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Gastrointestinal and Hepatic Complications of Immune Checkpoint Inhibitors

Peyton Cramer[1] · **Robert S. Bresalier**[1]

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Abstract
Purpose of Review Gastrointestinal complications are very common in patients undergoing cancer treatment. Some of these complications can be life threatening and require prompt and appropriate diagnosis and treatment. The purpose of this review is to address luminal gastrointestinal and hepatic complications associated with a new class of anticancer drugs, immune checkpoint inhibitors (CPIs), and focuses on the identification, evaluation, and management of the complications associated with this class of drugs.
Recent Findings It is now recognized that immune checkpoint inhibitors are frequently associated with luminal GI side effects such as diarrhea and enterocolitis and hepatic complications such as hepatitis. While colitis associated with CPIs, to some extent, mimics that found in idiopathic inflammatory bowel disease, the complex interplay of genes, the environment, the immune system, and the microbiome make it difficult to fully differentiate these conditions clinically. CPI-induced hepatitis is most often associated with a pattern of hepatocellular injury with panlobular hepatitis. A variety of biomarkers have been proposed to predict an adverse response to CPIs and are under investigation. It has been proposed that alterations in the microbiome may impact the risk of developing colitis, and these studies are reviewed. In contrast to idiopathic chronic inflammatory bowel disease, CPI-induced colitis is often reversible if rapidly treated in accordance with the immune-mediated adverse reaction management guidelines. Treatment algorithms have been suggested but are, to some extent, empiric and based on algorithms for the treatment of idiopathic inflammatory bowel disorders.
Summary CPIs may be associated with significant GI complications which impact their successful use in the treatment of neoplastic diseases. Much of what we currently know about the mechanisms and treatment of these complications is empiric and extrapolated from experience with idiopathic inflammatory bowel disease and other immune disorders. Current research focuses on understanding genetic predisposition and the role of the microbiome and identifying predictive risk markers for developing complications.

Keywords Checkpoint inhibitors · Immune modulation · Toxicity · Colitis · Hepatitis · CTLA-4 · PD-1 · Ipilimumab · Microbiome

Introduction and Overview

Checkpoint inhibitors (CPIs) are a new class of cancer treatments that target immune cell checkpoints in order to stimulate an antitumor response. Blocking immune checkpoints cytotoxic T lymphocyte antigen 4 (CTLA-4) and programmed cell death-1 (PD-1) promotes effector T cell activation and proliferation, allowing enhanced cellular immunity. Although these therapies have proven successful in treating melanoma, non-small cell lung cancer, and renal cell carcinoma, up to two thirds of patients experience widespread immune-related adverse events (irAEs). The gastrointestinal system is most significantly impacted, resulting in diarrhea, colitis, or hepatitis. Acute pancreatitis has been reported, but clinical pancreatitis is rare and may be considered anecdotal at this time. This review discusses the clinicopathologic findings

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✉ Robert S. Bresalier
rbresali@mdanderson.org

[1] Department of Gastroenterology, Hepatology and Nutrition, The University of Texas MD Anderson Cancer Center, 1515 Holocombe Boulevard, Unit 1466, Houston, TX 77030, USA

of gastrointestinal adverse events associated with three FDA-approved CPI therapies: ipilimumab (anti-CTLA-4) and nivolumab and pembrolizumab (PD-1 blocking antibodies). Ipilimumab is currently approved by the US Food and Drug Administration for the treatment of metastatic melanoma, and nivolumab and pembrolizumab are both FDA approved for the treatment of metastatic melanoma and non-small cell lung cancer. Nivolumab is approved for the treatment of renal cell carcinoma.

Background

Immune Response

The immunogenicity of tumor-associated antigens (TAAs) spans a wide range depending on the degree of mutation in self-antigens. Because most TAAs are ubiquitously expressed antigens that are not mutated or tumor specific, a robust autoimmune response is required for successful tumor eradication.

