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## Review of Immune-Related Adverse Events in Prostate Cancer Patients Treated with Ipilimumab: MD Anderson Experience

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### Abstract

Targeting a T cell inhibitory checkpoint with the anti-CTLA-4 monoclonal antibody, ipilimumab, represents a scientific breakthrough in immunotherapy for the treatment of cancer. However, ipilimumab therapy is also associated with unique side effects, known as immune-related adverse events (irAEs), which need to be recognized and managed with immunosuppressive agents. To date, the majority of our knowledge regarding ipilimumab-associated side effects is based upon clinical studies in melanoma. Here, we provide a review of ipilimumab-induced irAEs and our experience in a cohort of 44 patients with prostate cancer who were treated at M. D. Anderson Cancer Center on two different clinical trial protocols.

### Keywords

immune checkpoint blockade; anti-CTLA-4; toxicity; ipilimumab; immune-related adverse events

### Introduction

Optimal T cell activation requires at least 2 sets of intrinsic T cell signals. The first set is initiated by the interaction between the T cell receptor and tumor antigen bound to the major histocompatibility complex. This signal is further amplified by a second set of signals via binding of CD28 on the T cell surface to B7 proteins (B7-1 and B7-2) on antigen-presenting cells. Together, these two signals allow T-cells to become activated, which can result in

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tumor cell killing [1, 2]. To avoid unrestrained immune responses that can potentially harm normal tissues, T cell activation is tightly controlled by inhibitory co-receptors, including CTLA-4 (cytotoxic T-lymphocyte antigen-4). CTLA-4 is a homologue of the T cell co-stimulator CD28 but has a much higher binding affinity for CD28 ligands (B7-1 and B7-2). After T cell activation, CTLA-4 is mobilized from intracellular vesicles to the cell surface, where it outcompetes CD28 for binding to B7 proteins and, as a result, restricts T cell responses against tumor cells. In the presence of antagonistic anti-CTLA-4 antibodies, the inhibitory signaling from CTLA-4 is blocked, which results in transiently augmented T cell immune responses. Both animal models [1, 3] and clinical trials [4, 5] have shown that anti-CTLA-4 treatment resulted in enhanced T cell responses, which led to anti-tumor responses and survival benefit.

In addition to eliciting significant clinical benefit, anti-CTLA-4 therapy, ipilimumab, is associated with side effects, termed immune-related adverse events (irAEs). Among patients with metastatic melanoma treated with various doses of ipilimumab, more than 70% experienced side effects. Twenty-five percent of these events were severe, grade 3–4 toxicities such as dermatitis, colitis, hepatitis, and hypophysitis, as defined by CTCAE 4.0 (Common Terminology Criteria for Adverse Events) criteria [6]. Proper management of these irAEs is essential for maximizing the clinical use and benefit of ipilimumab.

Little is known about the mechanisms of ipilimumab-mediated toxicities; however, treatment of these toxicities rely on broad-spectrum immune suppression. Current treatment algorithms for management of ipilimumab-associated irAEs are largely based upon experiences in melanoma patients. Here, we report our experience in treating 44 prostate cancer patients with ipilimumab on two different clinical trials. In the first setting, we conducted a presurgical trial of androgen deprivation therapy (ADT; leuprolide acetate) and ipilimumab in patients with high-risk, localized prostate cancer (MDACC 2009-0135, N=17) to obtain matched tumor tissues and blood. In the second setting, we conducted a trial of ADT in combination with ipilimumab in non-castrate, metastatic prostate cancer patients (2009-0378, N=27). Through caring for the patients on these clinical trials, our multidisciplinary team was involved in the management of ipilimumab-associated irAEs. This review aims to share our experiences on managing these irAEs in patients with prostate cancer.

## **Ipilimumab has significant clinical activity**

Monoclonal antibodies that block the immune checkpoint molecule, CTLA-4, have been shown to potentiate T cell activation against a variety of tumors [1, 3, 7, 8]. In a Phase III clinical trial, ipilimumab was shown to improve median overall survival in patients with metastatic melanoma [4]. Although this prolongation of median overall survival was significant, the most striking feature of the trial was the notable durability of the clinical responses, which indicated ~23% of patients being alive for 4 or more years. This trial led to the approval of ipilimumab by the U.S. Food and Drug Administration (FDA) in March 2011 for the treatment of patients with advanced melanoma. A second randomized, Phase III clinical trial subsequently compared standard dacarbazine chemotherapy alone to dacarbazine plus ipilimumab, with the combination shown to significantly prolong median

overall survival in patients with metastatic melanoma [5]. Most recently, a pooled analysis of Phase II and III data for long-term survival indicated that patients with advanced melanoma who were treated with ipilimumab had durable survival benefit lasting for ten or more years in a subset of patients [9].

