Key issues in the management of gastrointestinal immune-related adverse events associated with ipilimumab administration

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Ipilimumab is an anticytotoxic T lymphocyte antigen-4 (CTLA-4) monoclonal antibody that attenuates negative signaling from CTLA-4 and potentiates T-cell activation and proliferation. Two phase 3 randomized trials in advanced melanoma demonstrated a significant improvement in overall survival, the first of which led to regulatory approval in the United States and Europe for treatment of unresectable or metastatic melanoma. Ipilimumab administration is associated with immune-related adverse events (irAEs). Gastrointestinal (GI) irAEs are among the most common and although they are typically mild to moderate in severity, if they are left unrecognized or untreated, they can become life-threatening. These toxicities can be managed effectively in almost all patients by using established guidelines that stress vigilance and the use of corticosteroids and other immunosuppressive agents when necessary. The goal of this review is to educate physicians on the recognition and challenges associated with management of GI irAEs.

T-cell activation is tightly regulated by diverse costimulatory and co-inhibitory signals that allow for feedback and fine-tuning of the immune response.[1] Cytotoxic T lymphocyte antigen-4 (CTLA-4) engagement transmits an inhibitory signal and may also regulate immune responses through its expression and function in regulatory T-cells.[1,2] Although preclinical studies have elucidated many of the biological consequences of CTLA-4 blockade, the exact mechanisms leading to antitumor responses and adverse events (AEs) in humans remain unknown. Ipilimumab is a fully human IgG1 anti-CTLA-4 monoclonal antibody. In two phase 3 trials in patients with previously treated[3] or previously untreated[4] metastatic melanoma, ipilimumab extended overall survival (OS) measured in both median and estimated 1-, 2-, and 3-year OS. The results of these trials led to the approval of ipilimumab for treatment of metastatic melanoma by regulatory authorities in the United States and Europe.[3,4]

Consistent with its mechanisms of action, antibody inhibition of CTLA-4 can cause AEs that are characteristically inflammatory in nature and are likely a direct result of potentiation of activity of T cells specific to self-antigens that are already present in the immune repertoire.[5] These tissue-specific inflammatory events, termed immune-related AEs (irAEs), most commonly involve the gastrointestinal (GI) tract or the skin without inducing generalized systemic autoimmunity.[6] More rarely, anti-CTLA-4 administration may also induce endocrinopathies, noninfectious hepatitis, uveitis, central and peripheral neuropathies, pneumonitis, arthritis, nephritis, or cytopenias. The overall incidence of irAEs in the 2 large phase 3 melanoma trials ranged from 60%-77%, and grade 3-4 events were observed in 10%-15% of patients who were treated with ipilimumab

TABLE 1 Grading of colitis and diarrhea in Common Terminology Criteria for Adverse Events v4.0

	Grade			
	1	2	3	4
Colitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated.	Abdominal pain; mucus or blood in stool.	Severe abdominal pain; change in bowel habits; medical intervention indicated; peritoneal signs.	Life-threatening consequences; urgent intervention indicated.
Diarrhea	Increase of < 4 stools a day over baseline; mild increase in ostomy output compared with baseline.	Increase of 4-6 stools a day over baseline; moderate increase in ostomy output compared with baseline.	Increase of ≥ 7 stools a day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared with baseline; limiting self-care ADL.	Life-threatening consequences; urgent intervention indicated.

Abbreviation: ADL, activities of daily living.

in the MDX010-20 study and 56.3% of patients treated with ipilimumab in combination with dacarbazine in study CA184-024. Extensive review of the entire irAE profile associated with ipilimumab has been previously published.[6,7]

Overview of ipilimumab-related GI irAEs

In clinical trials, GI irAEs associated with ipilimumab are generally reported as diarrhea, defined as a disorder characterized by frequent and watery bowel movements, and/or colitis, defined as a condition characterized by inflammation of the colon. Grading of colitis and diarrhea in the Common Terminology Criteria for Adverse Events v4.0 is listed in Table 1.

