

SECTION EDITOR'S NOTE: In this issue of *The Oncologist*, two articles describe the recent clinical experience with two novel antibodies that abrogate the function of CTLA-4, a molecule expressed on T cells that acts to exert a dampening effect on the immune system. These antibodies were produced using different types of mice with engineered immune systems, and are thus fully human, with long half-lives of 2–4 weeks. Both antibodies, one produced by Pfizer and the other from Bristol-Myers Squibb/Medarex, have been shown to have clinical activity against metastatic melanoma and other histologies. Their use is accompanied by a unique spectrum of autoimmune side effects that in some cases are associated with clinical response and long-term freedom from progression. The kinetics of response in patients receiving either of these antibodies can be unusually prolonged, and in some cases patients with mixed responses or even progressive disease may subsequently

achieve an objective response. Their clinical testing has ushered in a new era in immunotherapy, with a new set of side effects to be managed, and encouraging clinical activity that has driven the two companies to conduct four registration trials. If the trials are successful, and if one or both CTLA-4-antibodies are approved by the U.S. Food and Drug Administration, that would mark the first new agents approved for melanoma in over a decade. The initial success with these antibodies has encouraged the rapid development of new agonistic and antagonistic antibodies that alter immune regulation, such as anti-PD-1, anti-4-1BB, anti-CD40, and anti-OX-40. As new members of the co-stimulatory interactions between effector cells and antigen presenting cells are described, exciting new targets for immunotherapeutic intervention in oncology will be defined.

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Review: Anti-CTLA-4 Antibody Ipilimumab: Case Studies of Clinical Response and Immune-Related Adverse Events

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Key Words. Cytotoxic T lymphocyte antigen 4 • CTLA-4 • Ipilimumab • Melanoma • Immune-related adverse events

LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Describe the completed and ongoing clinical trials of ipilimumab in patients with advanced melanoma.
2. Discuss the nature of immune-mediated adverse events, which are often associated with ipilimumab treatment.
3. Describe several cases illustrating the kinetics of ipilimumab-mediated antitumor responses and the relationship to immune-mediated adverse events.

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ABSTRACT

The immune system is a powerful natural agent against cancer. Cytotoxic T lymphocyte antigen 4 (CTLA-4), a key negative regulator of T-cell responses, can restrict the antitumor immune response. Ipilimumab (MDX-010) is a fully human, monoclonal antibody that over-

comes CTLA-4-mediated T-cell suppression to enhance the immune response against tumors. Preclinical and early clinical studies of patients with advanced melanoma show that ipilimumab promotes antitumor activity as monotherapy and in combination with treat-

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ments such as chemotherapy, vaccines, or cytokines. Emerging data on the kinetics of response to ipilimumab and associated adverse events are increasing our understanding about how to manage patients treated with this therapy. For example, short-term tumor progression prior to delayed regression has been observed in ipilimumab-treated patients, and objective responses may be of prolonged duration. In some patients clinical improvement manifests as stable disease, which may also extend for months or years. Immune-related adverse events (IRAEs) have been

observed in patients after CTLA-4 blockade and most likely reflect the drug mechanism of action and corresponding effects on the immune system. Early clinical data suggest a correlation between IRAEs and response to ipilimumab treatment. This paper briefly reviews the results from several ongoing and completed ipilimumab clinical trials, provides a synopsis of current trials, and presents several cases that demonstrate the kinetics of antitumor responses and the relationship to IRAEs in patients receiving ipilimumab. *The Oncologist* 2007;12:864–872

Disclosure of potential conflicts of interest is found at the end of this article.

INTRODUCTION

Abrogating immune regulatory molecules such as cytotoxic T lymphocyte antigen 4 (CTLA-4) represents a new and promising strategy to induce tumor regression, stabilize disease, and prolong survival by manipulation of the immune system [1, 2]. CTLA-4 antibodies are currently being tested in phase II and III trials in melanoma, and in phase I/II trials in other tumor types. There are currently two human antibodies being tested, one from Medarex, Inc. (Princeton, NJ) and Bristol-Myers Squibb (New York), called ipilimumab (MDX-010), and one from Pfizer (New York), called CP 675,206. Evidence of tumor regression with prolonged time to progression has been seen in patients with melanoma who received either of the CTLA-4 antibodies [3, 4] and durable responses have been observed with ipilimumab in patients with melanoma [5], ovarian cancer [6], prostate cancer [7], and renal cell cancer [8]. Interestingly, antitumor responses may be characterized by short-term progression followed by delayed regression, and an important, possibly unique, clinical characteristic of anti-CTLA-4 antibodies is that the duration of clinical responses and even stable disease is often quite prolonged.