In addition, a Phase III trial in which men with castration-resistant prostate cancer (CRPC) that had progressed after docetaxel chemotherapy were treated with radiation therapy to a bone metastasis followed by either ipilimumab (10mg/kg every 3 weeks for a total of 4 doses) or placebo indicated that ipilimumab can prolong median overall survival in a select subset of patients lacking visceral disease and with favorable laboratory values [10]. Currently, more than 140 ongoing clinical trials (clinicaltrials.gov) are testing the efficacy of ipilimumab in other malignancies, including prostate cancer, breast cancer, non-small cell lung cancer, lymphoma, and leukemia.

### **Ipilimumab-associated irAEs**

The prevalence, kinetics, manifestation, and management of individual irAEs from anti-CTLA-4 therapy in melanoma patients have been previously reviewed [6, 11]. The spectrum of irAEs ranges from common reactions, such as dermatitis, colitis, hepatitis, and hypophysitis, to rare conditions such as uveitis, neuropathy, and lupus nephritis [6, 12, 13]. Overall, irAEs occur in more than 70% of patients treated with ipilimumab [4, 14]. There is a direct correlation between ipilimumab dose and irAE frequency and grade [15]. The majority of irAEs emerge during the first 14 weeks of therapy, although late irAEs can occur as well [6]. In patients treated with the standard dose of ipilimumab (3 mg/kg intravenously [IV] every 3 weeks for a total of 4 doses), irAEs of any grade occurred in about 60% of patients. The most common irAEs affect the skin (rash/pruritus, about 40%), gastrointestinal tract (diarrhea/colitis, about 30%), endocrine system (5–8%), and liver (about 3%). Grade 3–4 irAEs occur in 6–13% patients, predominantly in the gastrointestinal tract (5–8%), endocrine system (1–4%), and skin (1%) [11].

In a Phase I clinical trial in which patients with metastatic castration-resistant prostate cancer (mCRPC, N=30) were treated with a pox viral-based vaccine targeting prostate-specific antigen (PSA-Tricom) in combination with ipilimumab ranging from 1–10mg/kg, any grade of irAEs occurred in 40% of treated patients. Grade 3–4 irAEs occurred in 30% of patients including 13% colitis/diarrhea, 7% rash, 7% transaminitis, and 3% hypophysitis [16]. Patients treated with 10mg/kg ipilimumab had more frequent irAEs compared to those treated with 3mg/kg ipilimumab (46% vs. 28%). In another Phase I clinical trial whereby patients with mCRPC were treated with granulocyte-macrophage colony-stimulating factor-transduced allogeneic prostate cancer cells vaccine (GVAX) in combination with ipilimumab, any grade of irAEs occurred in 37.5% patients treated with 3mg/kg ipilimumab in the expansion cohort (N=16). These included 6% grade 3 hepatitis, 19% grade 1–2 colitis, and 13% grade 2 hypophysitis [17]. In a Phase III clinical trial in which patients with mCRPC (N=799) received radiation therapy followed by ipilimumab or placebo, any grade of irAEs occurred in 63% patients in the ipilimumab group and 22% patients in the placebo group. Grade 3–4 irAEs occurred in 26% and 3% of patients in the ipilimumab and placebo

group, respectively. Grade 3–4 irAEs associated with ipilimumab treatment include 15% diarrhea, 5% colitis, 4% liver enzyme elevation, and 1% endocrinopathy [10].

In our presurgical clinical trial MDACC 2009-0135, a total of 17 patients with localized, high-risk, hormone-sensitive prostate cancer received an intramuscular injection of leuprolide acetate (22.5 mg) followed by two doses of ipilimumab (10 mg/kg IV every 3 weeks) prior to radical prostatectomy. In the Phase II trial MDACC 2009-0378, a total of 27 patients with hormone-sensitive metastatic prostate cancer received ADT followed by four doses of ipilimumab (10 mg/kg IV every 4 weeks). Among a total of 44 patients treated with ipilimumab, grades 3–4 irAEs occurred in 45% (20/44) patients. The most common grade 3–4 irAEs included enterocolitis (15.9%; 7/44), hypopituitarism (13.6%; 6/44), hepatitis (9.1%; 4/44), and dermatitis (6.8%; 3/44).

