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REVIEW ARTICLES

Immune checkpoint inhibitor colitis, a rising issue in targeted cancer therapy era: A literature review

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Abstract. Research advances in the oncology treatment field have led to the widespread use of immunotherapy. The usage of immune checkpoint inhibitor (ICI) has improved the survival of cancer patients with metastases. This has also led to the rapidly expanding indications for ICI use. However, ICI usage may lead to toxicity, which may be immune-related, in different organ-specific targets. The immune-related adverse events (irAEs) of ICI may lead to increased morbidity, decreased quality of life, and early termination of ICI. The clinical manifestations of irAEs in the gastrointestinal system are variable, ranging from self-limited to life-threatening or fatal events. In this review article, we would like to focus on discussing ICI-induced colitis, which is one of the most common ICI irAEs in the gastrointestinal tract.

Keywords: Colitis; Enterocolitis; Immune checkpoint inhibitors; Immunotherapy; Review.

What is new? What is important?

Immune checkpoint inhibitor (ICI) may cause gastrointestinal immune-related adverse events (irAEs), such as immune-mediated colitis (IMC). The risk for IMC is greater in those using anti-CTLA-4 agent and combination therapy of anti-PD/PD-L1 with anti-CTLA-4 agent. Patients with IMC may present with bloody diarrhea, abdominal pain, nausea, and weight loss. Some recommended workups for IMC are blood tests, fecal calprotectin, Celiac disease panel, endoscopy, and histopathological examination. Management of IMC includes discontinuing ICI and administration of steroids and biologic agents. In this review, we also compared the recommendations of ASCO and AGA on the management of IMC.

INTRODUCTION

The advance of research in the oncology treatment field has led to the widespread use of immunotherapy. The usage of immune checkpoint inhibitor (ICI) has improved the survival of cancer patients with metastases [1]. Nowadays, the indication for ICI use also continues to expand rapidly [2]. ICI works by blocking specific pathways in cancer progression. Some of the approved ICI classes are cytotoxic T lymphocyte-associated protein-4 (CTLA-4), programmed cell death 1 (PD-1), and antibodies against PD-1 ligand (PD-L1) (Table 1) [3].

With the growing use of ICI, concerns regarding its acute and long-term toxicity have been increasing, including in Indonesia. Studies have shown that a majority of ICI toxicity present acutely. However, up to 40% of patients may have long-term toxicity. ICI toxicity has been proposed to be immune-related. Therefore, different classes of ICI may result in different toxicities in organ-specific targets. The immune-related adverse events

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(irAEs) of ICI may lead to increased morbidity, decreased quality of life, and early termination of ICI [1, 4]. The irAEs can affect the gastrointestinal tract such as the liver, pancreas, esophagus, biliary tract, and gut mucosa. The clinical manifestation of irAEs in the gastrointestinal system varies, ranging from self-limited to life-threatening or fatal events. The management of irAEs depends on the degree of severity [5]. In this review article, we would like to focus on discussing ICI-induced colitis, which is one of the most common ICI irAEs in the gastrointestinal tract.

Table 1

List of ICI and their indication [48, 49]

Drug	Approval Year	Approved Indication (may be approved for part of combination therapy)
PD-1 Inhibitors		
Nivolumab	2015	Melanoma Non-Small Cell Lung Carcinoma Renal Cell Carcinoma Hodgkin Lymphoma Head and Neck Cancer Urothelial Carcinoma Colorectal Cancer Hepatocellular carcinoma Esophageal carcinoma Gastric Cancer Malignant pleural mesothelioma
Pembrolizumab	2016	Melanoma Non-Small Cell Lung Head and Neck Cancer Squamous Carcinoma Hodgkin Lymphoma Primary mediastinal large B-cell lymphoma Urothelial Carcinoma Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) cancer Colorectal cancer Esophageal cancer Gastric Cancer, Cervical cancer Merkel cell carcinoma Renal Cell carcinoma Hepatocellular carcinoma Endometrial Carcinoma Cutaneous squamous cell carcinoma Triple negative breast cancer
Cemiplimab	2018	Cutaneous squamous cell carcinoma Basal cell carcinoma Non-Small Cell Lung Cancer
PD-L1 Inhibitors		
Atezolizumab	2016	Non-Small Cell Lung Cancer Small Cell Lung Cancer Hepatocellular Carcinoma Melanoma Alveolar Soft Part Sarcoma
Durvalumab	2016	Non-Small Cell Lung Cancer Small Cell Lung Cancer Hepatocellular Carcinoma Billiary Tract Carcinoma
Avelumab	2017	Merkel Cell Carcinoma Urothelial Carcinoma Renal Cell Carcinoma
CTLA-4 inhibitors		
Ipilimumab	2010	Malignant Melanoma
Tremelimumab	2022	Metastatic Non-Small Lung Cancer Unresectable Hepatocellular Carcinoma

CTLA-4: cytotoxic T lymphocyte-associated protein-4; ICI: Immune checkpoint inhibitor; PD-1: Programmed cell death 1; PD-L1: Programmed death ligand 1.

