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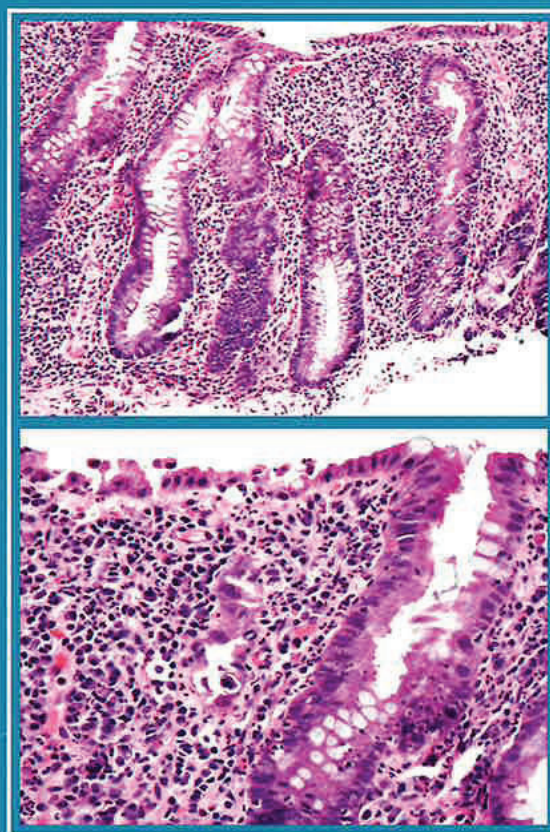
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Immunologic Checkpoints for Cancer Treatment: From Scientific Rationale to Clinical Application

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On the Cover: Enhancing T-cell response to tumor antigens has shown promising results in clinical trials involving patients with advanced-stage melanoma and renal cell carcinoma. Ultimately, these agents may be most useful in combination therapies to enhance tumoricidal response and to decrease systemic toxicity. Due to their mode of action, immune modulators may cause adverse immunologic events (AIEs). The cover figures (top, 20X; bottom, 40X) show an active colitis with crypt inflammation and crypt destruction secondary to an adverse immune reaction. AIEs most often involve the skin or gastrointestinal track. In the gut, an ulcerative colitis-like syndrome is not uncommon. Corticosteroids and drug cessation control most occurrences, but some reports cite the necessity of colectomy.

The Emerging Toxicity Profiles of Anti-CTLA-4 Antibodies Across Clinical Indications

Anna Maria Di Giacomo,^a Maurizio Biagioli,^b and Michele Maio^a

The promising new class of immunomodulating antibodies directed against cytotoxic T-lymphocyte antigen-4 (CTLA-4) has been extensively tested in clinical trials and found to be active against cutaneous melanoma and other tumor histotypes. Inhibition of CTLA-4 characteristically induces well-identified side effects for which the definition “immune-related adverse events” (irAEs) has been proposed. IrAEs mainly include colitis/diarrhea, dermatitis, hepatitis, and endocrinopathies; uveitis, nephritis, and inflammatory myopathy also have been reported occasionally. These unique side effects are likely a direct result of breaking immune tolerance upon CTLA-4 blockade and are generally mild, reversible, and manageable, following specific treatment guidelines that include symptomatic therapies or systemic corticosteroids. However, patient-physician communication and early treatment are also emerging as critical issues to successfully manage irAEs, thus avoiding major complications. The major experience in identifying and managing CTLA-4 treatment-related side effects has derived from studies in melanoma patients; nevertheless, accumulating clinical experiences are clearly demonstrating that irAEs are class-specific events, and that they are fully overlapping in patients with tumors of different histotypes. This review provides an overview of current safety data on CTLA-4 antagonists and of available strategies to optimize their clinical use in cancer patients.