## Enterocolitis

In melanoma patients, although the most common irAE of any grade from standard dose (3mg/kg) ipilimumab is dermatitis, the most common grade 3–4 irAE is enterocolitis/diarrhea [4, 11]. Of patients treated with ipilimumab at the standard dose, enterocolitis/diarrhea of any grade occurred in about 28–30% of patients, including grade 2 in about 5% and grade 3–4 in 5–8%. Less than 1% developed intestinal perforation [4, 11]. In our experience with prostate cancer patients on clinical trials MDACC 2009-0135 and 2009-0378 where ipilimumab was administered at a dose of 10 mg/kg, 11/44 (31.8%) patients developed grade 2 or less enterocolitis/diarrhea, whereas 7/44 (15.9%) developed grade 3–4 enterocolitis/diarrhea.

Successful management of ipilimumab-induced enterocolitis requires a high level of suspicion and early treatment with steroid [18]. For example, patient JM developed grade 3 diarrhea for which he was hospitalized and treated with methylprednisolone 1mg/kg/day. His diarrhea completely resolved after 3 days of treatment. His steroid was then changed to equivalent dose of oral prednisone (80 mg daily), but maintained for elevated lipase and eventually tapered off by 10 mg/week. However, not all patients with diarrhea responded to initial steroid treatment. For example, patient KK developed grade 1 diarrhea after receiving 2 doses of ipilimumab. He was treated with Medrol Dosepak (methylprednisolone; started at 24 mg orally on day 1, tapering by 4 mg/day, for a total of 6 days of treatment), but his diarrhea progressed to grade 3 after two days of treatment. His treatment was changed to IV methylprednisolone 1 mg/kg/day for a week while being hospitalized. After 3 days of treatment with IV methylprednisolone, his diarrhea persisted. Therefore, oral mycophenolate mofetil 500 mg twice daily was added to his treatment regimen. His diarrhea still did not improve after another 2 days of treatment. Therefore, one dose of infliximab 5mg/kg was added to the steroids and mycophenolate, which led to improvement within 48 hours and then resolution of diarrhea within one week. The patient remained on mycophenolate for about 5 weeks. He was eventually tapered off of steroids after a total of two months of treatment.

It should be noted that ipilimumab-associated colitis can result in significant morbidity and death. For example, patient WP received one dose of leuprolide acetate (22.5mg) followed

by only one dose of ipilimumab (10mg/kg) on clinical trial MDACC 2009-0135. He developed grade 2 diarrhea about two weeks post treatment. However, the patient did not seek medical attention until about a week after the onset of diarrhea. He received oral prednisone at 1 mg/kg/day, which resulted in improved diarrhea; however, as prednisone was being tapered, his diarrhea worsened and he was hospitalized for further treatment. He was treated with methylprednisolone 2 mg/kg/day IV for two weeks which improved his diarrhea from grade 3 to grade 2. However, upon steroid taper, he developed worsening diarrhea. Oral mycophenolate mofetil 500 mg twice daily was added to treatment. CT imaging indicated pan-colitis, which was confirmed by colonoscopy and biopsy. The patient was started on infliximab at 5 mg/kg IV. His diarrhea decreased to grade 1 within one week. Mycophenolate was discontinued after a total of one month of treatment. Steroid was also discontinued at this time. During this period of hospitalization, the patient's albumin level declined from normal level of 4.5 g/dL to 1.3 g/dL. As a result, he developed significant edema and required total parenteral nutrition treatment. The patient was eventually discharged home after two months in the hospital. Two weeks after discharge, he was seen in clinic. He was no longer on steroids and had complete resolution of diarrhea; however, he reported fatigue and generalized weakness. His albumin level was still markedly decreased at 2.0 g/dL. One week after his clinic visit, the patient had a near-syncope episode at home when getting up from a chair. He was taken to a local hospital closer to his home for evaluation. He was hospitalized at the outside hospital and unfortunately died from a cardiac event during that hospitalization. Although it is unlikely that ipilimumab contributed directly to the cardiac event, it is very likely that ipilimumab induced severe diarrhea and colitis that required prolonged steroid treatment, which were all contributing factors to the patient's clinical deterioration that may have subsequently led to the cardiac event.