Because ipilimumab-related diarrhea is a manifestation of inflammatory colitis or enteritis, separate classification of diarrhea and colitis is somewhat artificial. Moreover, ipilimumab-induced inflammatory responses may broadly involve the GI tract, including small intestine and upper GI tract, and the symptoms and signs of GI inflammation may extend beyond diarrhea to include abdominal cramping, nausea, vomiting, GI bleeding, fever, fatigue, dyspepsia, leukocytosis, hypoalbuminemia, and serum electrolyte abnormalities. In some patients, other symptoms predominate over diarrhea at the time of presentation and can reflect more severe and generalized GI inflammatory responses. Very rarely, the initial manifestation of ipilimumab-induced colitis may be bowel perforation.

A retrospective review of safety data from 1,498 patients treated in 14 completed phase 2 and 3 clinical trials of ipilimumab[8] confirmed that diarrhea is the most common irAE, occurring in just over one-third (37%) of all patients. Grade 3-4 diarrhea was observed in 6.9% of all patients, about one-fifth of all patients with diarrhea. Any-grade colitis was recorded in 8.0%, and grade 3-4 colitis was observed in 4.9%. Another 1.2% of patients (0.6% grade 3-4) developed enterocolitis. Among these 1,498 patients,

3 deaths (0.2%) were attributed to GI irAEs (colitis, large intestinal perforation, and intestinal perforation). The overall incidence and severity of colitis/diarrhea is dose dependent and can be altered by concurrently administered anticancer agents. For example, in study CA184-024, of the ipilimumab/dacarbazine combination, the incidence of liver enzyme elevations and grade 3-4 diarrhea/colitis were higher and lower, respectively, compared with prior experience with ipilimumab alone at the same dose of 10 mg/kg, suggesting that the dacarbazine modified the biological activity of ipilimumab in this trial. The spectrum of ipilimumab-induced colitis reported in patients with melanoma is comparable with that observed in ipilimumab-treated patients with other solid tumors.[5]

Endoscopic and histologic findings

In an analysis of data from 115 treatment-naïve or previously treated patients with unresectable stage III or IV melanoma who received ipilimumab (10 mg/kg every 3 weeks for 4 doses) with placebo or prophylactic oral budesonide, ipilimumab administration was commonly associated with neutrophilic and plasma cell infiltration in the lamina propria and focal neutrophilic and lymphocytic cryptitis.[9] Beck and colleagues observed 3 histopathologic patterns: neutrophil infiltrate (46% of patients), lymphocytic infiltrate (15%), or mixed neutrophil-lymphocytic infiltrate (38%).[10] A smaller report on 5 patients noted increased epithelial apoptosis.[11] Berman and colleagues observed that gut histologic evidence of neutrophilic/lymphocytic infiltration generally precedes grade 2 or higher diarrhea or colitis by several weeks, but abnormal endoscopic findings do not strictly correlate with occurrence of grade 2 diarrhea.[9]

Ipilimumab-related enterocolitis shares several similarities with graft-versus-host (GVH) disease and inflammatory bowel disease,[10] including acute and chronic

inflammatory changes, patchy areas of inflammation (skip lesions), and response to infliximab.[10] However, unlike Crohn's or ulcerative colitis, ipilimumab-related colitis involves the descending colon more than the sigmoid colon, ascending colon, or rectum.[12] In addition, ipilimumab-related enterocolitis may display a pattern of antibody positivity to enteric flora and other autoantibodies that is distinct from classical ulcerative colitis and Crohn's disease.[9] Previous data suggested that intestinal microflora and bacterial antigens may contribute to the enterocolitis seen in GVH.[13,14] The enteric flora alterations seen in ipilimumab-induced diarrhea and colitis suggest intestinal microflora and bacterial antigens may also contribute to ipilimumab-induced bowel inflammation.[9] Nevertheless, ipilimumab-related colitis and GVH disease are histologically distinct; the latter is characterized by prominent epithelial apoptosis and glandular destruction not seen with ipilimumab-associated colitis.[9]

Clinical characteristics and biomarkers of enterocolitis

Ipilimumab-related colitis may occur more frequently in patients with a family history of colitis.[15] The safety of ipilimumab in patients with underlying autoimmune syndromes is unknown because these patients were understandably excluded from early and late clinical trials. Although it seems likely that ipilimumab could cause severe GI toxicity by exacerbating an underlying autoimmune bowel inflammatory disorder, there currently is no evidence that underlying autoimmune syndromes (eg, thyroid disorders) increase the incidence or severity of enterocolitis. Because these patients could be treated with ipilimumab in postmarketing settings, prospective data regarding the relationship of prior autoimmunity and the safety profile of ipilimumab should be gathered in clinical trials.