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Preclinical data on targeted immunotherapy based on the use of antibodies that block the negative regulatory signals mediated by cytotoxic T-lymphocyte antigen-4 (CTLA-4), led to development of the two fully human therapeutic anti-CTLA-4 monoclonal antibodies (mAbs) ipilimumab and tremelimumab. Emerging data from phase II/III clinical trials are encouraging, and show antitumor activity of anti-CTLA-4 mAbs either used as single agents, or in combination with cytotoxic agents, or with other immunotherapies.^{1,2}

The kinetics of anti-CTLA-4-mediated disease control is clearly unique. In fact, while clinical response to traditional chemotherapy is usually rapid but frequently short-lived, disease control in response to anti-

CTLA-4 mAbs can be late in onset and may also occur after initial disease progression. These particular patterns of response to anti-CTLA-4 treatment are due to their unique immunologic mechanism of action and may persist over prolonged time periods, providing a sizeable proportion of patients with durable disease control. These findings require a paradigm shift in oncology practice, which will also include the use of novel response criteria. Along this line, the so-called immune-related response criteria have been recently proposed to assess clinical responses to immunotherapeutic strategies including CTLA-4 blockade.³

The accumulating clinical experience with anti-CTLA-4 mAbs also identified a novel syndrome of autoimmune or autoinflammatory side effects, which have been designated “immune-related adverse events” or irAEs. These typical side effects include mainly rash, colitis, hepatitis with increased liver function tests, and more occasionally hypophysitis and uveitis, and are considered the result of nonspecific or cross-reactive tissue damage caused by activated T cells. Therefore, it is not surprising that the safety profile of CTLA-4 blockade being reported is similar in melanoma patients and in individuals with solid tumors of different histologies. A dose-dependent increase in irAEs of any grade was also seen with increasing doses of ipilimumab. Generally, irAEs are mild and self-limiting, but grade 3/4

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events occur in a percentage of patients and may require supportive care and/or high-dose corticosteroids therapy, which do not appear to diminish the antitumor effects of CTLA-4 blockade. The most irreversible toxicity appears to be hypophysitis that is manageable with endocrine replacement therapy, whereas the most life-threatening effect is diarrhea/colitis, even if the incidence of bowel perforation requiring colectomy is less than 1%.⁴ Interestingly, the time course of irAEs development is variable and rather unpredictable, and likely dependent both on peak dosing and area under the curve of the drug.⁵ Failure to recognize and promptly treat early symptoms of irAEs, as well as poor compliance of patients with corticosteroid therapy had a prominent role in subjects who developed major complications. As more experience has been gained with anti-CTLA-4 treatment, mortality rates have dropped to approximately 1%. This finding demonstrates that while some of the toxicities can certainly be serious, proper education of patients and established algorithms for the effective management of irAEs should safely translate this therapeutic approach into community oncology practice. Interestingly, development and increasing severity of irAEs generally associate with tumor regression and with a prolonged time to relapse; nevertheless, this association is not absolute and patients without evidence of irAEs have also experienced significant clinical responses.⁶

PRESENTATION AND MANAGEMENT OF IMMUNE-RELATED ADVERSE EVENTS ACROSS CLINICAL INDICATIONS

Although safety data on anti-CTLA-4 mAbs derive essentially from clinical trials in cutaneous melanoma patients (Table 1), this novel therapeutic strategy also is being extensively tested in nonmelanoma indications such as lung, prostate, and renal cancer. These studies are clearly showing that completely overlapping irAEs can be observed, regardless of tumor histotype, identifying them as class-specific

toxicities. In the following sections the major irAEs observed with ipilimumab and tremelimumab in melanoma patients and their management will be discussed, together with a detailed description of irAEs in nonmelanoma indications.

Dermatologic irAEs

The diverse irAEs associated with CTLA-4 blockade affect most frequently the skin and include rash, vitiligo, and alopecia areata. The most common reported rash is a macular and papular exanthem affecting trunk and extremities; photodistributed patterns and photoexacerbation also have been reported.⁷

The histopathologic feature of the dermatitis is represented by epidermal spongiosis, papillary dermal edema, and perivascular lymphocytic and eosinophilic infiltrate with a preponderance of CD4⁺ T cells in the dermis; a notable increase of eosinophil count also has been observed.

Hair depigmentation in the course of anti-CTLA-4 therapy also has been reported to occur: six of 43 patients developed sudden hair depigmentation starting with the eyebrows, with subsequent complete depigmentation of all body hair or diffused vitiligo. Median time to depigmentation was 10 months. These patients also developed other irAEs such as pruritus (*n* = 4), rash (*n* = 6), diarrhea (*n* = 4), and hypophysitis (*n* = 2), and experienced a stable disease or a complete response ranging from 24 to 36 months.⁸ Recently, Lim et al reported the unique clinical presentation of a skin eruption that was predominantly intertriginous and follicular, with histopathologic features of follicular-based inflammation.⁹ Noteworthy, these dermatologic irAEs were generally mild and a symptomatic relief was provided by antihistamines (ie, diphenhydramine), while grade 3/4 autoimmune dermatitis was successfully treated with slowly tapered corticosteroids.