## Endocrinopathies

Endocrinopathies induced by ipilimumab include primary hypothyroidism due to thyroiditis, adrenal insufficiency, hypophysitis, and panhypopituitarism. Endocrinopathy occurred in 5–8% of melanoma patients treated with the standard dose of ipilimumab. Grade 2 endocrinopathy occurred in about 2% of ipilimumab-treated patients and grade 3–4 endocrinopathy in about 3% of treated patients [4, 11, 18]. The median time to onset of moderate to severe immune-mediated endocrinopathy was 11 weeks after the initiation of ipilimumab [18]. Hypophysitis/hypopituitarism occurred in about 1.5% of patients treated with standard dose of ipilimumab [4, 19, 20]. In our clinical trials (MDACC 2009-0135 and 2009-0378), in which patients with prostate cancer were treated with ADT and ipilimumab, hypopituitarism occurred in 18.2% (8 of 44 patients; 4.5% grade 0–2 and 13.6% grade 3–4). This is similar to the occurrence rate of hypopituitarism (13%, grade 2–3) in the two Phase I clinical trials of ipilimumab in patients with mCRPC [16, 17].

Since hypophysitis/hypopituitarism is a serious and potentially fatal side effect of ipilimumab, patients receiving this agent should be monitored for clinical signs and symptoms such as fatigue, headache, mental status changes, abdominal pain, fever, and hypotension. Laboratory tests including baseline and post-treatment prolactin, growth hormone, insulin-like growth factor-1, adrenocorticotrophic hormone (ACTH), cortisol, thyroid-stimulating hormone (TSH), and free T4 levels should be obtained for diagnosis of

hypopituitarism. Magnetic resonance imaging of the brain should be used to assist in diagnosis of hypophysitis/hypopituitarism, although this test is neither sensitive nor specific. Infection/sepsis should be empirically treated and ruled out in patients with fever and hypotension.

Patients who develop hypopituitarism while on ipilimumab should be managed by a multidisciplinary team including Endocrinology and Medical Oncology. For patients with primary hypothyroidism, long-term supplementation with thyroid hormone has been required. In patients with panhypopituitarism, the thyroid axis may recover in 3 to 6 months and thyroid hormone replacement therapy may be discontinued after a slow withdrawal. In all patients who were not treated long-term with ADT, testosterone levels improved to baseline. Contrary to the thyroid and gonadal axis, the adrenal axis does not seem to recover fast or at all, and they have required long-term therapy with cortisol as it has not been possible to withdraw steroid replacement therapy in most patients.

As an example of hypopituitarism, patient JK developed headache and significant fatigue after receiving 2 doses of ipilimumab. Due to suspicion of hypopituitarism, the patient was started on 1mg/kg/day of oral prednisone. MRI of the brain indicated diffuse changes of the pituitary, suggesting hypophysitis. His TSH and cortisol levels were normal at this time. Therefore, he was treated as an outpatient with a plan of tapering prednisone by 10 mg every week. Bactrim and omeprazole were given for *Pneumocystis jiroveci* pneumonia (PCP) and gastrointestinal prophylaxis, respectively.

Unfortunately, during the steroid taper, he returned to the clinic with fever and headache when prednisone was decreased to 60 mg daily. Thyroid stimulating hormone (TSH), prolactin, follicle-stimulating hormone (FSH), and luteinizing hormone (LH) were below normal limits, although free T4 (thyroxine) and cortisol levels were normal at this time. The patient was started on methylprednisolone at 2 mg/kg/day IV. He was also started on antibiotics for empiric treatment of sepsis. Endocrinology and Rheumatology consultations were obtained. After 2 days of treatment, his headache persisted. Therefore, oral mycophenolate 500 mg twice a day was started. Subsequently, after he was cleared for tuberculosis infection, infliximab 3 mg/kg IV was administered. He was also started on oral levothyroxine 50 µg daily due to decrease of free T4.