Several studies have attempted to identify prognostic or diagnostic biomarkers for inflammatory bowel disorders. These include measurement of calprotectin and lactoferrin in the feces, or measurement of C-reactive protein, erythrocyte sedimentation rate, and antibodies to perinuclear antineutrophil cytoplasmic proteins or *Saccharomyces cerevisiae* in the blood.[16,17] A study of ipilimumab GI toxicity, however, failed to identify a reliable predictive marker.[9] In that study, ipilimumab induced an increase in fecal calprotectin, but the increase was not specific for diarrhea or colitis. Furthermore, analysis of a potential relationship between worst-grade GI irAEs and genetic polymorphisms in 10 immune-related genes demonstrated no association for any of the 18 polymorphisms analyzed.[9] Thus, there are currently no clinically relevant surrogate biomarkers for ipilimumab-associated GI irAEs outside of the previously described cellular inflammatory findings.

A subtype of CD4+ lymphocytes, Th17 cells, play an important role in GI mucosal immunity, and Th17 cytokines (IL-17, IL-22) have been implicated in the development of colitis.[18-21] Furthermore, CTLA-4 blockade potentiates Th17-mediated autoimmunity[22] and increases levels of circulating Th17 cells in patients.[23] Among patients treated with ipilimumab at 10 mg/kg, those who developed colitis exhibited pretreatment IL-17 levels similar to patients who did not develop irAEs (Figure 1).[24] However, the development and resolution of colitis symptoms temporally correlated with increases and decreases in serum IL-17, respectively. Once clinical symptoms were resolved, IL-17 levels decreased to levels comparable with those in patients without colitis. This pattern of IL-17 fluctuation was not observed with other cytokines studied.

Management of enterocolitis and diarrhea

Current treatment guidelines have recommendations for a sequential treatment algorithm for GI toxicities (Figure 2).[25] Implementation of diarrhea treatment guidelines (DTG) for all clinical trials with ipilimumab began in January 2005 and resulted in decreased occurrence of serious GI complications, GI perforation, and colectomy rates (decrease from 0.9% to 0.5%) despite an increase in ipilimumab dose from 3 mg/kg to 10 mg/kg.[26] A later report confirmed that use of protocol-specified guidance facilitated resolution of diarrhea and colitis during ipilimumab treatment.[27]

As described in the algorithm, signs and symptoms suggestive of mild colitis can be treated supportively and expectantly, and may resolve without use of immunosuppressive agents. In cases of moderate to severe enterocolitis, treatment of ipilimumab-related GI irAEs is directed to the underlying GI inflammation and the resulting symptoms (eg, diarrhea). Treatment of symptoms alone in the more severe cases can lead to catastrophic consequences due to the persistence of GI inflammatory responses.