Inhibition of CTLA-4 in patients characteristically induces side effects that are called immune-related adverse events (IRAEs). These IRAEs are inflammatory in nature and may represent a breaking of tolerance to self-antigens [8, 9]. The most common IRAEs are rash, colitis, and hepatitis. Other types of inflammation, like hypophysitis, are rarer. Interestingly, IRAEs appear to be associated with tumor regression in patients with renal cell cancer and metastatic melanoma, and with prolonged time to relapse in those with resected high-risk melanoma [5, 10–12]. Thus, there is a linkage between breaking of tolerance and clinical benefit in melanoma and renal cell cancer, and there is likely a similar phenomenon in prostate cancer [7]. The timing of the onset of IRAEs is highly variable, and is probably dependent both on peak dosing and area under the curve of

drug. Similarly, the timing of the onset of antitumor responses can be variable and prolonged for weeks after cessation of ipilimumab [13] (J. Weber, unpublished data).

In this article, I briefly describe findings from several ongoing and completed trials with ipilimumab, present a summary of ongoing trials that reflect current strategies in the development of immunomodulators, and present several cases that highlight the kinetics of antitumor responses and the relationship to IRAEs in patients receiving the CTLA-4 antibody ipilimumab. If these agents, and others like them that are entering early testing, become approved for the treatment of solid tumors, then understanding the kinetics of antitumor responses, their relationship to IRAEs, and how to manage and minimize IRAEs will take on great importance.

SUMMARY OF ONGOING AND COMPLETED TRIALS WITH IPILIMUMAB

Ipilimumab has been used as monotherapy or combined with other therapies including chemotherapy, vaccines, and cytokines (Table 1). In the first phase I trial, 17 patients with malignant melanoma received a single i.v. dose of 3 mg/kg ipilimumab. The findings showed that ipilimumab was well tolerated and provided clear evidence of immunologic and antitumor activity, providing a basis for further trials [14]. In another phase I trial, Hodi and colleagues reported that a single dose of ipilimumab (3 mg/kg) may have increased antitumor immunity in previously immunized patients with metastatic melanoma. In addition, there were no serious adverse events in the seven treated patients [6].

Because of the mechanism of action of ipilimumab, an initial focus was to evaluate its effectiveness in combination with vaccination. In 2005, Attia et al. [5] reported that ipilimumab (3 mg/kg every 3 weeks or 3 mg/kg initial dose then 1 mg/kg every 3 weeks) plus a peptide vaccine resulted in two complete responses and five partial responses among 56 patients with progressive stage IV melanoma. The com-

Table 1. Summary of activity and immune-related adverse events (IRAEs) in phase I and II trials of ipilimumab in patients with metastatic melanoma

Ipilimumab dose	CR, % (n); duration	PR, % (n); duration	SD, % (n); duration	Most common grade III/IV or serious IRAEs
Ipilimumab + vaccine (pretreated) [5]				
3 mg/kg every 3 wks or 3 mg/kg initial dose then 1 mg/kg every 3 wks	3.6 (2/56); 30+ and 31+ mos	8.9 (5/56); 4, 6, 25+, 26+, and 34+ mos	N/A	Colitis and dermatitis
Ipilimumab + vaccine (resected disease) [13]				
3 mg/kg every 8 wks for 12 mos	6 of 25 patients had relapsed after a 12-mo follow up (no deaths)			Colitis, rash, and hypophysitis
Ipilimumab (first line) [16]				
3 mg/kg/mo × 4	0	5.4 (2/37); 16+ and 18+ mos	10.8 (4/37); 3, 4, 9, and 14 mos	Rash, colitis, uveitis, and adrenal insufficiency
Ipilimumab + DTIC (first line) [16]				
3 mg/kg/mo × 4	5.7 (2/35); 017+ and 20+ mos	11.4 (4/35); 3, 3, 4, and 21+ mos	11.4 (4/35); 4, 6, 7, and 8 mos	
Ipilimumab + IL-2 [15]				
0.1–3 mg/kg every 3 wks	8.3 (3/36); 13+, 13+, and 16+ mos	13.9 (5/36); 7, 11, 11+, 14+, and 19+ mos	N/A	Enterocolitis
Abbreviations: CR, complete response; DTIC, dacarbazine; IL-2, interleukin 2; N/A, not available or not reported; PR, partial response; SD, stable disease.				

plete responses were ongoing at 30 and 31 months, and three of the partial responses were ongoing at 25, 26, and 34 months (the other two partial responses lasted for 4 and 6 months) [5]. A vaccine combination trial is ongoing with ipilimumab plus a multi-peptide vaccine in the adjuvant setting (patients with resected stage IIIC/IV melanoma and no evidence of disease). After a median follow-up of 12 months, six of the 25 treated patients had relapsed. The relapses were managed either surgically or with biochemotherapy and all patients were alive, one with disease, at the time of reporting [13].