T cell activation requires a binding antigen in the context of MHC as well as co-stimulation through the CD28 receptor. CD28 binds ligands of the B7 family (CD80 and CD86), triggering T cell proliferation and migration toward the neoplastic site harboring those specific TAAs [1]. Upon T cell activation, CTLA-4 is also expressed on the surface and competes with CD28 for binding B7 ligands. Because CTLA-4 has even higher affinity for these ligands, the co-stimulatory signal is eliminated and the lymphocytes are arrested in G1 of the cell cycle. CTLA-4 is thus defined as an immune checkpoint because it plays an important inhibitory role in preventing autoimmunity and establishing tolerance to self-antigens [2]. PD-1 serves as another immune checkpoint expressed on the surface of activated T cells. This receptor is similar in structure to CTLA-4 but with distinct function and ligands. Programmed cell death-ligand 1 (PD-L1) is selectively expressed on many tumors and on cells within the tumor microenvironment in response to inflammatory stimuli, such as IFN-γ [3, 4]. PD-L1 is the primary PD-1 ligand that is upregulated in solid tumors, and signaling through this pathway results in inhibition of cytokine production and apoptosis of PD-1+, tumor-infiltrating T cells [5].

Treatment of Cancer Patients With Checkpoint Inhibitors

Inhibiting immune checkpoints has shown a significant benefit to a variety of cancer patients, with overall survival rates of 20% at 5 years [6]. Ipilimumab, an IgG1 monoclonal antibody targeting CTLA-4, was approved in 2011 for the treatment of metastatic or unresectable melanoma. It was subsequently approved in 2015 as an adjuvant treatment for cutaneous melanoma or as a combination therapy with nivolumab for BRAF V600 wild-type, unresectable, or metastatic melanoma [7]. Nivolumab and pembrolizumab are IgG4 monoclonal antibodies targeting PD-1. Nivolumab was initially approved for the treatment of metastatic or unresectable melanoma following ipilimumab administration (2014) and then later for non-small cell lung cancer (NSCLC) and advanced renal cell carcinoma (2015). Pembrolizumab was approved in 2015 for the treatment of unresectable or metastatic melanoma as well as NSCLC [7].

Although CTLA-4 and PD-1 receptors play an inhibitory role with respect to effector T cells, they paradoxically play an important stimulatory role in regulatory T cells [4]. Antibody blockade of these immune checkpoints thus results in momentous amplification of effector T cells with simultaneous depletion of regulatory T cells. Depletion of regulatory T cells removes one of the most important anti-inflammatory mechanisms of the immune system because these cells are responsible for the production of the inhibitory cytokines transforming growth factor-β (TGF-β), interleukin-10 (IL-10), and IL-35 [8••]. Therefore, bypassing immune checkpoints with a CPI therapy severely compromises tolerance to self-antigens and results in widespread immune dysregulation.

Approximately 61% of patients experience irAEs in response to checkpoint inhibitor treatment [9]. Because the amplified immune response is not restricted to the tumor-specific lymphocytes, these adverse events could potentially affect any organ system. Gastrointestinal events are the most frequent result of CPI administration and will be the primary focus of this review.

Luminal Gastrointestinal Events

Gastrointestinal tract irAEs following anti-CTLA-4 administration range from mild diarrhea to severe colitis, intestinal perforation, and even death [10]. Diarrhea is the most common presentation (27%) [9], followed by colitis, characterized by inflammation of the colon (CTCAE) [11]. Up to 12% of patients may develop severe enterocolitis unresponsive to immunosuppressive therapy and may even require a subtotal colectomy for bleeding, perforation, or intractable diarrhea [12]. The median onset time of ipilimumab-induced colitis is 34 days or on average following approximately three treatment doses [8••]. There is no significant correlation between the dosage of anti-CTLA-4 treatment and adverse events; however, there is a correlation between adverse events and tumor regression [8••].