Table 1. Safety Profile of Ipilimumab Across Phase II Trials in Melanoma

irAEs	Study 008		Study 022				Study 007			
	10 mg/kg		0.3 mg/kg		3 mg/kg		10 mg/kg		10 mg/kg + Placebo	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Skin %	49	3	13	0	45	1	47	4	68	0
GI %	31	8	17	0	32	3	39	16	46	23
Hepatitis %	9	8	0	0	0	0	3	3	9	7
Hypophysitis %	6	1	0	0	6	3	4	1	5	5

Gastrointestinal irAEs

Diarrhea due to immune-mediated colitis is the most frequent gastrointestinal (GI) irAE; if untreated, it may lead to serious complications such as intestinal perforation.¹⁰ Grade 2 or worse diarrhea occurs in about 35% of patients treated with ipilimumab. Colitis appears to be the dose-limiting toxicity, and treatment guidelines developed in cooperation with GI experts have been successfully implemented into ipilimumab clinical trials. These guidelines, developed for the phase II ipilimumab clinical trials recommended the use of budesonide for grade 2, and high-dose corticosteroids for grade 3–4 diarrhea. Prophylactic budesonide was not recommended for the prevention of grade ≥ 2 diarrhea.¹¹ Although grade 3–4 diarrhea is generally reversible with standard anti-inflammatory therapies, experience suggests that patients with colitis treated with high-dose corticosteroids combined with mesalamine, and with seeming resolution of the side effects, can have an early recrudescence of the symptoms requiring either prolonged corticosteroid administration, tumor necrosis factor (TNF) blockade with infliximab at 5 mg/kg, or prolonged bowel rest with total parenteral hyperalimentation.

The interval from diarrhea onset ranged from 5 to 36 days, with a median of 14 days. The diarrhea was generally described as loose or watery, nonbloody stool, occurring four to eight times without fever, nausea, vomiting, or weight loss but sometimes associated with abdominal pain. No major blood chemistry abnormalities were found, and infectious diarrhea was excluded with stool analysis for parasites and *Clostridium difficile* toxin. Most subjects with diarrhea had endoscopic evidence of colitis, with grossly normal-appearing rectosigmoid mucosa. Colitis was consistently identified in the distal colon, although in some cases mucosal involvement was noncontiguous or patchy. Macroscopic abnormalities included erythema, edema, friability, erosions, and visible bleeding. Microscopic findings ranged from normal histology to severe inflammation, with neutrophil invasion and destruction of surface epithelium and crypts in most severely affected ipilimumab recipients. In the latter case, the lamina propria was heavily infiltrated by lymphocytes and neutrophils; crypt microabscesses were also occasionally seen. Moreover, rectosigmoid mucosal biopsy revealed mononuclear cells in the lamina propria with nuclear staining for forkhead box protein 3 (FoxP3); the frequency of FoxP3⁺ T-regulatory cells, as a percentage of CD3⁺ T cells, did not correlate with the severity of diarrhea or histologic inflammation.¹²

This spectrum of autoimmune colitis described in melanoma patients is fully comparable to that observed in other solid tumors treated with ipilimumab, both in terms of clinical presentation and management. Therefore, since this is a class-specific toxicity, the ability to adequately treat it through the implementation of com-

mon colitis treatment guidelines across clinical indications, will play a key role in the successful management of anti-CTLA-4 treatment in tumors of different histologies. Consistent with this notion, a recent analysis of the effectiveness of specific guidelines for the management of ipilimumab-mediated colitis in melanoma showed that treatment algorithm was effective in reducing the occurrence of serious GI complications.¹³