Ipilimumab has also been given in combination with cytokines. In 2005, Maker and co-workers reported data from a trial of ipilimumab (0.1–3 mg/kg every 3 weeks) with interleukin 2 (IL-2) in 36 patients with advanced melanoma. Three patients had a complete response and five had a partial response, giving an overall response rate of 22%. Responses occurred in one of each of the three patients treated at 0.3, 1, and 2 mg/kg, and in 5 of 24 patients treated at 3 mg/kg. Six of the eight responders had ongoing responses at between 11 and 19 months [15].

Finally, a phase II trial of ipilimumab (3 mg/kg per month × 4) in combination with dacarbazine (DTIC) in chemotherapy- and vaccine-naïve patients with metastatic melanoma has been completed. The most recent data show that there are two patients with a partial response and four

with stable disease among the 37 patients who received ipilimumab alone. Among the 35 patients given the combination, there were two patients with a complete response, four with a partial response, and four with stable disease. Many of the responses are durable: the two partial responses in the ipilimumab-alone patients are ongoing at 16 and 18 months. In the combination arm, the complete responses are ongoing at 17 and 20 months, respectively, and a partial response is ongoing at 21 months. The median progression-free survival time is 2.7 months in the ipilimumab-alone arm and 3.3 months in the combination arm [16]. Evidence of durable response has been observed with ipilimumab in this trial, and also in patients with renal cell cancer [8] and ovarian cancer [6]. The ongoing phase II and III trials will show if these durable responses translate into a survival benefit.

As noted in the introduction, ipilimumab treatment is often associated with adverse events that are primarily immune in nature. Although IRAEs are often mild, in the aforementioned studies the incidences of grade III/IV events have been reported (Table 1). Grade III/IV IRAEs are generally reversible, and most are treated with standard anti-inflammatory therapies (i.e., corticosteroids). Experience suggests that patients with colitis who have been treated with high-dose steroids with seeming resolution of the side effects can have an early recrudescence of the

symptoms requiring either prolonged steroid administration, tumor necrosis factor (TNF) blockade with infliximab, or prolonged bowel rest with total parenteral hyperalimentation (J. Weber, unpublished data). The vast majority of grade III/IV IRAEs will resolve completely after systemic immune suppression that is sometimes prolonged. Life-threatening, severe adverse events are rare; Beck and colleagues reported the incidence of bowel perforation or colectomy to be <1% [10].

Increasing evidence suggests that IRAEs may correlate with response to ipilimumab. Attia and colleagues reported that ipilimumab-treated patients experiencing grade III/IV IRAEs had a significantly higher rate of tumor regression than those without IRAEs (36% versus 5% of patients) [5]. As reported by Beck and associates, the objective response rate was significantly higher in ipilimumab-treated melanoma patients who developed enterocolitis compared with those who did not (36% versus 11%) [10]. Preliminary results also suggest that the association may hold true in the adjuvant setting [13]. Further studies will help to elucidate the relationship between IRAEs and response to ipilimumab treatment.

Clinical trials are in progress with ipilimumab in various regimens. One is a phase II, multicenter, single-arm trial of ipilimumab (10 mg/kg) for previously treated patients with stage III (unresectable) or IV melanoma. The target enrollment is 150 patients and endpoints include response rate, progression-free survival rate, and overall survival. Enrollment into this trial is closed and results are expected by the end of 2007. Many ipilimumab trials are open for enrollment. The largest is a phase III trial of ipilimumab (10 mg/kg) plus DTIC versus DTIC plus placebo for untreated patients with stage III (unresectable)/IV melanoma. The primary outcome measure is the overall progression-free survival rate at 6 months and 500 patients are expected to be enrolled.