After 5 days of treatment, his headache improved significantly. He was discharged from the hospital and maintained on 100 mg of prednisone twice a day, which was tapered by 10 mg every week, and 500 mg of mycophenolate twice a day, which was discontinued after 3 weeks of treatment. At that time, oral azathioprine 50 mg twice a day was started in place of mycophenolate due to lack of insurance coverage of the latter. After another 7 weeks of treatment, prednisone was tapered to 5 mg daily, which was changed to hydrocortisone 20 mg in the morning and 10 mg in the evening. Azathioprine was discontinued at this time. The patient has remained on such doses of hydrocortisone and levothyroxine to date without other significant problems.

## Hepatotoxicity

Hepatotoxicity includes elevation of serum liver transaminases and/or bilirubin. Hepatotoxicity of any grade occurred in about 2–9% of melanoma patients treated with ipilimumab [4, 14, 15]. Grade 2 hepatotoxicity (defined as  $2.5 \times \text{UNL}$  [upper normal limit]  $\text{AST/ALT}$   $5 \times \text{UNL}$ ; or  $1.5 \times \text{UNL}$  total bilirubin  $3 \times \text{UNL}$ ) occurred in about 2.5% of patients treated with ipilimumab. Grade 3–5 hepatotoxicity ( $\text{AST/ALT} > 5 \times \text{UNL}$ ; or total bilirubin  $> 3 \times \text{UNL}$ ) occurred in 2% of ipilimumab-treated patients, with fatal hepatic failure in 0.2% [18]. Hepatotoxicity generally occurs between week 6 and week 14 after initiation of ipilimumab treatment [6]. In our experience with prostate cancer patients, grade 2 or less hepatotoxicity occurred in 18/44 (40.9%) patients, whereas grade 3–4 hepatotoxicity happened in 4/44 (9.1%) patients.

Baseline and post-treatment AST, ALT, and total bilirubin levels should be obtained in all patients treated with ipilimumab. In patients who develop ipilimumab-induced hepatotoxicity, hepatology consultation should be obtained, and infectious and autoimmune hepatitis should be ruled out. For patients who develop hepatotoxicity of grade 2 or greater, ipilimumab should be withheld and methylprednisolone 1 mg/kg/day IV should be administered [18]. If patients require treatment with mycophenolate mofetil and/or infliximab, rheumatology consultation should be obtained to guide the use of the immune-suppressive medications. Ipilimumab should be permanently discontinued in patients with grade 3–5 hepatotoxicity.

As an example of ipilimumab-induced hepatitis management, patient LS developed grade 3 transaminitis after receiving 4 doses of ipilimumab at 10 mg/kg every 3 weeks. He was immediately hospitalized and treated with 1 mg/kg/day methylprednisolone IV. After a week of treatment, transaminitis improved to grade 2. Steroid was changed to oral prednisone 100 mg daily with plan of tapering by 10 mg weekly. Bactrim and omeprazole were given for PCP and gastrointestinal prophylaxis, respectively. After about 3 months of treatment with slight fluctuations of transaminases, prednisone was eventually tapered to 30 mg daily. Unfortunately, the patient developed left foot drop, which was suspected due to ipilimumab-induced neuropathy. At this time, the patient was treated with oral mycophenolate 500 mg twice a day for a month. His prednisone was then completely tapered off with resolution of both transaminitis and neuropathy.

## Dermatitis

Dermatitis is the most common irAE in melanoma patients treated with ipilimumab, occurring in as many as 44% treated patients [4, 11]. Grade 2 dermatitis occurred in about 12% of treated patients. Grade 3–5, life-threatening dermatitis, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration/necrosis, occurred in only about 2.5% of ipilimumab-treated patients. The median time to onset of moderate or severe dermatitis was 3 weeks from the initiation of ipilimumab therapy, but the time to onset ranged up to 17 weeks [4, 11, 18]. In our clinical trials, grade 0–2 dermatitis occurred in 27/44 (61.4%) prostate cancer patients, whereas grade 3–4

dermatitis occurred in 3/44 (6.8%) patients. These toxicity rates are similar to what have been described in the literature.

For grade 1 dermatitis, symptomatic treatment with a skin moisturizer, antipruritic medication, or topical steroid is generally sufficient. For grade 2 dermatitis, a short course of an oral steroid such as methylprednisolone for 6 days, along with an antipruritic medication and a topical steroid, is usually sufficient. Ipilimumab can be continued if symptoms improve or resolve with this therapy. However, if symptoms persist or worsen, dermatology consultation should be obtained and ipilimumab should be withheld.