Anti-PD-1 therapies result in considerably less adverse events compared to anti-CTLA-4 therapies [13]. PD-1 signaling acts more peripherally than CTLA-4 and thus may result in fewer systemic effects [1]. Following nivolumab therapy, diarrhea or colitis was observed in 17% of melanoma patients, with only 1.2% of patients experiencing grade 3 toxicities. Colitis was observed in up to 2.8% of those receiving pembrolizumab, with a positive correlation between dosage

and adverse events. The median time of irAEs was much longer for pembrolizumab (~18 weeks) than that for nivolumab (~6 weeks) [13].

Histological Findings

Although diarrhea is the most common irAE associated with CPI treatment, colonic examination is only recommended for persistent grade 2 or higher diarrhea due to the risks associated with endoscopic procedures [13]. Endoscopic examination often shows inflammatory changes in a continuous pattern throughout the gastrointestinal tract, such as exudates, granularity, loss of vascularity, and ulcerations [14]. However, even if these signs of inflammation are not present upon gross examination, biopsies should be taken and are required to confidently rule out colitis [12].

In a study of patients with histological evidence of ipilimumab-induced enterocolitis, 83% had more than one positive biopsy sites and 32% had three or more positive biopsy sites [12]. Biopsies often show marked mixed inflammatory cell infiltrates in the lamina propria, foci of neutrophilic cryptitis, crypt abcesses, glandular destructions, and erosions of the mucosal surface [14]. Many of these lower GI findings are similar to those found in chronic idiopathic inflammatory bowel disease (IBD) (Table 1).

Among 22 patients undergoing esophagogastroduodenoscopy, one had a mid-esophagus ulceration, nine had gastritis, and two had erosive duodenitis. Chronic duodenitis was observed in 44% of duodenal biopsies, characterized by crypt distortion, villus shortening, inflammatory infiltrates, and hyperplasia of Brunner's glands. Over half (53%) of the gastric biopsies showed chronic gastritis without *Helicobacter pylori* infection [8••].

A less common presentation has been reported in which a patient had extensive ulceration and inflammatory infiltration restricted to the terminal ileum [18]. Other cases have shown inflammation confined to the stomach or duodenum. Restriction of disease to the stomach, duodenum, ileum, or colon suggests the possibility of immune mechanisms directed toward region-specific epitopes.

Comparison With Idiopathic Inflammatory Bowel Disease

The gastrointestinal irAEs associated with immune checkpoint inhibitor therapy share many overlapping features with chronic idiopathic IBD. Although autoimmunity plays a role in these inflammatory states, further analyses are needed to understand what makes each condition unique from the others.

Chronic idiopathic IBD is subclassified into Crohn's disease (CD) and ulcerative colitis (UC) because of differences in clinical presentation and underlying pathology. Patients with Crohn's disease have a unique $CD4^+$ T cell population expressing NKG2D that have been shown to produce significant amounts of the inflammatory cytokines IL-17 and IL-22 [19]. The most discriminate histological features of CD are granulomas, focal inflammation, focal crypt distortion, and ileal involvement. In contrast, patients with ulcerative colitis predominantly show type II natural killer cells that produce significant amounts of IL-13 in response to lyso-sulfatide. Lyso-sulfatide is a self-glycolipid prevalent in the gut; therefore, this

Table 1 Differential diagnoses of IBD

	Crohn's disease	Ulcerative colitis	CPI irAE
Primary location of inflammation	Anywhere along the GI tract (most commonly involves the terminal ileum)	Colon (increasing intensity distally)	Anywhere along the GI tract
Distribution	Patchy, transmural	Continuous, superficial	Continuous, superficial
Histological findings	- Granulomas - Skip lesions - Crypt distortion - Cryptitis	- Basal plasmacytosis - Paneth cell metaplasia - Mucin depletion - Crypt distortion - Cryptitis	- Granulomas - Cryptitis
Predominant antibodies	- CBir1 - ASCA - OMP C (*E. coli*)	- Anti-tropomyosin IgG - pANCA	- pANCA - OMP C (*E. coli*)
Predominant cell type	TH1 + TH17	TH2 + type II NKT	TH1
Predominant cytokines	IL-12, IFN-γ, IL-17, IL-21	IL-5, IL-13	IFN-γ, IL-17
Suspected etiology	Excessive T cell expansion - Resistant to apoptosis due to reduced Bcl2 [15] and survivin [16] Impaired bacterial clearance - Reduced NOD2 surveillance leads to excessive inflammatory infiltration [17]	Type II NKT - Targets lyso-sulfatide self-antigen	CTLA-4 or PD-1 inhibition - T cell activation - Treg depletion