Other ipilimumab trials of interest are: (a) an exploratory study of ipilimumab monotherapy (two dose levels) in patients with metastatic melanoma amenable to biopsy to determine potential predictive markers of response and/or toxicity in patients with unresectable stage III or IV melanoma; (b) two trials (one using an extended ipilimumab dosing schedule) examining ipilimumab plus multi-peptides emulsified with Montanide ISA 51 (ISA) for patients with resected stage III/IV melanoma; (c) a phase II study of ipilimumab extended-treatment monotherapy or follow-up for patients previously enrolled in ipilimumab trials—the main objective is to evaluate the safety of using ipilimumab in a reintroduction or maintenance setting. More information about ipilimumab trials can be obtained from <http://www.clinicaltrials.gov>.

IPILIMUMAB CASE PRESENTATIONS

Methods

The patients described herein were treated in two trials conducted at the University of Southern California (USC)/Norris Comprehensive Cancer Center in Los Angeles. In one phase II trial evaluating ipilimumab plus a melanoma-specific peptide vaccine, NCI P-6446, patients had resected stage III or IV melanoma by the 2001 modified American Joint Commission on Cancer staging system and were rendered free of disease surgically. In the second phase II trial (ongoing, CA184-007) they had unresectable and measurable stage IV melanoma. All patients had a magnetic resonance imaging or computed tomography (CT) scan of the brain and CT imaging of the chest, abdomen, and pelvis performed within 4 weeks of therapy. Eligibility criteria for both trials included age ≥ 18 , creatinine < 2.0 mg/dl, bilirubin < 2.0 mg/dl, platelet count $\geq 100,000/\mu\text{l}$, hemoglobin ≥ 9 g/dl, and total WBC $\geq 3,000/\mu\text{l}$. HIV, hepatitis C antibody, and hepatitis B surface antigen titers were required to be negative. All patients in the vaccine trial were HLA-A*0201 positive by a DNA polymerase chain reaction assay. Patients in both trials were required to comprehend and sign an informed consent form approved by the Cancer Therapy Research Program of the National Cancer Institute and the Los Angeles County and USC Institutional Review Board. Exclusion criteria included active autoimmune disease, steroid dependence, and prior treatment with ipilimumab. Ipilimumab at 10 mg/kg (provided by Medarex, Inc.) was administered i.v. over 90 minutes in both trials.

In the vaccine trial for resected melanoma [13], NCI P-6446, ipilimumab was administered every 8 weeks for 12 months and ipilimumab infusions were accompanied by 12 vaccinations of three separate s.c. injections of 1 mg of a peptide emulsified in ISA in one extremity. Patients received tyrosinase₃₆₈₋₃₇₆ (370D), gp100₂₀₉₋₂₁₇ (210M), and MART-1₂₆₋₃₅ (27L) peptides. A leukapheresis procedure with exchange of 5–7 liters to obtain peripheral blood mononuclear cells for immune analyses was performed immediately before and 6 months after the initial vaccination. Repeat CT scans of the neck, chest, abdomen, and pelvis were performed with and without contrast every 3 months for the year of treatment and for 2 years thereafter. Patients were followed until relapse.

In the phase II trial in metastatic melanoma patients (CA184-007), antibody was administered four times, at 3-week intervals, at weeks 1, 4, 7, and 10. All patients were randomly allocated to receive either a placebo or budesonide at 9 mg daily by mouth in a double-blinded fashion. Patients were evaluated for response at week 12 with repeat CT scans of the neck, chest, abdomen, and pelvis performed

with and without contrast. Scans were also repeated at weeks 16, 20, and 24 in patients with stable or regressing disease to verify response. In those with stable disease or a response at week 24, additional booster doses of ipilimumab could be given at 12-week intervals.

Results

Gastrointestinal Toxicity Case History #1

The patient is an 82-year-old man with a history of relapsed melanoma with multiple pulmonary metastases that were noted on routine scanning after a resection of a primary melanoma in 2004. He received ipilimumab (10 mg/kg) every 3 weeks, four times, in a double-blinded, randomized trial in which patients received oral budesonide at 9 mg daily or placebo for 12 weeks during their initial treatment course with ipilimumab. The budesonide or placebo was then tapered off over 4 weeks. After the first two doses, the patient complained of diffuse myalgias that responded to ibuprofen or an occasional hydrocodone tablet, but did not prevent him from performing routine activities of daily life. One week after the third dose, the patient complained of watery diarrhea up to seven times in one day, was febrile, and was admitted to an outside hospital. He developed bloody diarrhea the day after admission, and was treated with i.v. steroids. Colonoscopy showed diffuse colitis with punctuate hemorrhage. He was treated with i.v. methylprednisolone (Solu-Medrol®; Pfizer Pharmaceuticals, New York) at tapering doses from 125 mg twice a day down to 60 mg daily after 1 week, and then placed on a 30-day tapering course of prednisone starting at 60 mg by mouth daily; open-label budesonide at 9 mg by mouth daily was continued for a total of 30 days during the prednisone taper, and the diarrhea abated. He was discharged from the hospital after 12 days, and his first evaluation by CT scanning at week 12 after starting therapy showed significant regression of all mediastinal and pulmonary disease. His week 16 scans showed continued regression, and week 20 scans showed a stable partial response. At week 24 after starting ipilimumab therapy he is well, without diarrhea, abdominal pain, nausea, or vomiting, with a performance status of 90%.