For patients with grade 3–5 dermatitis, hospitalization is necessary. These patients should be treated with methylprednisolone 1 mg/kg/day IV [18]. After dermatitis is controlled, the corticosteroid may be tapered, over a period of at least 1 month. Ipilimumab should be permanently discontinued in patients with Stevens-Johnson syndrome, toxic epidermal necrolysis, rash complicated by full thickness dermal ulceration, or necrotic, bullous, or hemorrhagic manifestations.

### **Uveitis, iritis, and episcleritis**

Although uveitis, iritis, or episcleritis have been seen in less than 1% of patients treated with ipilimumab [21], these irAEs must be handled with extreme caution because of the vital function of the eyes. Patients in whom these symptoms are suspected should be immediately evaluated by an ophthalmology consultant. Patients who develop grade 1 uveitis, iritis, or episcleritis should be treated with corticosteroid eye drops. For grade 2 or greater ocular toxic effects, both topical and systemic corticosteroids should be administered. Ipilimumab should be permanently discontinued in cases of immune-mediated ocular disease that is unresponsive to local immunosuppressive therapy. For a detailed example of managing ipilimumab-induced uveitis, please refer to our previous publication (Sun et al.) [22]. In our prostate cancer trials, we did not have patients with uveitis.

### **Neuropathies**

Although extremely rare (<1%), neuropathy in various forms, such as Guillain-Barré syndrome, peripheral motor neuropathy, myasthenia gravis, aseptic meningitis, enteric neuropathy in the form of extreme constipation, and optic neuritis, has been reported to be associated with ipilimumab treatment [18, 22–25]. For mild neuropathy, a short course of an oral steroid such as methylprednisolone may be tried. For moderate to severe neuropathy, ipilimumab should be withheld and methylprednisolone 1 mg/kg/day IV be administered [18]. Neurology consultation should be obtained to guide management of moderate to severe neuropathy. Ipilimumab should be permanently discontinued in patients with severe neuropathy that interferes with daily activities, such as Guillain-Barré syndrome. In our two prostate cancer trials, there was only one patient who developed grade one neuropathy and this patient improved after treatment with Medrol Dosepak (methylprednisolone; started at 24 mg orally on day 1, tapering by 4 mg/day, for a total of 6 days of treatment) and gabapentin for a total of 3 weeks.



## Other irAEs

The following clinically significant irAEs were each seen in less than 1% of ipilimumab-treated patients: nephritis including lupus nephritis, pneumonitis, pericarditis, hemolytic anemia, hemophilia, myocarditis, angiopathy, temporal arteritis, vasculitis, polymyalgia rheumatic, leukocytoclastic vasculitis, erythema multiforme, psoriasis, pancreatitis, arthritis, autoimmune thyroiditis, sarcoidosis, neurosensory hypoacusis, encephalitis, myositis, polymyositis, and ocular myositis [4, 11, 12, 18]. As with other more common types of irAEs, a high level of suspicion for these ipilimumab-induced events and early initiation of treatment is essential for effective management. A short course of an oral steroid such as methylprednisolone can be used for grade 1 side effects considered to be caused by ipilimumab treatment. A systemic corticosteroid at a dose equivalent to methylprednisolone 1 mg/kg/day IV should be given for severe irAEs [18]. Ipilimumab should be permanently discontinued for these clinically significant or severe irAEs.

A rare case of ipilimumab-induced irAE that we encountered was aplastic anemia. Patient WJ with metastatic prostate cancer to bone and pelvic lymph nodes was treated with ADT and two doses of ipilimumab at 10 mg/kg per protocol 2009-0378. The patient initially developed grade 3 AST/ALT elevation and was started on 2 mg/kg of methylprednisolone for 7 days, 1 mg/kg for 7 more days, and then transitioned to oral methylprednisolone. After methylprednisolone was tapered to 8 mg BID, the AST/ALT increased again, and the patient was started on azathioprine 50 mg PO BID. After 7 weeks of azathioprine treatment, transaminitis resolved. However, the patient developed profound pancytopenia, likely due to aplastic anemia as shown by a bone marrow biopsy. To differentiate between the possibility of azathioprine- vs. ipilimumab-induced aplastic anemia, thiopurine methyltransferase (TMPT) genotyping (Prometheus Laboratories, San Diego, CA) of three polymorphisms (G238C, G460A, and A719G) relevant to the metabolism of azathioprine was performed and revealed homozygous alleles associated with normal TMPT enzyme activity. The patient was then treated with cyclosporine in addition to transfusion support without success. Two subsequent courses of anti-thymocyte globulin (ATG) treatment did not result in improvement either. However, 4 months of treatment with the non-peptide thrombopoietin receptor agonist eltrombopag (75mg po daily) appears to have alleviated the need for frequent transfusions.