Hepatic irAEs

Hepatitis is uncommonly (<5%) associated with anti-CTLA-4 mAb treatment and generally presents in asymptomatic patients as a rise in the levels of aminotransferases (AST and ALT) with a lower rise in bilirubin. In most cases, if detected early during routine monitoring and if AST/ALT are below five times normal (ie, grade 2 toxicity), skipping a dose of mAb and waiting 3 weeks or more until the next scheduled dose is acceptable, if the liver toxicity decreases during this interval to grade 1. In the event of grade 3 liver toxicities, treatment should be discontinued and oral corticosteroids given for a minimum 30-day course. Liver functions should be monitored closely every 48–72 hours until they return to normal. A grade 4 liver toxicity requires high-dose intravenous (IV) corticosteroids, followed by mycophenolic acid at 5 mg/kg IV; if AST/ALT do not decrease within 48 hours, infliximab should be administered at 5 mg/kg IV.¹⁴ Liver biopsies performed in patients with hepatitis revealed acute hepatic inflammation with ballooning degeneration and diffuse lymphocyte infiltrates. Immunohistochemistry demonstrated predominantly CD4⁺ cells in the periportal regions and CD8⁺ cells in hepatic lobules.¹⁵

Though being potentially lethal, liver toxicities associated with anti-CTLA-4 treatment have been demonstrated to be reversible and manageable in the different solid tumors in which CTLA-4 blockade has been tested; however, routine blood chemistry screening and tight adherence to the treatment guidelines are strongly recommended.

Endocrine irAEs

Hypophysitis

The endocrine spectrum of irAEs associated with anti-CTLA-4 therapy is mainly characterized by the development of hypophysitis and autoimmune thyroid diseases. As opposed to cutaneous or GI irAEs, the onset of endocrinopathies is generally delayed, with a median time of 9–10 weeks from treatment initiation.

Autoimmune hypophysitis has been reported in up to 17% of patients with melanoma and renal cell carcinoma (RCC) treated with ipilimumab, with evidence of decreased levels of serum cortisol, adrenocorticotrophic hormone (ACTH), thyroid-stimulating hormone (TSH), and/or free T4.¹⁶ Subjects with hypophysitis had con-

comitant swelling of the pituitary gland on magnetic resonance imaging. Clinical symptoms were generally nonspecific and included fatigue, headache, memory loss, personality changes, and loss of libido. Although the symptoms of pituitary failure may be nonspecific, the enlargement of the hypophysis may cause headache and visual impairment. In rare cases, autoimmune hypophysitis also involved the neurohypophysis, with clinical signs of diabetes insipidus.

Histologic examination of the pituitary gland typically showed immune infiltration by lymphocytes, plasma cells, and macrophages. Unlike other irAEs, hypophysitis often did not improve with high-dose corticosteroids, and permanent hormone replacement therapy was required. The hypothalamic-pituitary (HP)-gonadal and HP-thyroidal axes frequently recovered, but only few patients were able to discontinue glucocorticoid (GC) replacement therapy, due to a persistent secondary adrenal insufficiency (SAI).¹⁷ Encouragingly, therapeutic doses of GC to treat irAEs do not seem to abrogate the antineoplastic benefits of anti-CTLA-4 treatment.

Based on these evidences, it is prudent to undertake screening for autoimmune hypophysitis for all patients undergoing CTLA-4 therapy. Subject developing signs and symptoms of hypophysitis and SAI, such as previously unreported or severe headache, visual impairment, polyuria, polydipsia, nausea, and vomiting, should undergo prompt medical evaluation. Likewise, given the potential morbidity and mortality associated with unrecognized hypopituitarism, it is recommended that early empiric GC replacement be initiated, pending biochemical confirmation, followed by high-dose GC and cessation of anti-CTLA-4 therapy upon confirmation. Treatment with levothyroxine should be delayed pending adequate treatment of GC deficiency so as not to precipitate adrenal crisis. Given the possible rapid onset of autoimmune hypophysitis during treatment, laboratory testing, including morning cortisol, free T₄, TSH, and clinical evaluation should be performed 2 weeks after the dose, and every 3–4 weeks during treatment. Moreover, since magnetic resonance imaging can detect pituitary enlargement before the onset of complete pituitary failure, it is highly recommended in the case of clinical suspicion of hypopituitarism.

Thyroiditis

An additional frequent presentation of the anti-CTLA-4-related endocrinopathies is autoimmune thyroid disease (AITD); of note, previous studies suggested that *CTLA-4* is a candidate gene for conferring susceptibility to thyroid autoimmunity.¹⁸ AITD generally occurs in two common forms: hyperthyroidism in Graves' disease and thyroid destruction with hypothyroidism in Hashimoto thyroiditis. Therefore, serum concentra-

tions of TSH, T₄, and T₃, and of autoantibodies against thyroid peroxidase (TPOab) and thyroglobulin (TGab), have to be tested during treatment. In most cases the AITD is subclinical and characterized by hyperthyroidism with increased serum TSH concentrations, normal T₃ and T₄, and presence of TPOab (less commonly TGab) or hypothyroidism, requiring long-term thyroid hormone supplementation.