Hepatic Toxicity Case History #1

The patient is a 65-year-old man with a facial melanoma primary and multiple pulmonary metastases who had been treated with a prior vaccine therapy and progressed. He received two doses of ipilimumab at 10 mg/kg and developed grade II diarrhea that was treated with open-label budesonide and diphenoxylate and atropine (Lomotil®; Pfizer Pharmaceuticals, New York). His third dose was delayed to

allow the diarrhea to abate, and at the time he came to clinic for the fourth dose he felt well, with only one or two diarrheal bowel movements a day, but his liver function tests (LFTs) were abnormal, with alanine aminotransferase (ALT) of 736 U/ml, aspartate aminotransferase (AST) of 664 U/ml, and alkaline phosphatase of 364 μ U/ml. His bilirubin was 2.4 mg/dl. Treatment was held, and 3 days later his ALT was 818 U/ml with an AST of 782 U/ml, and his bilirubin had increased to 2.9 mg/dl. The patient was started on a prednisone taper over 30 days on an outpatient basis, and his LFTs rapidly normalized, with an ALT of 64 U/ml and AST of 34 U/ml 2 weeks after starting steroids by mouth. The patient's pulmonary metastases significantly decreased at his week 12 evaluation. At week 16, there was a questionable new pulmonary nodule noted, which by week 20 had decreased, and continued to decrease at the week 24 assessment. The patient currently feels well, with a performance status of 100%.

Gastrointestinal Toxicity Case History #2

The patient is a 49-year-old man with a history of resected stage IV melanoma rendered free of disease by removal of a liver metastasis resected 3 months prior to starting an adjuvant trial with ipilimumab at 10 mg/kg. One week after receiving the first dose of ipilimumab, the patient complained of diarrhea that rapidly progressed to 10 times a day. He was initially treated with oral budesonide, diphenoxylate and atropine, and loperamide (Imodium®; McNeil Consumer Health Care, Fort Washington, PA), but 10 days after the dose of ipilimumab, he was treated with oral doses of prednisone. There was a decrease in the rate of diarrhea, but a week later, he was admitted to the hospital because of worsening diarrhea and cramping abdominal pain. He was started on i.v. steroids and given a dose of infliximab at 5 mg/kg. Upright abdominal and flat plate kidneys, ureters, bladder (KUB) films showed a mild ileus. The pain and diarrhea diminished and the patient was discharged 5 days later on a 3-week steroid taper by mouth. One week after discharge, he complained of worsening abdominal pain and severe nausea and vomiting. He was readmitted to the hospital, where an acute abdominal series showed a very dilated transverse colon, and the physical exam showed a very tense and tender abdomen. He was treated with high doses of i.v. steroids, another dose of infliximab at 5 mg/kg, made nil per os (NPO) with nasogastric suction and started on total parenteral nutrition (TPN). After 7 days of treatment, serial x-rays showed no improvement, and a CT scan showed a very dilated transverse colon with air in the bowel wall. He was taken to the operating room on the seventh day of admission for an ileostomy and so-called "blow-hole" procedure for the transverse colon to decompress it. Ste-