## Potential mechanisms for ipilimumab-associated irAEs

The exact mechanisms for irAEs are not completely understood. However, increasing clinical and research data have offered potential mechanistic insights into ipilimumab-induced irAEs. It appears that immune cell infiltration at the site of toxicity, autoreactive T cells and antibodies, and inflammatory cytokines may play roles in ipilimumab-associated irAEs.

### Immune cell infiltration and auto-antibodies

Immunohistochemistry studies of skin biopsy specimens indicate significant infiltration of CD4 T lymphocytes, CD8 T lymphocytes, and CD20 B lymphocytes in areas of dermatitis occurring after ipilimumab treatment [26–29]. The dominant immune cell type in the skin

infiltrate appears to be CD4 T cells, with significantly increased eosinophils [29, 30]. Interestingly, patients who developed dermatitis after ipilimumab treatment had significant increases of eosinophils in the peripheral blood as well [29]. In patients who developed colitis after ipilimumab treatment, biopsy of the colon in the areas with active colitis revealed infiltration of neutrophils, T lymphocytes, and plasma cells [27, 28, 30]. A separate study in patients with enterocolitis from ipilimumab treatment also showed mixed inflammatory cell infiltrates that included lymphocytes, neutrophils, plasma cells, and eosinophils at the sites of inflammation [31]. Collectively, these data suggest that ipilimumab-induced dermatitis and colitis may be mediated by local infiltration of immune cells, although it remains to be investigated which type(s) of immune cells is predominant in these infiltrations.

In patients who developed grade 2 or higher colitis, ipilimumab treatment was associated with more frequent production of antibodies against perinuclear anti-neutrophil cytoplasmic antibody (pANCA) and OmpC, two antigens that are known to be associated with inflammatory bowel disease [31]. Ipilimumab was also reported to induce production of circulating anti-double-stranded DNA antibodies, as well as IgG and IgM antibody deposits, in the kidney biopsy of a patient with metastatic melanoma who developed lupus nephritis after ipilimumab treatment [13]. In three patients who developed thyroiditis after ipilimumab therapy, levels of circulating anti-thyroid peroxidase antibody and thyroglobulin antibody were significantly higher than pretherapy baseline levels [32]. In a patient who developed hemophilia A after ipilimumab treatment, autoantibodies to factor VIII were found in the peripheral blood [33]. Ipilimumab may cause toxicity via augmented autoimmune T cell-specific responses against self-antigens shared by tumors and normal tissues. The induction of antibodies against tumor-associated antigens in peripheral blood and the presence of plasma cells and antibody deposits at the sites of toxicity suggest that ipilimumab may also cause toxicity via production of antibodies against these shared self-antigens.

## Cytokines

Inflammatory cytokines, including interleukin-17 (IL-17) and tumor necrosis factor alpha (TNF- $\alpha$ ), have long been known to cause inflammation and tissue damage. To determine whether inflammatory cytokines mediate anti-CTLA-4-induced side effects, researchers investigated the correlation between cytokine production and toxicity profiles in patients treated with another anti-CTLA-4 antibody, tremelimumab [34]. Although tremelimumab did not induce significant increase of IL-17 in the peripheral blood, IL-17 production was elevated in *ex vivo* activated peripheral blood mononuclear cells (PBMC) from tremelimumab-treated patients. Peripheral Th17 cell frequency also increased after anti-CTLA-4 treatment. Furthermore, there was significantly greater IL-17 production from the PBMC and CD4 T cells of patients who had dose-limiting side effects after anti-CTLA-4 treatment than from those of patients without significant side effects [34]. Complementary to these results was our finding that expression of the anti-inflammatory cytokine IL-10 dramatically decreased in a patient who developed uveitis and pancreatitis from ipilimumab treatment. The level of IL-10 returned to the baseline level after this patient's immune-related toxic effects started to resolve [22]. These findings suggest that anti-CTLA-4

treatment may induce a certain subset of inflammatory cytokines and in the meantime, inhibit anti-inflammatory cytokines. The imbalance of these inflammatory and anti-inflammatory cytokines may result in unwanted side effects.