With the increasing experience deriving from clinical trials, oncologist and endocrinologists should be aware of the potential endocrine toxicities that may occur in patients treated with these novel immunomodulatory mAbs. Given the evidences of autoimmune hypophysitis and thyroiditis during anti-CTLA-4 therapy, appropriate screening procedures and algorithms for early therapeutic intervention have been incorporated into clinical trials.

Uncommon irAEs

Infusion-related anaphylactic reactions to anti-CTLA-4 mAb administration are extremely uncommon, making it safer by comparison to other therapeutic mAbs that contain small amounts of nonhuman residual sequences.

Pancreatitis, with increases in amylase and lipase associated or not with diarrhea and abdominal pain, was described in 1% to 3% of patients; moreover, evidence of asymptomatic increases of pancreatic enzymes, generally reversible with oral corticosteroids, also has been reported.¹

Ocular side effects during treatment with anti-CTLA-4 mAbs are rare (1%–2%), and generally associated with a decrease in visual acuity, photophobia, and painful tearing from both eyes.¹⁹ The ophthalmologic examination is generally characterized by an autoimmune uveitis, with posterior synechiae and irregular pupils, or episcleritis. Histopathologic examination showed superficial perivascular lymphocyte infiltrate with a CD3⁺CD8⁺ phenotype. Periocular corticosteroid injections and corticosteroid eye drops, generally led to a complete resolution within 4–7 days.

Inflammatory myopathy²⁰ and lupus nephritis,²¹ as well neutropenia²² and immune-related red blood cell aplasia,²³ are occasionally reported in patients with metastatic melanoma treated with ipilimumab. A case of severe refractory constipation has been reported during treatment with ipilimumab. Colonic wall biopsies showed a prominent inflammatory infiltrate with inflammation around the myenteric plexus. Although constipation has not been traditionally perceived as an irAE, it is consistent with the immune-mediated inflammatory neuropathy related to ipilimumab.²⁴

In light of the evidences above, the complex mechanism of action of anti-CTLA-4 mAbs makes their toxicity profile extremely varying; therefore, prompt recognition also of uncommon irAEs is essential for the

Table 2. Incidence of Grade 3/4 irAEs in NSCLC Patients Treated With Ipilimumab

irAEs	Concurrent Ipilimumab + Chemotherapy (N = 71)		Phased Ipilimumab + Chemotherapy (N = 67)		Placebo Chemotherapy Only (N = 65)	
	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
Dermatologic	4.2*	0	3.0	0	1.5	0
Pruritus	0	0	0	0	1.5	0
Rash	2.8	0	3.0	0	1.5	0
GI	7.0	0	6.0	0	3.1	0
Diarrhea	7.0	0	4.5	0	3.1	0
Colitis	0	0	3.0	0	0	0
AST	2.8	0	0	0	0	0
ALT	2.8	0	1.5	0	0	0

Data derived from Lynch et al.²⁵

Abbreviations: irAEs, immune-related adverse events; NSCLC, non-small cell lung cancer; GI, gastrointestinal.

*% observed.

optimal comprehensive management of anti-CTLA-4 therapy.

Ipilimumab-Mediated irAEs in Nonmelanoma Indications

The toxicity profile associated with ipilimumab treatment of lung, prostate, renal, and pancreatic cancer patients, was substantially similar to that observed in melanoma, being characterized by “conventional” irAEs such as cutaneous rash, colitis, diarrhea, and/or hepatitis. Recent data from a phase II trial of ipilimumab and paclitaxel/carboplatin in first-line stage IIIb/IV non-small cell lung cancer (NSCLC) patients showed that the toxicity profile was consistent with previous studies in melanoma. The key drug-related side effects were typically irAEs, and grade 2–3 dermatologic (pruritus and rash) and GI (colitis and diarrhea) toxicities were commonly observed; two patients experienced grade 1–2 hypothyroidism, while no instances of grade 4 dermatitis or colitis were observed

(Table 2).²⁵ Figure 1 shows the cutaneous rash observed in a patient with NSCLC treated within this phase II trial. In NSCLC patients dermatitis had clinical and histopathologic features overlapping to those observed in melanoma, and was successfully treated symptomatically and/or with corticosteroids.