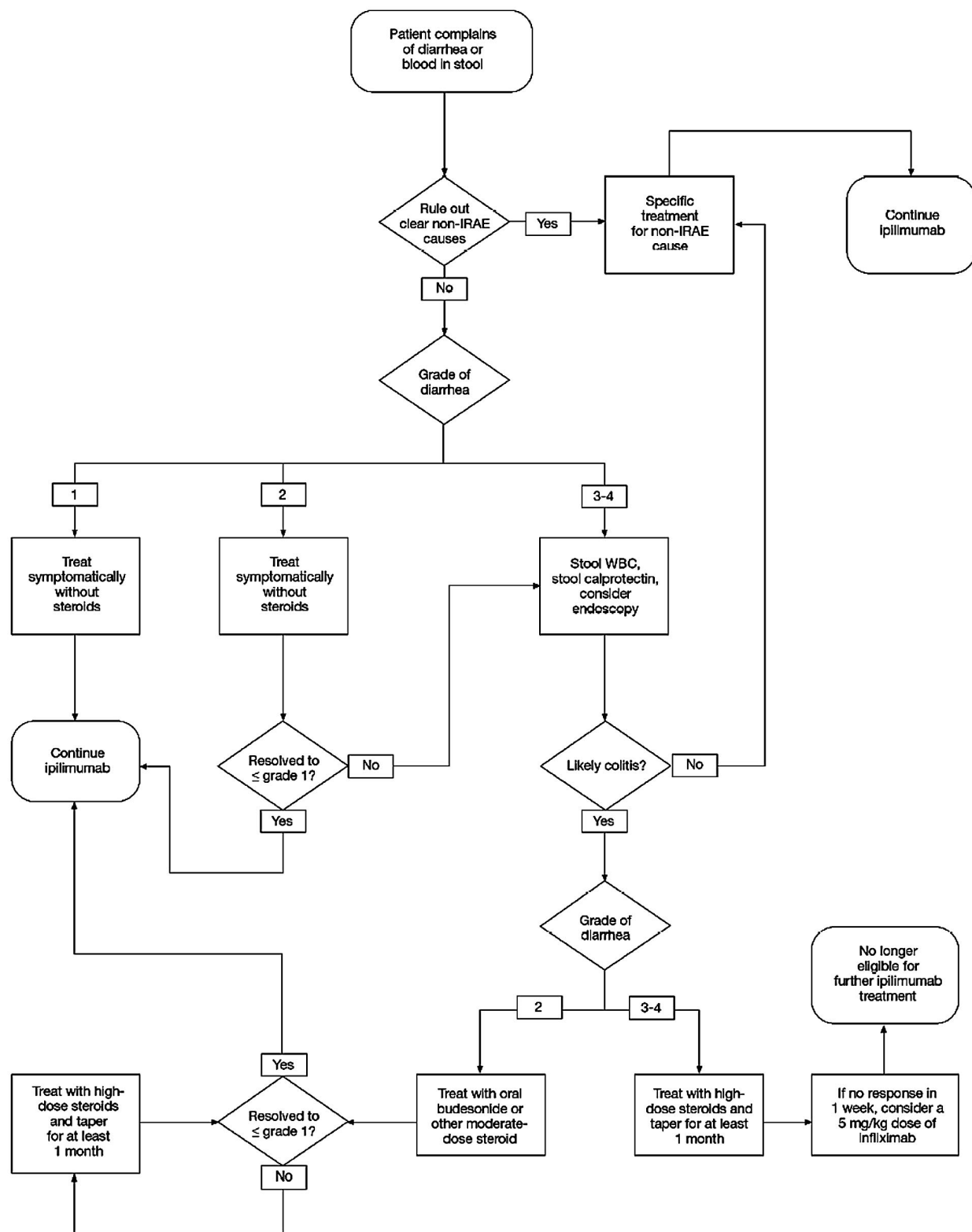


Figure 1. Guidelines for the management of anti-CTLA-4 monoclonal antibody-associated diarrhea. Abbreviations: CTLA-4, cytotoxic T lymphocyte antigen 4; IRAE, immune-related adverse event.