## Discussion

Although anti-CTLA-4 therapy represents an unprecedented success of modern immunotherapy in prolonging survival of cancer patients, it is also associated with side effects known as irAEs. Understanding the mechanisms responsible for irAEs associated with anti-CTLA-4 therapy is, therefore, important for maximizing clinical benefit for patients and for the development of improved strategies to manage ipilimumab-associated irAEs.

Previous studies have indicated significant infiltration of immune cells, including CD4 T cells, CD8 T cells, neutrophils, plasma cells, and eosinophils, at the sites of toxicity after ipilimumab treatment [26–31]. Previous data have also indicated that anti-CTLA-4 can lead to decrease in regulatory T cells [35] which may lead to diminished immunosuppression and potentiation of irAEs. Anti-CTLA-4 therapy may also augment Th17 responses and shift Th2 responses to increased Th1 responses [36, 37], which may also contribute to increased inflammatory conditions and potentiation of irAEs. Additional studies are needed to better understand these mechanisms in order to develop specific treatments for irAEs. Future studies are also needed to delineate whether there is a direct relationship between inflammatory cytokines such as IL-17 and any specific type of ipilimumab-associated irAE (e.g., enterocolitis). These studies will be important for testing novel agents such as anti-IL-17 antibody, a very promising agent for treatment of autoimmune/inflammatory diseases such as psoriasis with little toxicity [38], as a treatment option for ipilimumab-associated irAEs.

Plasma cells were also found at the tissue sites of ipilimumab-induced irAEs. Multiple reports have indicated that ipilimumab treatment was associated with autoantibodies against tumor- or self-antigens [13, 32, 33, 39–41]. These data suggest that autoimmune antibody response may be at least partially responsible for ipilimumab-induced irAEs. Further study is needed to confirm whether certain tissue-specific autoantibodies are responsible for side effects induced by ipilimumab, as this may be used as the prognostic and/or diagnostic measure for predicting ipilimumab-induced irAEs.

There have been a number of attempts to develop algorithms for management of ipilimumab-induced irAEs [6, 12, 42]. In our experience, the key for managing ipilimumab-associated irAEs is to have a high level of suspicion and start corticosteroid therapy as early as possible with close monitoring. In addition, when irAEs improve to grade 1 after high-dose steroid treatment, the steroid dose should be tapered slowly, at a prednisone equivalent rate of 5–10 mg per week over at least a month. More rapid tapering of the steroid dose may cause rebound of irAEs. Furthermore, for organ-specific irAEs, early consultation of the pertinent specialist, such as a gastroenterologist, endocrinologist, dermatologist, ophthalmologist, neurologist, or rheumatologist, is important for successful management.

Patients who are on prolonged treatment with steroids need to be monitored closely for steroid-induced side effects including hyperglycemia (especially in diabetic patients), gastrointestinal ulceration/bleeding, opportunistic infection, hypertension, myopathy, and mental status change. In general, patients on high-dose steroids would require a proton pump inhibitor for gastrointestinal ulceration prophylaxis. In addition, an anti-infective agent such as bactrim or dapsone should be administered as prophylaxis for PCP. Regular follow-up with the primary care physician and medical oncologist is necessary to monitor these side effects associated with long-term steroid use.

Although irAEs are common with anti-CTLA-4, the potential for long-term clinical benefit outweighs the risks. Therefore, education regarding identification and treatment of irAEs is key for successful integration of anti-CTLA-4 into clinical practice. Many years ago, the chemotherapy agent cisplatin was considered too toxic to be used; however, due to its significant clinical benefit, physicians developed algorithms to manage the toxicities, including renal failure and nausea/vomiting, which helped to integrate cisplatin into clinical practice. Similarly, immunotherapy with agents such as anti-CTLA-4 have a novel set of toxicities as compared to chemotherapy agents, therefore, education regarding these novel toxicities will enable the development of treatment algorithms that will permit integration of these immunotherapy agents into clinical practice for the benefit of patients.

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