autoimmune activation is likely to contribute to the epithelial cell cytotoxicity [20]. The most reliable features of UC are diffuse chronic inflammation, diffuse crypt atrophy, mucin depletion, and the absence of ileal inflammation [21]. Table 1 compares some of the main identifying features of both idiopathic and CPI-induced inflammatory bowel disease; however, the complex interplay of genes, the environment, the immune system, and the microbiome make it difficult to fully differentiate these conditions clinically [22].

Hepatic Complications

Hepatic adverse events from CPIs are much less frequent compared to those of the luminal GI tract, occurring in approximately 3.8% of patients receiving these drugs [23]. Immune-mediated hepatitis often manifests as asymptomatic increases in liver function tests, specifically aspartate aminotransferase (AST) and alanine aminotransferase (ALT) with mildly elevated total bilirubin. However, symptomatic events also arise, ranging from fever and malaise to fulminant hepatitis and death [24]. Hepatitis most often becomes clinically evident 8 to 12 weeks after initiation of checkpoint inhibitor therapy but may occur at any time.

Hepatic Histological Findings

Hepatic findings on abdominal CT vary depending on the severity of adverse events. In relatively mild cases, findings may appear normal. However, more severe cases may be characterized by hepatomegaly, periportal edema, attenuated liver parenchyma, and periportal lymphadenopathy. Ultrasonography findings may include prominent periportal echogenicity and gallbladder wall edema.

The limited histologic data (mostly from case series) on ipilimumab-induced hepatitis most often describes a pattern of hepatocellular injury with panlobular hepatitis, but bile duct injury has also been reported [24]. The differential diagnosis should be based on a thorough history and physical exam, laboratory evaluation, and histological findings [25]. Acute hepatitis is also commonly associated with other medications, autoimmunity, viral infection, and alcohol abuse. Features associated with each condition are shown in Table 2.

Distinguishing between autoimmune hepatitis and drug-induced hepatitis is difficult because they share many characteristics. Both can present with elevated liver function tests, eosinophilia, and hypergammaglobulinemia and respond to corticosteroids. Although both show portal eosinophil and lymphocyte infiltration, a differentiating factor is that plasma cells predominate in autoimmune hepatitis while neutrophils predominate in drug-induced hepatitis. Drug-induced hepatitis rarely presents with cirrhosis or rosette formation, which are prevailing findings in autoimmune hepatitis [26].

Table 2 Differential diagnoses of acute hepatitis

Cause of acute hepatitis	Clinical presentation	Common findings
Drug-induced liver injury associated with immune checkpoint inhibitors [25, 26]	- Temporal relationship with treatment (generally 8–12 weeks after initiation of checkpoint inhibitor) - Immediate lasting remission with treatment	- Aspartate aminotransferase and alanine aminotransferase elevations, with lesser elevations in total bilirubin - Histologic picture varies with panlobular hepatitis most commonly, but bile duct injury has been reported - Absence of cirrhosis
Idiopathic autoimmune hepatitis [26, 27]	- Temporal relationship with treatment - 2–4 years of therapy to achieve lasting remission	- Portal plasma cell infiltrate - Cirrhosis - Rosette formation - Autoantibodies
Acute viral hepatitis [28]	Positive viral serology - Hep A - Hep B - Hep C - Hep D - EBV - CMV - HSV - VZV	- Hyperbilirubinemia - Elevated transaminases
Acute alcoholic liver disease [29]	- History of alcohol abuse - Rapid-onset jaundice - Ascites - Proximal muscle loss - Encephalopathy - Hepatomegaly	- Steatohepatitis - Mallory bodies surrounded by neutrophils - Intrasinusoidal fibrosis - AST >>> ALT