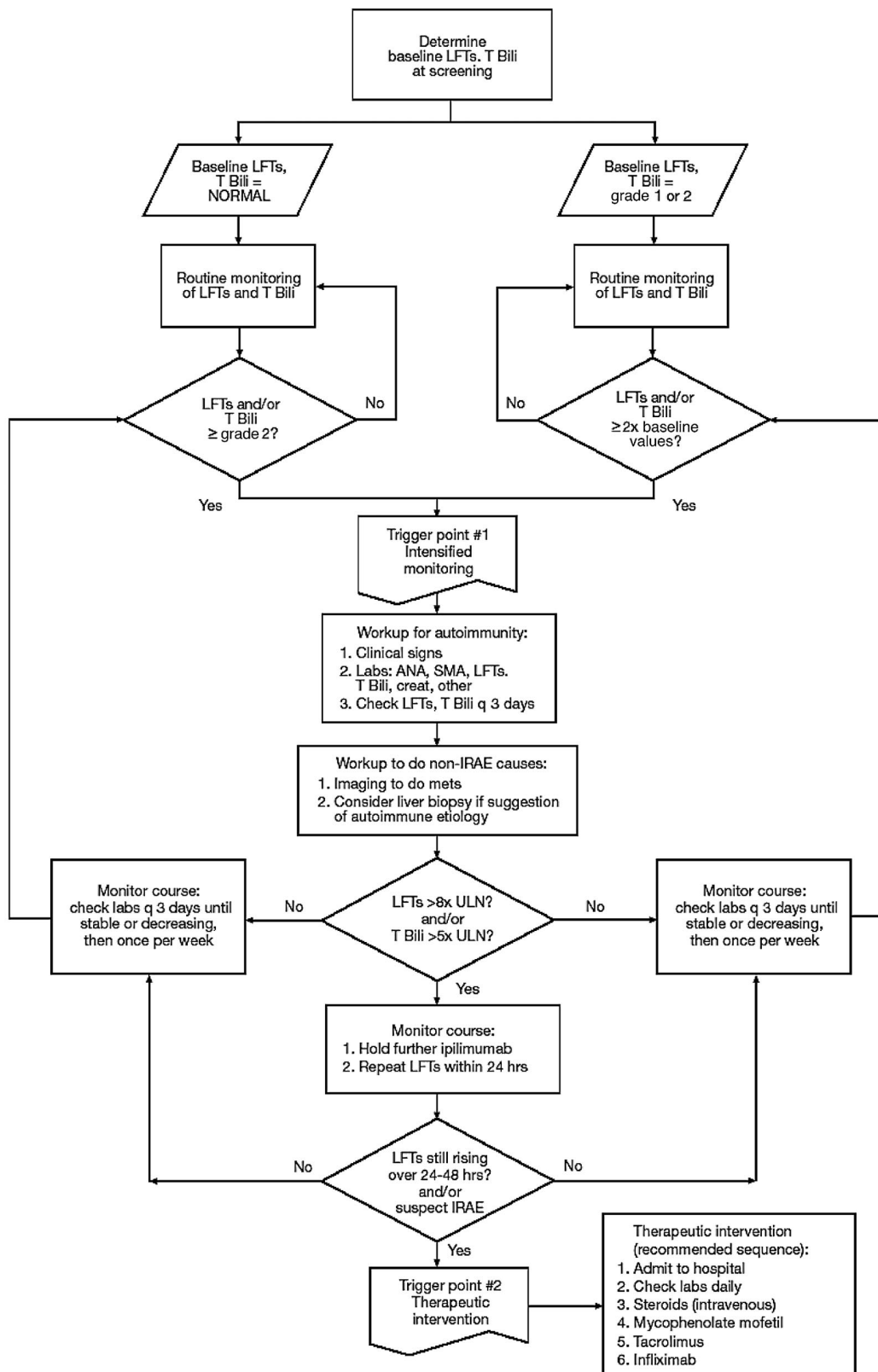


Figure 2. Guidelines for the management of anti-CTLA-4 monoclonal antibody-associated hepatotoxicity.

Abbreviations: ANA, antinuclear antibody; creat, creatinine; IRAE, immune-related adverse event; LFTs, liver function tests; q, every; SMA, smooth muscle antibody; T Bili, total bilirubin.

roids were tapered, and TPN continued. The patient restarted feedings by mouth, was placed on a 6-week steroid taper to zero, and was discharged 2 weeks after admission, 1 week postoperatively. He successfully had a take-down of the ileostomy 12 weeks after surgery, and remains free of disease by CT scanning.