Final results of phase I/II studies of CTLA-4 blockade for metastatic castration-resistant prostate cancer (mCRPC) showed that the most frequently observed toxicities involved the GI tract and the skin, and were also attributed to the activation of the immune system. Among the 36 patients treated in a phase I trial with ipilimumab and granulocyte-macrophage colony-stimulating factor (GM-CSF) for mCRPC, irAEs were generally grade 1–2, while grade 3 irAEs included rash (five patients), panhypopituitarism (one patient), temporal arteritis (one patient), and diarrhea (three patients).²⁶

In a pilot study using ipilimumab at 3 mg/kg IV in mCRPC, treatment was well tolerated overall. The most

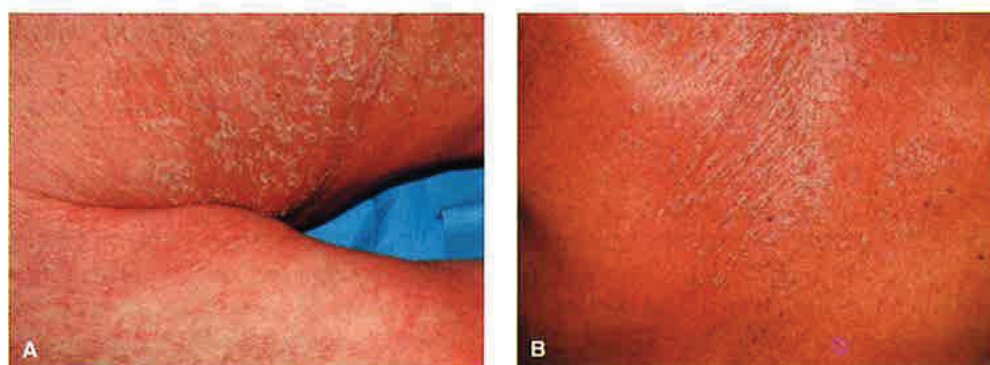


Figure 1. Dermatitis in a lung cancer patient treated with ipilimumab. Dermatitis as macular rash occurred on the lower limbs (A) and trunk (B) of a 72-year-old man with NSCLC treated with ipilimumab.

frequently reported adverse events included arthralgia (50%), malaise (43%), bone pain (43%), pallor (36%), back pain (36%), constipation (29%), fatigue (29%), and decreased appetite (19%). The majority of these events were grade 1 and 2. Grade 3 toxicities consisted of asthenia in one patient (7.1%), limb pain in one patient (7.1%), and cutaneous rash in one patient (7.1%). Fourteen serious adverse events were reported in six patients, but only in two cases were they considered related to treatment: one patient had grade 3 fatigue and the other had grade 3 rash and pruritus. The patient with grade 3 fatigue had no other clinical evidences of autoimmunity, although testing for hypophysitis (hypothyroidism/hypoadrenalism) was not undertaken. The second patient had moderate rash and pruritus that started on day 12, worsened by day 23 (grade 2 pruritus and grade 3 rash), and were unresponsive to treatment with hydroxyzine, diphenhydramine, cimetidine, and ibuprofen. However, treatment with prednisone 20 mg orally twice daily, starting on day 28, resulted in rapid resolution of symptoms that did not re-occur after prednisone was discontinued. One patient had an episode of grade 3 diarrhea, that began on day 42 and lasted for 16 days, and that was attributed to a *Clostridium difficile* infection. No clinically significant changes in laboratory values, physical examination results, electrocardiogram, or chest radiograph were observed in any patient, and no patient discontinued therapy due to toxicity. In this pilot study autoimmune hypophysitis was not observed, although no screening for hypophysitis was undertaken.²⁷

That safety profile of ipilimumab treatment of mCRPC patients did not substantially differ from that observed during treatment of second line metastatic melanoma patients, as indicated by the incidence of grade 3/4 irAEs reported in Table 3.

A phase II trial of single-agent ipilimumab in patients with RCC showed a typical toxicity profile characterized by enteritis, dermatitis as an extensive generalized rash, and endocrine disorders. Among

the 21 patients enrolled in cohort A, three patients (14%) had a grade 3 colitis presenting with diarrhea, while 17 of 40 the patients enrolled in cohort B (43%) developed clinically meaningful irAEs (14 grade 3, two grade 2, one grade 5). Enteritis alone was observed in 13 patients, hypophysitis in one patient, and both in one patient.⁹ As previously reported for melanoma, the earliest manifestations of autoimmune hypophysitis were decreased levels of serum cortisol, ACTH, TSH, and free T4 and pituitary swelling. These toxicities benefited of brief courses of high-dose IV corticosteroids.