Corticosteroids are the standard treatment for colitis but have the potential to inhibit T-cell function, and in theory they may decrease the clinical efficacy of ipilimumab therapy.[28] However, clinical data suggest that corticosteroids administered after the onset of an irAE do not negatively impact ipilimumab's antitumor efficacy. Data from 283 patients, 119 of whom received steroids to manage irAEs, revealed no evidence that steroid use prevented ipilimumab-induced anti-tumor responses or adversely affected responses once achieved.[29] However, in animal models and possibly in patients, prophylactic systemic immunosuppression to prevent GI and other ipilimumab-induced irAEs may antagonize ipilimumab antitumor effects.[6,28]
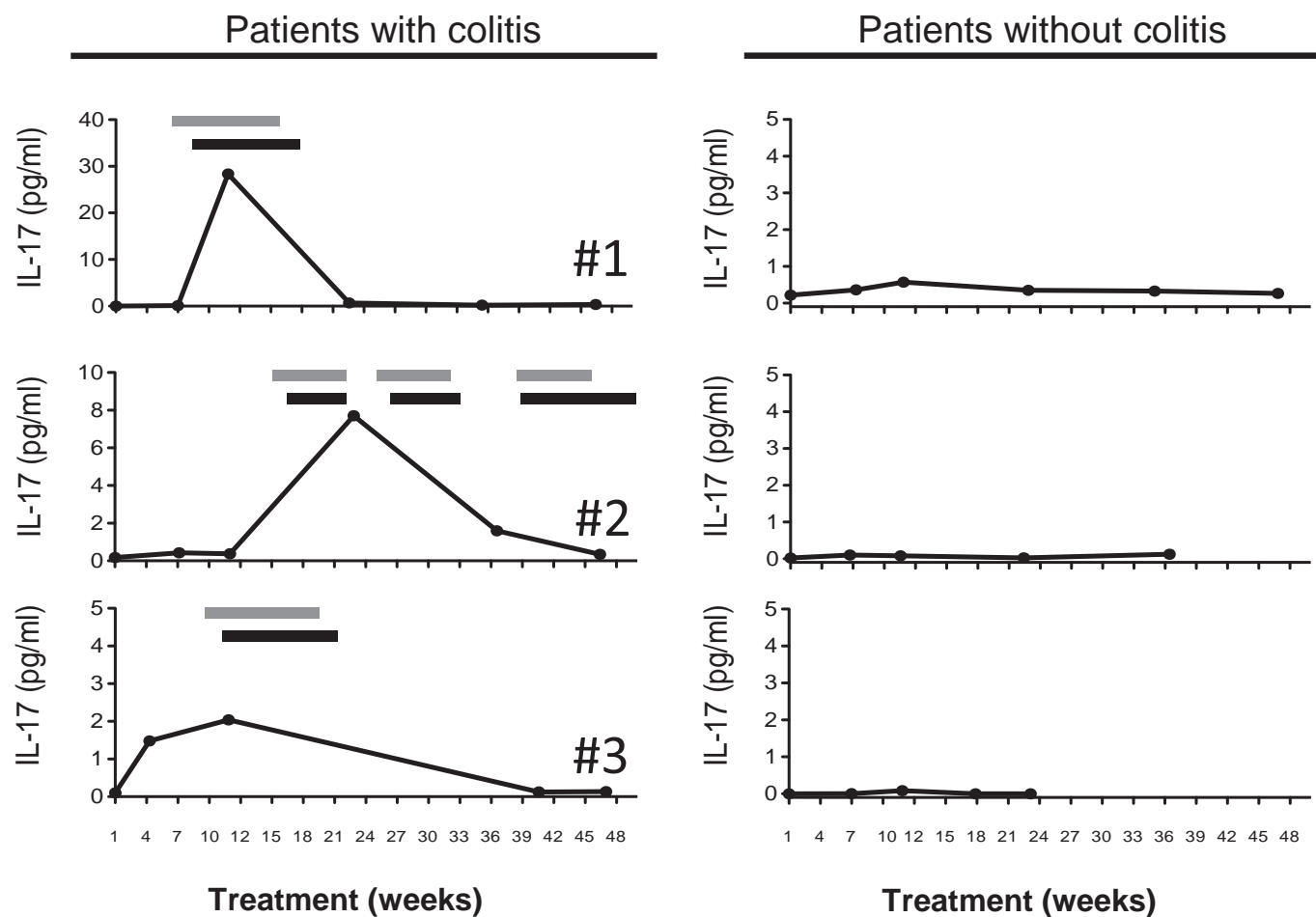
Grey bar = colitis symptoms

Black bar = steroid treatment

FIGURE 1 Serum levels of IL-17 correlate temporally with symptoms of colitis.[24] "Reprinted with permission. ©2011 American Society of Clinical Oncology. All rights reserved." Callahan MK, et al: *J Clin Oncol.* 29(suppl) 2011: Abstract 2505.