Role of Genetics

The predominant role of CTLA-4 in suppressing T cell function is demonstrated by CTLA-4−/− mice that develop a severe lymphoproliferative disease with multiorgan infiltration and tissue destruction [30]. Defective CTLA-4 function is associated with exaggerated T cell responses and subsequent inflammation in the intestinal mucosa that leads to the development of IBD. The development of gastrointestinal toxicities with CTLA-4 blockade may be influenced by CTLA-4 allele polymorphisms. The 2q33 gene encodes the CTLA-4 receptor, and CT60 GG alleles have been associated with reduced CTLA-4 expression on the T cell surface. This polymorphism has been associated with inflammatory bowel disease [31]; however, a significant association between CTLA-4 polymorphisms and irAEs has not yet been determined [14].

In a meta-analysis of 1475 patients treated with nivolumab and pembrolizumab, antitumor efficacy was significantly higher in PD-L1+ tumors compared to those lacking PD-L1 [32]. However, baseline PD-L1 expression does not have a predictive value of treatment efficacy [33] and even PD-L1-negative patients showed response to anti-PD-1 monotherapy [34]. This can be explained by the fact that PD-L1 is inducible and shows dynamic expression over time. However, there are currently no validated genes or biomarkers that have been proven predictive of developing adverse events with anti-PD-1 treatment [35].

Biomarkers Predictive of Developing irAEs

In a study by Shahabi et al. [36•], whole blood samples were obtained from 162 advanced melanoma patients at baseline, 3 weeks, and 11 weeks after the start of ipilimumab treatment to identify potential biomarkers of GI irAEs. Pretreatment blood samples showed higher baseline levels of immune-related genes (CD3E, IL2RG, CD4, CD37, IL-32, and RAC2), cell cycle-associated genes (SPTAN1, BANF1, BAT1, PCGF1, FP36L2, and WDR1), and genes involved in vesicle trafficking (PICALM, SNAP23, and VAMP3) in patients that developed GI irAEs compared to those that did not. Biomarkers which were elevated after 3 weeks of ipilimumab administration were of particular interest, since this is when many symptoms start to occur. The marker which discriminated the most between the GI irAE and non-GI irAE groups after 3 weeks of treatment was CD177, a unique neutrophil surface marker that plays a role in neutrophil activation and mediates migration in the context of inflammatory cell recruitment. However, because of the marker's low sensitivity and large interindividual variability, it cannot be used alone to predict the development of irAEs. Other neutrophil-associated proteins were analyzed to develop a multimarker panel for predicting irAE development with increased sensitivity. Carcinoembryonic antigen-related cell adhesion molecule (CEACAM), an adherence mediator important in neutrophil migration, was also found to be significantly increased in the GI irAE group. Because these activation steps occur early in neutrophil recruitment, changes in CD177 and CEACAM expression could serve as a more sensitive biomarker than peripheral blood absolute neutrophil count [36•].

An inflammatory cytokine, IL-17, has also been proposed as a predictor of irAEs, because baseline IL-17 levels were significantly correlated with the development of grade 3 GI toxicities [37]. This cytokine is particularly notable because it is also known to play a pathological role in Crohn's disease. IBD patients also present with antibodies toward enteric flora; however, the ipilimumab response pattern is not consistent with that for UC or CD as shown in Table 1. The most common positive markers described in patients with grade 2 or greater irAEs are the perinuclear-staining antineutrophil cytoplasmic antibody (pANCA) and OmpC antibody (*Escherichia coli*). Anti-*Saccharomyces cerevisiae* antibody (ASCA)- and pANCA-positive titers are highly predictive for idiopathic IBD [38]; however, these markers were not significantly associated with CPIs. Antibody titers significantly fluctuated in the ipilimumab-treated patients, reflecting changes in the state of T cell activation and dysregulation of the GI mucosa [14].