Tremelimumab-Mediated irAEs in Non-melanoma Indications

Several phase I/II trials have investigated the safety and efficacy of tremelimumab in tumors of different histologies; treatment was generally well tolerated and most frequent therapy-related irAEs were diarrhea, rash, pruritus, and endocrine abnormalities.

In a phase I study in hormone-responsive advanced breast cancer, 26 patients received tremelimumab (3 or 6 mg/kg) every 28 days, or (6 or 10 mg/kg) every 90 days plus exemestane 25 mg daily; the toxicity profile observed with this combination was consistent with the known safety profile established for tremelimumab in other tumor histologies. Adverse events were mild to moderate, the most common being diarrhea (46%), pruritus (42%), constipation (23%), and fatigue (23%). No grade 4 irAEs were observed. As reported for ipilimumab, the histopathologic features of the tremelimumab-associated colitis were characterized by a lymphocytic infiltration in the colon.²⁸ Evidence from other clinical trials had suggested that a 28-day dosing schedule might worsen the severity and frequency of tremelimumab-specific diarrhea; therefore, enrollment of patients in the every-28-days schedule was discontinued. This evidence emphasizes the importance of dose and schedule for safely delivering anti-CTLA-4 mAbs.

Table 3. Grade 3/4 irAEs in Metastatic Castration-Resistant Prostate Cancer and Melanoma Patients Treated With Ipilimumab Compared Across Different Trials

irAEs	mCRPC (ipilimumab dose)		Melanoma (ipilimumab dose)	
	3 mg/kg (n = 82) Grade 3–4	5 mg/kg (n = 20) Grade 3–4	10 mg/kg (n = 20) Grade 3–4	10 mg/kg (n = 155) Grade 3–4
Skin %	—	5	—	3
GI %	12	15	15	8
Hepatitis %	1	10	15	7
Endocrine %	7	15	5	1

Abbreviations: irAEs, immune-related adverse events; mCRPC, metastatic castration-resistant prostate cancer.

A randomized phase II clinical trial compared tremelimumab with best supportive care (BSC) in 87 NSCLC patients who had failed to respond to a first-line platinum-based regimen. The progression-free survival (PFS) analysis did not demonstrate superiority of tremelimumab over BSC; however, the safety and tolerability of this agent were similar to that observed in previous clinical trials in melanoma patients. Treatment-related adverse events were observed in 27 (61.4%) patients receiving tremelimumab and in three (7.0%) receiving BSC. Nine patients (20.5%) receiving tremelimumab reported grade 3 or 4 irAEs compared to none receiving BSC. The most common grade 3 or 4 irAEs attributed to tremelimumab were diarrhea and colitis ($n = 4$, 9.1%). However, treatment was considered to be feasible and safe.²⁹

In a phase I dose-escalation study combining tremelimumab with sunitinib (SU) in 21 patients with mRCC, two of five patients in the SU 50 mg plus tremelimumab (6 mg/kg) cohort experienced dose-limiting toxicities (DLTs), with one grade 5 ruptured diverticulum and one prolonged grade 3 mucositis and fatigue. Further exploration of this schedule for SU was halted. In the SU 37.5 mg daily continuous cohorts, no DLTs were observed at 6 mg/kg tremelimumab ($n = 3$), one of six patients treated with 10 mg/kg tremelimumab in the protocol-defined cohort suffered sudden death, and three of six patients treated with 15 mg/kg tremelimumab + SU experienced DLTs, including one grade 3 acute renal failure and grade 3 lymphopenia, one grade 3 elevated creatinine, and one worsening grade 3 dyspnea. Therefore, SU 37.5 daily + tremelimumab 10 mg/kg every 12 weeks was considered the maximum tolerated dose. Further exploration of this combination in mRCC was advised as treatment with tremelimumab at 10 mg/kg every 12 weeks + SU 37.5 mg daily was tolerable and associated with signs of antitumor activity.³⁰