Identifying and assessing severity of enterocolitis

Clinicians face several challenges in identifying and assessing the severity of ipilimumab-associated enterocolitis irAEs, and also in determining when to start immunosuppressive treatment, what dose of steroids to give initially, when to re-escalate the steroid dose for recurrence of symptoms, or when to add a second more potent agent such as infliximab. Although other causes for symptoms, such as infection, must be excluded, the presence of infection does not necessarily rule out concurrent ipilimumab-induced enterocolitis. Close contact with the patient is

required throughout treatment because time to onset of enterocolitis symptoms may vary. For example, grade 2 or higher diarrhea may develop from 2-16 weeks after initiation of the first of 4 initial ipilimumab doses, and the median time to resolution (to grade 1) of grade 2-4 diarrhea or clinical colitis can vary from 2-3.4 weeks.[3,9,30]

Clinicians may underestimate the severity of the enterocolitis by focusing solely on the amount of diarrhea. In particular, patients who complain of low-grade diarrhea with associated symptoms and signs, including moderate abdominal cramping, nausea with or without vomiting, GI bleeding or mucous in stools, fever, leukocy-
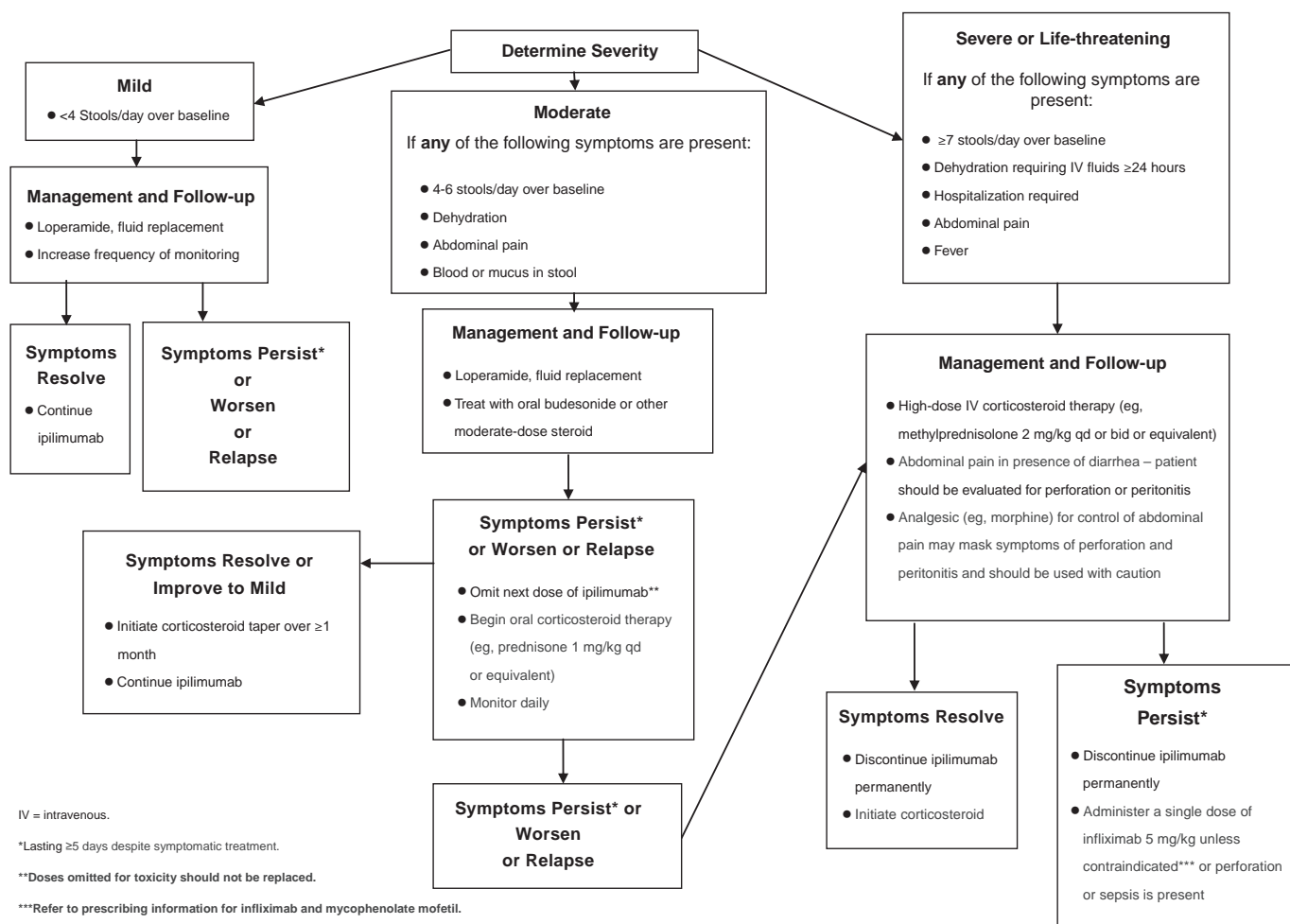
FIGURE 2 Algorithm for managing GI irAEs.[25]