Role of the Microbiome

Complex microbial populations occur in the healthy colon, and changes in the microbial flora of the colon may be associated with various disease states. CTLA-4 blockade in germ-free mice significantly reduces tumor regression, suggesting that anti-CTLA-4 tumor destruction relies on the gut microbiota. Further analysis showed that a single injection of CTLA-4 Ab significantly altered the microbiome to the genus level, inducing a rapid alteration in the *Bacteroides* species. The fecal abundance of *Bacteroides fragilis* negatively correlated with tumor size following CTLA-4 blockade. Because the *B. fragilis* polysaccharide capsule is known to induce IL-12-dependent TH1 immune responses, these immunogenic bacteria show potential to act as "anticancer probiotics" [39•].

Certain microbial species play an important role in maintaining mucosal tolerance by promoting T regulatory cell expansion or stimulating anti-inflammatory cytokines. In a prospective study, the intestinal microbial composition was sampled from 34 melanoma patients prior to CTLA-4 blockade. Although the patients all shared a similar proportion of Firmicutes, the Bacteroidaceae family was underrepresented in the patients that later developed immune-mediated colitis. Bacteroidetes exert anti-inflammatory effects through various pathways. These bacteria have an abundant polyamine transport system. Polyamine export promotes colonic epithelial cell proliferation in order to maintain the epithelial barrier. Bacteroidetes also play an important role in the endogenous synthesis of water-soluble B vitamins. Although the roles of these vitamins in gut homeostasis are not fully understood, thiamine (vitamin B_1) and riboflavin (vitamin B_2) concentrations have shown to be significantly reduced in Crohn's patients [40] and pantothenate (vitamin B_5) is known to decrease throughout the progression of inflammatory bowel disease [41]. Further studies are needed to better understand the connection between vitamin B production and intestinal immunity. The combination of the polyamine transport system and the biosynthesis of vitamins riboflavin (B_2), pantothenate (B_5) and thiamine (B_1) resulted in 70% sensitivity and 83% specificity for predicting patients at risk of developing colitis [42]. Because intestinal reconstitution of germ-free mice with the combination of *B. fragilis* and *Burkholderia cepacia* reduced histopathological signs of colitis [39•] and previous studies have shown these genera to improve antitumor efficacy, fecal

transplants hold promise as an adjuvant to CPI therapy to diminish undesirable immune-mediated toxicities.

Safety in Autoimmune Patients

Because CPIs non-specifically induce self-reactive T cells, there has been significant hesitation in using these treatments in patients with underlying autoimmune disorders. These patients are often excluded from trials of checkpoint inhibitors; therefore, minimal data is available concerning the safety and efficacy of CTLA-4 or PD-1 inhibitors in patients with underlying autoimmune diseases.

In a retrospective study [43], 30 patients with underlying autoimmune disorders were treated with ipilimumab. Twenty-seven percent had an exacerbation of their underlying disease, mainly recurrent or increased manifestations of prior symptoms. New grade 3–5 irAEs were experienced by 33% of patients. Fifty percent of patients experienced neither autoimmune flares nor irAEs. Only two of the six patients with prior inflammatory bowel disease experienced colitis during treatment. Both the exacerbations and irAEs were easily managed by standard treatment algorithms, and the incidence of irAEs was similar to that reported in previous clinical trials [43].

A patient with stage IV melanoma and preexisting ulcerative colitis developed grade 3 colitis following a first dose of ipilimumab. Colonoscopy showed diffuse erosions, ulcerations, and pseudopolyps which resolved with infliximab therapy. Treatment with ipilimumab was withheld, and 5 months later, he presented with sigmoid perforation. Following colectomy, ipilimumab was again administered, and a complete response of the patient's melanoma was observed within 6 months. Tracheobronchitis, grade 1 rash, and grade 3 autoimmune endocrinopathy were associated with this treatment. While little data is available, some have raised the possibility of prophylactic colectomy prior to ipilimumab therapy in patients with active underlying IBD who have no other treatment options [44].

Limited clinical experience suggests that ipilimumab can be administered to patients with underlying autoimmune disorders, but close monitoring is essential [43]. It has been estimated that 20 to 50 million individuals in the USA have autoimmune disorders [45], and further study is necessary to determine the safety of CPIs in patients with underlying autoimmune disorders.

