Cancer Immunology Miniatures

Anti-PD1 Following Ipilimumab for Mucosal Melanoma:
Durable Tumor Response Associated with Severe Hypothyroidism and Rhabdomyolysis

Le Min and F. Stephen Hodi

Abstract

Treatment with fully human monoclonal antibodies against programmed death 1 (PD1) receptor has shown great promise for a number of advanced malignancies. Although inflammatory adverse events have been well described with anti-CTLA-4 therapy (2–4), experience with the range of adverse effects of anti-PD1 remains comparatively limited. Here, we report on a patient with advanced mucosal melanoma who received four doses of MK-3475, a fully human monoclonal antibody against PD1, and experienced a durable near-complete response but developed severe hypothyroidism, rhabdomyolysis, and acute kidney injury. To our knowledge, this is the first case reported of a patient with advanced mucosal melanoma who responded to anti-PD1 therapy. With the promising antitumor effects of anti-PD1 in a wide array of tumors, we expect an increasing number of patients to be exposed to anti-PD1 therapies. Recognition of infrequent presentations of adverse events such as elevated creatine kinase levels and thyroid disorders in patients who receive anti-PD1 therapy is important. Cancer Immunol Res; 2(1); 15–18. ©2013 AACR.

Introduction

Immunotherapy has emerged as a promising therapeutic method for patients with metastatic melanoma. In clinical studies, monoclonal antibodies targeting immune checkpoint proteins have elicited long-lasting antitumor response (1–4). In 2011, the U.S. Food and Drug Administration (FDA) approved the use of ipilimumab, a CTL antigen 4 (CTLA4) monoclonal antibody for treatment of metastatic melanoma. Monoclonal antibodies against programmed death 1 receptor (PD1) and its ligand (PD-L1), the second-generation immunomodulatory antibodies, demonstrated significant durable benefits in patients with metastatic melanoma (4–6). However, our knowledge is very limited about the efficacy of immunotherapy for patients with metastatic mucosal melanoma, and the efficacy of anti-PD1 therapy for this melanoma subtype is unknown. Inflammatory adverse events have been well described in patients who received anti-CTLA4 therapy (7). In phase I anti-PD1 clinical trials, adverse events such as pulmonary disorder (pneumonitis), renal disorders (acute renal failure and tubulointerstitial nephritis), hepatic disorders [alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevations], gastrointestinal disorders (colitis and diarrhea), skin disorders (rash, vitiligo, and pruritus), and endocrinopathies (hypothyroidism, hyperthyroidism, hypophysitis, and adrenal insufficiency) were observed with limited detail about the time frame for the onset of these adverse events.

Case Presentation

A 46-year-old man with advanced mucosal melanoma was enrolled in the clinical trial of MK-3475 (Merck), a fully human monoclonal antibody against PD1, at a dose of 10 mg/kg of body weight, given intravenously every 3 weeks. Four years ago, he was diagnosed with mucosal melanoma following a history of prolonged sinus complaints. He underwent maxillectomy, septectomy, and dacryocystorhinostomy followed by 60 Gy in 30 fractions via intensity-modulated radiotherapy (IMRT) technique to the surgical bed. Subsequently, lung and spinal metastases developed, which were resistant to treatments with temozolomide and ipilimumab therapies. Four months before initiation of MK-3475 therapy, he received one course of 30 Gy in 10 fractions of radiotherapy to cervical vertebrae six-thoracic vertebrae 1 (C6-T1), which involved radiation exposure to parts of the thyroid gland. During MK-3475 therapy, he had thyroid function tests (TFT) routinely as per the clinical trial protocol. During the first 15 weeks of anti-PD1 therapy (five doses), he had normal TFTs and remained active. Upon presentation to the clinic for evaluation before his sixth dose of MK-3475, he complained of significant myalgias, tender muscles, and fatigue. He was hospitalized following laboratory results that were significant for elevated transaminases: AST 858 U/L (reference range, 10–50) and ALT 289 U/L (reference range, 10–50; Fig. 1). The levels of alkaline

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phosphatase, bilirubin, and γ-glutamyl transferase in the blood were normal, but the level of creatine kinase (CK) was significantly elevated at 30,980 U/L (reference range, 55–170; Fig. 1), supporting the diagnosis of rhabdomyolysis rather than hepatic injury. After aggressive hydration, rhabdomyolysis improved but was not resolved. Acute renal injury developed subsequently with his serum creatinine level increasing from baseline 0.9–1.1 to 1.4–1.6 mg/dL (reference range, 0.7–1.3). Over the course of a week, he complained of progressing signs and symptoms of hypothyroidism, including fatigue, weight gain, constipation, dry skin, and bradycardia. Further laboratory testing revealed severe hypothyroidism; thyroid-stimulating hormone (TSH) was 145 and peaked at 187.8 mIU/L (reference range, 0.5–5; Fig. 1) with undetectable free thyroxine. Adrenal insufficiency was ruled out by a random blood cortisol level of 9 mg/dL (reference range, 6–24). Given his young age and no history of heart disease, levothyroxine, 150 μg (≈1.6 μg/kg body weight) daily was started. His TFTs, CK level, and renal function normalized with levothyroxine replacement; TSH returned to normal within 22 weeks after initiation of hormone replacement.