tosis, low albumin, or electrolyte abnormalities should be assessed for moderate to severe enterocolitis and considered for treatment with high-dose steroids (1-2 mg/kg per day of methylprednisolone), similar to patients presenting with grade 3 or 4 diarrhea. The associated symptoms may suggest more generalized inflammation of the GI tract, including enteritis. Persistent low-grade diarrhea lasting 5-7 days, even without associated symptoms, could indicate the need for at least a short course of moderate-dose steroids. Patients receiving maintenance ipilimumab every 12 weeks (included in several trials but currently not standard of care) may rarely experience late-onset severe diarrhea or colitis (unpublished observations).

Colonoscopy in diagnosing ipilimumab-induced GI irAEs

In early clinical trials, many patients with prolonged grade 2 colitis or diarrhea and grade 3-4 colitis or diarrhea were admitted to the hospital for evaluation. A typical work-up consisted of routine stool cultures, including assay for *Clostridium difficile* toxin and fecal leukocytes, and colonoscopy.[15] In our experience, when colonoscopy could not be performed within a reasonable time frame, a computed tomography (CT) of the abdomen and pelvis with oral and IV contrast often provided relevant diagnostic information (eg, signs of inflammation within or surrounding bowel). A key question is whether colonoscopy is required for every patient. In our clinical experience, colonoscopy is not essential for diagnosis of colitis, but it can be useful in differentiating mild from moderate-to-severe colitis in equivocal cases and can identify deep scattered ulcers or potential sites of bleeding. A normal-appearing mucosa on colonoscopy does not exclude colitis,[6] and a final diagnosis should be withheld pending pathologic results of random biopsies. For patients with signs and symptoms suggestive of colitis, appropriate algorithm-based treatment should not be withheld while considering colonoscopy.

Complications of ipilimumab-related enterocolitis

Because of the potentially long-term recovery period for ipilimumab-associated GI toxicities, early detection and treatment of moderate-to-severe colitis, or mild colitis that is not self-resolving within 5-7 days, especially during the induction phase of treatment, may help prevent progression to more serious conditions and may allow continued ipilimumab therapy. If untreated, immune-related colitis can lead to intestinal perforation[28] and a greater risk of enteric/systemic infection. Whole colectomy may be required for patients who develop a bowel perforation or intractable bleeding. GI irAEs may also occur concurrent with or following irAEs affecting other organs (eg, rash, uveitis, or endocrinopathies). Clinicians should be alert to the development or concurrent presence of other irAEs which may require additional treatment, such as thyroid hormone replacement in ipilimumab-induced hypophysitis or thyroiditis.