Treatment Algorithms

In contrast to idiopathic chronic inflammatory bowel disease, CPI-induced colitis is often reversible if rapidly treated in accordance with the immune-mediated adverse reaction management guidelines. Treatment algorithms have been suggested but are, to some extent, empiric and based on algorithms for the treatment of idiopathic bowel disorders. The grading system of adverse events as defined by the National Cancer Institute [46] is shown in Table 3 and should be referenced during the treatment and management of such events.

When CPI adverse reactions are suspected, it is important to perform a detailed history and physical examination and rule out infectious colitis. For mild (grade 1) symptoms, it is recommended to continue CPI therapy with symptomatic treatment and close monitoring for worsening symptoms. Prophylactic use of budesonide is no longer recommended because administration does not significantly affect the development of adverse events [47]. NSAIDs are also not recommended during CPI therapy because there is a substantial correlation between NSAID usage and the development of ipilimumab-induced colitis [8••].

For moderate (grade 2) bowel symptoms, CPI therapy should be withheld. The use of antidiarrheal agents is recommended for symptomatic treatment. If symptoms persist for up to 1 week, it is recommended to start systemic corticosteroids at 0.5 mg/kg/day prednisone (some recommend higher doses) or equivalent. Glucocorticoids are associated with a wide range of immunosuppressive effects; however, studies have shown that they do not impair antitumor activity. In vitro proliferation assays revealed acute inhibition of naive $CD8^+$ cells by dexamethasone, without a significant effect on activated cells [48]. The use of steroids for short-term symptom management has not been demonstrated to affect tumor regression. If corticosteroid treatment reduces symptoms to grade 1, CPIs can be resumed while the steroids are tapered over a 1-month period. More rapid tapering may lead to worsening or recurrence of symptoms and should be avoided.

If severe (grade 3 and 4) symptoms develop, CPIs should be permanently discontinued and corticosteroids should be initiated. If bowel symptoms worsen or persist after 3 to 5 days of corticosteroid treatment, a non-corticosteroid immunosuppressive agent such as infliximab should be considered. Infliximab, a monoclonal antibody against the inflammatory cytokine TNF-alpha, has been shown to dramatically improve GI irAEs within 24 h [49], suggesting cytokine release by activated T cells as a potential mechanism for irAEs [50]. Early administration of infliximab is recommended in corticosteroid-resistant cases [2]. The effect of infliximab on tumor progression remains unknown [51]. Targownik and Bernstein found the risk of developing new cancers to be increased with the use of TNF inhibitors; however, this risk should be carefully weighed against the short-term risks of GI perforation and death from ipilimumab-induced colitis [52].

Treatment with corticosteroids has also been recommended for severe hepatitis associated with the use of checkpoint inhibitors. In most cases, however, the use of these CPIs is associated with only mild asymptomatic elevations in transaminases. In severe refractory cases,

Table 3 The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), version 4

Adverse effect	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4–6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase of 7 or more stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death
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	Death
Hepatitis	AST or ALT 1–2.5× ULN and/or T-BIL 1–1.5× ULN	AST or ALT 2.5–5× ULN and/or T-BIL 1.5–3× ULN	AST or ALT >5× ULN and/or T-BIL >3× ULN	AST or ALT >8× ULN	Death

the use of other suppressive agents such as mycophenolate mofetil or tacrolimus has been suggested, but data is limited. Infliximab is not recommended for the treatment of hepatitis due to its potential hepatotoxic effects.

Conclusion

Immunomodulatory checkpoint inhibitors represent a potent class of therapy for a growing number of neoplastic disorders. The use of these drugs, however, is associated with the potential for substantial toxicity, including inflammation of the luminal GI tract and liver. Much of our understanding with regard to the toxicity of these agents and how to manage them is based on limited data and extrapolation from other inflammatory disorders. A better understanding of the role of genetics and the microbiome in the development of irAEs holds significant potential for reducing immune-related adverse events resulting from checkpoint inhibitor treatment.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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