Tremelimumab was recently tested also in a phase II trial in patients with refractory metastatic colorectal cancer who had failed to respond to standard treatment. Patients received 15 mg/kg tremelimumab IV every 90 days until disease progression; treatment was generally well tolerated. Although tremelimumab did not demonstrate meaningful antitumor activity, the overall toxicity profile was as expected for this class of agents. No tremelimumab-related hypersensitivity reactions during infusion were observed. Grade 3–4 treatment-related irAEs were diarrhea ($n = 5$; 11%), ulcerative colitis ($n = 5$; 2%), fatigue ($n = 1$; %), autoimmune thrombocytopenia ($n = 1$; 2%), and hypokalemia ($n = 1$; 2%) that resolved spontaneously or with treatment. No significant endocrine irAEs were observed. Additional irAEs included grade 1 uveitis ($n = 1$; 2.1%) and grade 1 rash ($n = 4$; 8.5%). These irAEs were usually transient and did not worsen with continued therapy (Table 4).³¹

Table 4. Treatment-Related irAEs in Patients With Refractory Metastatic Colorectal Cancer Treated With Tremelimumab

	Grade 1	Grade 2	Grade 3
Diarrhea	19.1 ^b	6.4	10.6
Fatigue	8.5	4.3	2.1
Nausea	8.5	4.3	0
Pyrexia	12.8	0	0
Vomiting	4.3	6.4	0
Constipation	2.1	4.3	0
Rash	8.5	0	0
Colitis	4.3	0	2.1

Data derived from Chung et al.³¹

Abbreviation: irAEs, immune-related adverse events.

^a% observed.

Tremelimumab was also investigated in a phase II trial as second-line treatment for patients with metastatic gastric or esophageal adenocarcinomas. Drug-related toxicities were generally mild and characterized by itch (50%), rash and eosinophilia (33%), and diarrhea and fatigue (28%). Most cases of diarrhea were self-limiting; however, there was a single death due to a bowel perforation that complicated colitis. Dermatitis was generally a maculopapular eruption distributed on the limbs and torso, and was reversible and manageable with corticosteroid creams.³²

Ipilimumab-Mediated irAEs Outside Clinical Trials

Confirming the efficacy and safety of anti-CTLA-4 mAbs as promising therapeutic tools, two single-institution experiences with ipilimumab in advanced melanoma patients have been collected within an Expanded Access Program (EAP) activated in the United States³³ and in Europe (Di Giacomo AM, et al, unpublished data). This program included patients with life-threatening, unresectable stage III or IV melanoma who had failed or could not tolerate previous treatments, and for whom no alternative treatment was available. Both experiences have shown a safety profile absolutely comparable to that previously observed in clinical trials in metastatic melanoma patients. Grade 3/4 irAEs occurred in 29% (51 patients, United States) and 26% (27 patients, Europe) of patients, the most common being pruritus, rash, colitis with diarrhea, hepatitis, and thyroiditis. Also in this setting, which more closely mirrors the daily clinical practice, irAEs were generally mild and manageable symptomatically and/or with corticosteroids. These experiences demonstrate that ipilimumab treatment is feasible, safe, and clinically effective also in the common daily practice, and in heavily pretreated, progressing, metastatic melanoma patients.

CONCLUSIONS

The novel immunotherapeutic approach based on CTLA-4 targeting by therapeutic mAbs is a promising strategy that will likely impact the current management of human tumors of different histotypes. Well-defined irAEs are commonly associated with CTLA-4 blockade and represent the toxicity profile to be expected with this therapeutic approach. Noteworthy, the clinical experience built with anti-CTLA-4 mAbs in recent studies has demonstrated a better safety profile as compared to earlier trials, suggesting that a more skilled identification and management of irAEs significantly improves the safety of anti-CTLA-4 treatment. In this respect, guidelines and algorithms for the treatment of irAEs have been developed and demonstrated to be useful to manage them. These guidelines are extensively described by Kaehler et al in this issue of *Seminars in Oncology*. The experience gained so far with anti-CTLA-4 mAbs also shows that educating patients about irAEs symptoms is essential, because they can emerge at any time during therapy and prompt treatment can prevent more severe or life-threatening events.

The overlapping toxicities of ipilimumab and tremelimumab identified across different indications, demonstrate that the optimal management of their class-related toxicity profiles will allow treatment to be safe and manageable in daily clinical practice outside referral institutions. To achieve this goal an extensive and careful education of the oncologists also will contribute to the most appropriate management of patients on anti-CTLA-4 therapy.

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