Management of complications

Patients with grade 1-2 diarrhea and no features suggestive of more severe colitis

Below is a proposed recommendation for management of patients developing grade 1 and grade 2 diarrhea.[25] Initially the severity of enterocolitis should be determined. Moderate toxicity is defined as 4-6 stools per day over baseline and no other concerning associated symptoms or signs; in these cases, ipilimumab should be withheld. Antidiarrheal treatment can be offered while the etiology of the enterocolitis is investigated, although in some patients we prefer to withhold antidiarrheal medications to better assess the evolution of symptoms and response to treatment. In some cases, oral budesonide, a nonabsorbed corticosteroid, is useful in mild or moderate cases of colitis which have been ongoing for only a few days. If symptoms improve to mild severity or resolve, ipilimumab can be resumed. However, if symptoms continue beyond 5-7 days, systemic corticosteroids (eg, 0.5-1.0 mg/kg per day of prednisone or equivalent) should be started. These patients can generally be managed as outpatients and will not require colonoscopy. Steroid therapy should be continued until improvement to mild severity or resolution and tapered as medically appropriate. Typically, steroid taper should occur over at least 3-6 weeks, although in select patients with mild symptoms, steroids can be discontinued after 1-2 weeks. Ipilimumab can be resumed if symptoms were not severe at presentation and have improved to at least mild severity, and steroid dose is 7.5 mg prednisone equivalent or less. In general, we prefer to hold ipilimumab until steroids have been discontinued completely and the patient remains symptom-free for several days after completion of steroids.

An unresolved question is how long to wait before beginning systemic steroids for low-grade GI toxicity. Early treatment of diarrhea on the day of commencement has been recommended.[31] However, this would potentially result in steroid use for a subset of patients whose colitis would resolve rapidly without intervention. Grade 1 diarrhea can be treated with symptomatic therapy, such as use of loperamide and fluid replacement, and initiation of a bland diet can also help manage low-grade symptoms. Grade 2 diarrhea can also be initially managed symptomatically; if symptoms do not resolve to grade 1 or lower within 24-48 hours, an oral steroid such as budesonide (9 mg daily) can be administered. Diagnostic endoscopy is optional at this time. Persistence of the grade 2 symptoms for 5-7 days total should trigger institution of systemic steroids. In a randomized study of 115 previously treated and treatment-naïve patients with unresectable stage III or IV melanoma who received ipilimumab (10 mg/kg every 3 weeks for 4 doses) with daily blinded budesonide or placebo through week 16, rates of grade 2 or higher diarrhea did not differ between the respective groups (35.0% vs 32.7%), suggesting that budesonide is not effective as a prophylactic therapy for ipilimumab-related diarrhea of grade 2 or higher.[32]

Patients with features suggestive of more severe colitis

In cases of severe or life-threatening enterocolitis (ie, patients experience 7 or more stools a day over baseline, have peritoneal signs consistent with bowel perforation, ileus, or fever) ipilimumab should be permanently discontinued. Severe enterocolitis should also be suspected when the frequency of diarrhea only meets grade 1-2 criteria but patients have associated systemic signs and symptoms, including blood per rectum, cramps, fever, nausea, elevated white blood cell count, low albumin, or electrolyte abnormalities. Endoscopic evaluation should be considered, and where there is no bowel perforation, systemic corticosteroids of 2 mg/kg a day of prednisone or equivalent should be administered. In general, we prefer to manage patients with suspected severe enterocolitis in the hospital until resolution to grade 1, and those with bloody diarrhea or severe colitis on endoscopic evaluation should be hospitalized and receive high-dose intravenous steroids. Regardless of improvement, the initial steroid dose should be maintained for at least 7 days, but can be converted to oral administration if the patient is discharged from the hospital. Once symptoms resolve, steroids should be tapered over 3-6 weeks. For patients not responsive to steroids, it may be prudent to rest the bowel (withhold oral liquids and food) until symptoms resolve. Rarely, in cases of particularly severe and prolonged colitis, a period of total

parenteral nutrition may be necessary. Patients with severe colitis who appear to be responding to steroids should be reassessed frequently for recurrence of symptoms requiring further escalation of the steroid dose or administration of a second immunosuppressive agent.

