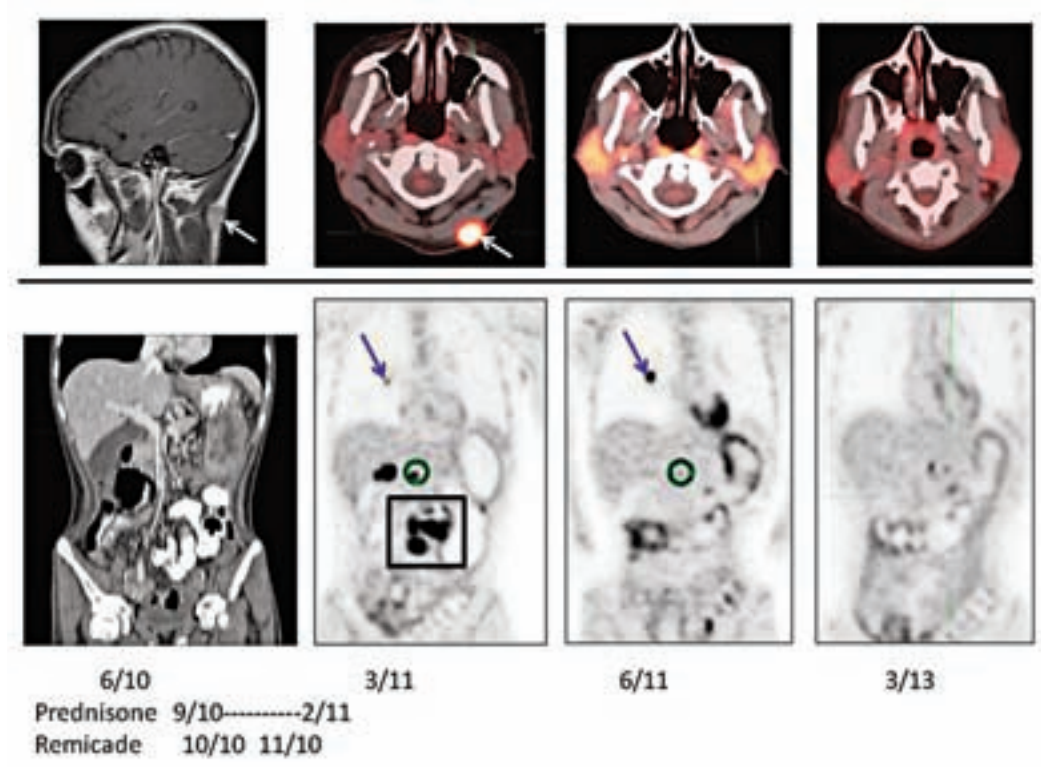

FIGURE Disease course. Top panel, Occipital lesion present prior to treatment, and its resolution. Lower panel, Peripancreatic lesion (circle) and a hilar lesion (arrow) develop after treatment and progress before complete resolution. The abdominal recurrence (square) was resected in April 2011.

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ted for further evaluation. No infectious etiology was found for his diarrhea, and it was attributed to the ipilimumab. He received methylprednisolone sodium succinate (125 mg) twice daily and was then transitioned to prednisone (1 mg/kg) after diarrhea resolved to grade 1.

At 7 days after discharge, his diarrhea recurred with associated abdominal pain while he was receiving prednisone. The patient was admitted; his diarrhea improved on methylprednisolone sodium succinate but the abdominal pain persisted. A colonoscopy demonstrated a chronic active ileitis/colitis with scattered areas of ulceration. He was started on infliximab (5 mg/kg) and his symptoms resolved within 48 hours. He was discharged on prednisone (1 mg/kg) and budesonide 3mg by mouth 3 times a day. He was given a second dose of infliximab (5 mg/kg) 3 weeks after discharge when his diarrhea worsened to grade 2. His prednisone was slowly tapered and finally discontinued in February 2011. In March 2011, the imaging studies revealed hilar, peripancreatic lesions (Figure). Budesonide was discontinued in April 2011. Also in April 2011, he had a recurrence at the site of the previous resection, and the recurring lesion was resected. Imaging studies in June 2011 showed improvement of the occipital and peripancreatic lesions and worsening of the hilar lesion, which resolved on subsequent scans (Figure). Scans in March 2013 showed the patient to be in complete remission (Figure). The patient did not receive any other therapy for his melanoma after the ipilimumab.

Discussion

Clinical studies of ipilimumab have demonstrated maximum disease control rates of about 35%, and durable disease control in up to 14% of patients. The pivotal study has noted 12- and 24-month survival rates of 45.6% and 23.5%, respectively.[2] Yet because of the ipilimumab's side effect profile, some of these patients may require treatment with immunosuppressive drugs, which leads to a decreased overall survival rate.[3]

This patient's imaging showed disease progression 8 months after therapy initiation, while he was still on glucorticoids, before showing partial response 11 months after treatment. This is not the pattern or tempo of response seen with conventional cytotoxic agents. Delayed response with ipilimumab has been shown in other studies, even with a 100% increase in tumor burden before response.[4]

The signs of apparent progressive disease are hypothesized to be the result of infiltration of the tumor by immune cells, rather than actual disease progression. These unique response patterns have led to the development of proposed Immune-Related Response Criteria (irRC) for evaluation of efficacy with immunotherapy. Although this case represents an uncommon situation, it highlights the difficulty in determining when a patient has truly failed ipilimumab treatment. Given the variability of responses with ipilimumab, we would recommend any physician using this agent consider the irRC before discontinuing treatment.

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