DISCUSSION

The three case histories presented herein establish a number of important points relevant to the management of the side effects of CTLA-4 abrogating antibodies, and illustrate the unique kinetics of antitumor response and IRAEs. One important point is that IRAEs can occur quite rapidly, with a normal colonoscopy on day 3 after the first dose of ipilimumab, and diffuse colitis with crypt abscess formation seen on colonoscopic biopsy 4 days later, after the onset of diarrhea, as in patient #2. A second point is that symptoms should be treated early with steroids and for a prolonged period of time. Care should be taken to avoid tapering the steroids too rapidly. Grade III colitis requires initial dosing with i.v. high-dose methylprednisolone. A 30-day taper of prednisone starting at 60 mg per day is the minimum required schedule, with 45 days needed in some cases. A tapering schedule that is too rapid may lead to recurring symptoms, with consequent need for infliximab, prolonged steroids, and restriction of oral intake with a requirement for insertion of a central venous catheter and institution of TPN, as occurred in the second case above. A key issue is the importance of treating diarrhea early, the day it begins. Grade 1 (<4 stools per day over baseline) diarrhea can be treated with symptomatic therapy (diphenoxylate and atropine, and loperamide). Grade 2 diarrhea (an increase of 4–6 stools per day over baseline) may also be initially treated with symptomatic therapy; however, if the symptoms do not resolve to grade ≤ 1 in severity, then an oral steroid (budesonide) may be added and a diagnostic endoscopy performed. Patients with bloody diarrhea and severe colitis observed on endoscopy should be hospitalized and started on i.v. steroids. Severe diarrhea (grade 3 or 4: an increase of ≥ 7 stools per day over baseline or diarrhea resulting in life-threatening consequences) also requires immediate treatment with high-dose i.v. steroid therapy to control initial symptoms. Patients with ipilimumab-induced diarrhea or colitis that does not respond to appropriate corticosteroid doses within 1 week of initiation or relapse following a steroid taper should be administered infliximab at 5 mg/kg, unless contraindicated. Infliximab may be repeated within 2 weeks, but symptoms of colitis should resolve by then. Prolonged diarrhea in spite of steroids, bowel rest, TPN, and infliximab is an indication for either a diverting ileostomy or partial/complete colectomy. General guidelines for the

management of diarrhea are given in Figure 1. The incidence of life-threatening perforation is quite rare, and has been 4 in 700 cases at doses of ipilimumab of 3 mg/kg or more.

Hepatitis has been an uncommon IRAE following treatment with ipilimumab, and generally presents in asymptomatic patients as a rise in LFTs such as ALT and AST but with a lesser rise in bilirubin. Biopsies have revealed acute hepatic inflammation with ballooning degeneration and diffuse lymphocytic infiltrates. Grade 2 (>2.5 times normal) LFT elevations in patients with normal baseline LFTs should trigger a workup to exclude nonimmune-related causes of transaminitis. Meanwhile, LFTs should be monitored frequently (every 3 days) and further ipilimumab dosing stopped until the LFTs have returned to baseline. Patients with LFT elevations of more than eight times the upper limit of laboratory normal should receive high-dose corticosteroid therapy, and ipilimumab treatment should be stopped permanently. In these patients, LFTs should be checked daily until stable or declining for three consecutive days. LFTs should be then monitored for at least two consecutive weeks to ensure sustained treatment response. In patients without response to corticosteroid therapy within 3–5 days, additional immunosuppression with mycophenolate mofetil should be considered after a gastroenterology/hepatology consult. Patients receiving immunosuppression for more than 4 weeks should be evaluated for prophylaxis of opportunistic infections according to institutional guidelines. General guidelines for the management of hepatotoxicity are given in Figure 2.

CONCLUSION

The anti-CTLA-4 antibody ipilimumab is an active agent in metastatic melanoma. Durable partial and complete responses with monotherapy and in combination with tumor-specific vaccines or IL-2 have been observed in early trials, and in one trial it appears to add to the clinical benefit of chemotherapy [16]. A significant proportion of responses appear to be sustained over time, even after administration of steroids and infliximab, a TNF blocking agent. Patients with resected high-risk melanoma treated with a dose of ipilimumab >1 mg/kg with a peptide vaccine have had an encouraging rate of progression [13] compared with the control arms of recent adjuvant trials [17]. Formal dose-response evaluation at doses >1 mg/kg is under way. The benefit of adding a tumor-specific vaccine to ipilimumab therapy merits further evaluation. The antitumor mechanism of action of CTLA-4 blockade is also unclear, and it appears to be unlikely that CTLA-4 antibodies alter numbers or the function of T regulatory cells [18] (J. Weber et al., unpublished data). The IRAEs seen with ipilimumab administration have ranged from quite well tolerated at grades 1 and 2 in the majority of patients

to severe and life-threatening at grades 3 and 4. These safety events require a high degree of patient and physician education and awareness, as well as excellent communication between physician and patient to permit timely and effective treatment. Ipilimumab is currently in a phase III registration trial for front-line therapy of metastatic melanoma, and in a single-arm, phase II second-line registration trial. Several additional phase II trials are under way to better define the pharmacokinetics and dose response of ipilimumab, and a novel phase II randomized trial will test the utility of budesonide, a non-absorbed steroid, to impact on the incidence of diarrhea and colitis. The important connection between IRAEs and clinical benefit is not yet fully understood for ipilimumab. It is hoped that a comprehensive understanding of how ipilimumab's clinical effects are linked to IRAEs

will yield important insights into immune regulation, tolerance, and effector activity in tumor immunology, as well as provide guidance for patient management.

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DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST

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