**Discussion**

PD1 is an immune-checkpoint receptor that negatively regulates T-cell activation (8). Anti-PD1 antibody induces durable responses in patients with advanced solid tumors (3, 6). The current patient with mucosal melanoma, a rare form of melanoma, had an initial near complete response to MK-3475 therapy (Fig. 2) and has remained in remission for 14 months after discontinuing treatment. Our understanding of immunotherapy efficacy in patients with mucosal melanoma is inadequate. A recent study showed that in patients with mucosal melanoma, the overall response rate to ipilimumab therapy is low (9). Here, we report the first case of a patient with metastatic mucosal melanoma who experienced a durable response to anti-PD1 treatment following CTLA4 blockade. Our findings provide insight for immunotherapy efficacy in

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**Figure 1.** Changes in thyroid-stimulating hormone (TSH), CK, and ALT levels before and after MK-3475 therapy. The trends of serum levels of TSH (reference range, 0.5–5 mIU/L), CK (reference range, 55–170 U/L), and ALT (reference range, 10–50 U/L) were plotted. Time 0 represents the first dose of MK-3475. Time for ipilimumab (Ipi) treatment and radiotherapy are indicated as well.

**Figure 2.** Tumor response to anti-PD1 immunotherapy. The images of chest computed tomography (CT) before, 2, and 14 months after initiation of MK-3475 therapy.
patients with mucosal melanoma and inform future drug development. Severe hypothyroidism is likely associated with the MK-3475 therapy or a combined effect of ipilimumab followed by MK-3475. It is unlikely that this is a sole effect of ipilimumab as time to onset of ipilimumab-related endocrinopathies including thyroiditis is usually between 7 and 20 weeks of initial ipilimumab therapy (10, 11). This patient remained euthyroid for 43 weeks after completing ipilimumab. Radiation-induced hypothyroidism is usually subclinical (12), but whether radiation precipitates immunotherapy-related autoimmunity is unknown. The patient’s rhabdomyolysis could be a consequence of hypothyroidism or autoimmune-related myositis. He did not receive any glucocorticoid treatment. Because normalization of TFTs by levothyroxine replacement was associated with normalization of his CK, it is likely that his rhabdomyolysis is directly associated with the severe and acute onset of hypothyroidism. Nonetheless, given the nature of inflammatory adverse events associated with anti-PD1 therapy, autoimmune myositis and hepatitis cannot be excluded. The association of hypothyroidism with rhabdomyolysis and acute renal injury has been reported (13) in a woman who presented with weakness, anorexia, dysuria, and typical signs of severe hypothyroidism, including hypothermia, hoarse voice, and mental status change. She also had a long history of Hashimoto thyroiditis but stopped thyroid hormone replacement several years before her presentation. The relatively mild signs of hypothyroidism in our case correlate well with its nature of rapid onset. Both patients had remarkably high TSH and very low T4, elevated CK, creatinine, and alanine aminotransferase. Replacement with levothyroxine corrected the biochemical abnormalities in both cases. Before beginning levothyroxine replacement, it is important to rule out adrenal insufficiency, which is a relatively common adverse event in patients receiving immunotherapy, as levothyroxine may trigger adrenal crisis in patients with uncorrected adrenal insufficiency (14). The initial dose of levothyroxine depends on the age and heart condition of the patient. In young patients without heart disease, as in this case, the average replacement dose of T4 is approximately 1.6 μg/kg body weight daily, but the range of required doses is broad. For further levothyroxine dose titration, TSH and free T4 should be measured 4 to 6 weeks after the initiation of levothyroxine replacement. In older patients or patients with coronary artery disease, levothyroxine should be started at a low dose, usually 12.5 to 25 μg daily, and increased slowly, 12.5 to 25 μg every 4 to 6 weeks. The rapid development of severe hypothyroidism and the unusual manifestation of hypothyroidism presenting as rhabdomyolysis underscores the importance of TFTs in all patients on immune checkpoint blockade, as well as the range of clinical presentations and clinical recognition of the wide variety of autoimmune-related adverse effects. TFTs before each ipilimumab infusion are included in the ipilimumab package insert. Here, we recommend that all patients on anti-PD1 therapy have their TSH and free T4 checked before each dose of anti-PD1 and be screened for the clinical manifestations of hypothyroidism and myositis. Blood CK level should be measured if the patient develops symptoms and signs of myositis such as myalgias.

Disclosure of Potential Conflicts of Interest
F.S. Hodi has received commercial research support from Bristol-Myers Squibb and Merck and is a consultant/advisory board member of Merck and Bristol-Myers Squibb. No potential conflicts of interest were disclosed by the other authors.

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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): L. Min, F.S. Hodi
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): L. Min, F.S. Hodi
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Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): L. Min, F.S. Hodi
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