If symptoms persist or recur, patients should be continually evaluated for evidence of GI perforation or peritonitis and a repeat endoscopy should be considered. In some patients, doubling the dose of systemic corticosteroids may be sufficient to resolve the symptoms. The clinical effect of administering even higher doses of steroids (ie, a gram of solumedrol) is unknown. Alternative immunosuppressive therapy should be considered when symptoms persist at grade 2 or higher beyond 7 days after initiation of the steroids, or earlier than 7 days if symptoms are severe and the patient appears clinically ill. Agents such as infliximab at 5 mg/kg or other tumor necrosis factor (TNF)-blocking agents are usually effective when steroids fail.[28,33] Infliximab therapy can be repeated approximately every 2 weeks,[31] although some patients will require an escalated dose to 10 mg/kg and up to a total of 3-4 doses before the colitis resolves. The steroid taper can be continued after initiation of infliximab. In patients responding to steroids who develop a recurrence of symptoms during the steroid taper, escalating the dose of steroids for 5-7 days and a return to a taper schedule over 3-4 weeks may be effective and may obviate the use of anti-TNF agents.

Inhibition of TNF is associated with the risk of developing serious infectious diseases and difficulty in clearing infections once they have developed,[34] but in a report on 5 patients who developed colitis after anti-CTLA-4 therapy (ipilimumab, 1 patient; tremelimumab, 4 patients) that failed to respond to a 1-week course of high dose corticosteroids, diarrhea was successfully treated with infliximab and no infections were reported.[33] However, it is not known whether infliximab impacts the antitumor response of metastatic melanoma to CTLA-4 antibodies,[33] and clinicians should therefore carefully consider risks and benefits of infliximab therapy in patients with chronic or recurring infections.[35] Antibiotic prophylaxis for opportunistic infections should be considered in the rare patient requiring continued immunosuppression beyond 2 months.

Continuing and restarting immunotherapy

Patients who experience disease progression after achieving an objective response or stable disease of at least 24 weeks (by standard or immune-related response criteria) may benefit from ipilimumab retreatment.[3,27] Furthermore, patients unresponsive to ipilimumab may be candidates for other types of standard or investigational immune therapies (eg, high-dose interleukin-2, other cytokines, adoptive cell transfer, or one of the other co-inhibitory antagonists such as anti-PD-1).

There are little published data to determine whether ipilimumab-related colitis of any severity should exclude patients from receiving ipilimumab re-induction or future immunotherapies. Extreme caution should be used with ipilimumab re-induction in a patient with a history of severe colitis during a prior induction course, even if the colitis occurred remotely. For unresolved colitis, the risk of bowel toxicity from subsequent immunotherapies may be increased. Smith and colleagues have reported a possible increase in bowel perforation incidence in patients receiving IL-2 after therapy with ipilimumab.[36] In a retrospective analysis of data in 22 patients previously treated with ipilimumab and subsequently given high-dose IL-2, 3 patients (13.6%) developed bowel perforations during IL-2 treatment and required emergency laparotomy. Two of the 3 patients had experienced symptoms of colitis after ipilimumab. Histopathologic analysis revealed active chronic colitis with intraepithelial lymphocytosis in all 3 patients. The perforation incidence of 13.6% was significantly higher than the previously reported rate of 1% or more observed in patients receiving high-dose IL-2 alone, which has prompted recommendations for diagnostic colonoscopy to rule out chronic active colitis in anti-CTLA-4-experienced patients before initiating IL-2 or any other broad immune activating agent. It is not known whether patients are more likely to develop ipilimumab-related colitis if they have experienced GI toxicity from other prior immunotherapies, but the observation by Smith and colleagues suggests it is appropriate to assess such patients for chronic colitis prior to commencing ipilimumab therapy.

Summary

GI irAEs are among the most common AEs observed with ipilimumab therapy. Left unrecognized or untreated, these irAEs can rapidly escalate in severity and become life-threatening. Implementation of established management guidelines for ipilimumab-associated GI toxicities appears effective in controlling GI toxicities and allowing patients to benefit from planned ipilimumab treatment. Prompt recognition and treatment, including exclusion of other etiologies, are important to successful management of GI irAEs. Low-grade toxicities can be managed symptomatically, but use of corticosteroid therapy, dose interruption, or discontinuation of ipilimumab may be required for higher-grade GI toxicities. For cases refractory to corticosteroid therapy, other immunosuppressants (eg, infliximab) may be indicated. The successful management of GI irAEs requires education, cooperation, and open

communication by both the healthcare team and the patient.

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