DEFINITION

Several terminologies have been used in reporting ICI-induced colitis, such as ICI-induced colitis and immune-mediated colitis (IMC). The American Gastroenterological Association (AGA) has released a clinical practice guideline regarding the diagnosis and management of ICI colitis and hepatitis in 2021. In their guideline, AGA did not specify the definition for ICI colitis; however, they stated that ICI may be accompanied by enteritis and commonly presented with diarrhea [6]. In 2021, the American Society of Clinical Oncology (ASCO) published a guideline regarding the management of irAEs in patients treated with ICI. They stated that ICI-related gastrointestinal toxicities may manifest as colitis, which is commonly characterized by abdominal pain, nausea, diarrhea, blood and mucous in the stool, and fever [7]. In a review by Bellaguarda *et al.* [8], it was pointed out that IMC may be diagnosed clinically without colonoscopy or specific gut inflammation biomarkers.

EPIDEMIOLOGY

According to several systematic reviews and meta-analyses, the reported incidence of IMC varied from 0.7% to 13% [9–11]. A study by Baxi *et al.* [9] revealed that 0.7% (0.4%–1.0%) of 3803 cancer patients receiving ICI had IMC, with 0.3% (0.1%–0.8%) occurring in those receiving nivolumab, 0.5% (0.2%–1.4%) with atezolizumab, and 1.1% (0.6%–1.7%) with pembrolizumab. Another study investigating irAEs due to ICI reported an incidence rate of 2.3% (206 patients) out of 5422 cancer patients. Those receiving ICI had 7.6 times higher risk for IMC compared to those in the non-ICI group [10]. A study by Wang *et al.* also reported an incidence rate of 10–13% among those who received nivolumab or BMS-936559 [11].

The type of ICI appears to affect the incidence rate of IMC in cancer patients. Those who received anti-CTLA-4 agent were reported to have a higher incidence rate of IMC when compared to PD-1/PD-L1 inhibitors [10, 12]. De Velasco *et al.* [10] found that those treated with ipilimumab had a higher incidence of colitis (9.1%) when compared to those treated with anti-PD-1 (1.4%) such as nivolumab or pembrolizumab, or anti-PD-L1 (1.0%) such as atezolizumab. Study by Yao *et al.* [12] also reported a significantly lower rate of colitis in the PD-1/PD-L1 inhibitor group compared to the anti-CTLA-4 group (RR 0.18; p<0.00001).

Furthermore, usage of anti-CTLA-4 agent also led to a higher incidence of high-grade colitis compared to PD-1/PD-L1 inhibitor. A study by Wang *et al.* found that patients receiving ipilimumab therapy had a higher incidence of grade 3–4 colitis (6.8%) compared to those receiving anti-PD-1 (0.9%) and anti-PD-L1 (0.6%) [13]. Another study also reported that usage of ipilimumab had a higher risk for high-grade colitis when compared to anti-PD-1 [(RR 22.5; 95% CI 6.37–79.4) vs. (RR 2.47; 95% CI 0.90–6.72); p=0.021] [10]. Combination therapy of ICI also led to a higher incidence of IMC when compared to monotherapy. One study reported that combination of ipilimumab and nivolumab led to a higher incidence of IMC and a higher rate of grade 3–4 colitis, compared to monotherapy [13].

RISK FACTORS

Race appears to be one of the risk factors in developing IMC. One retrospective study that investigated the incidence of IMC in 327 cancer patients reported that Caucasian patients were more likely to develop IMC when compared to other races (OR 5.76; 95% CI 2.03–16.36; P = 0.001) [14].

Elderly patients also had a higher incidence of IMC when compared to younger patients (< 65 years: 2.4%; > 65 years: 4.1%; > 70 years: 5.2%) [15]. One study reported that patients with body mass index (BMI) ≥ 30 had a higher incidence of IMC compared to those with BMI ≤ 25 (11.4% vs. 7.9%; p=0.029). This study also found that those with lower BMI tend to have more severe colitis (p=0.03) [16].

The type of malignancy also appears to affect the risk of developing IMC. It was found that the all-grade and grade 3–4 colitis incidence were highest in melanoma when compared to non-small cell lung cancer (NSCLC) and renal cell carcinoma (RCC). In addition, a higher dosage of ICI was also related to the incidence of IMC. A higher dosage of ipilimumab at 10 mg/kg caused a higher incidence of all grade colitis (6.6%), grade 3–4 colitis (5.1%), and grade 3–4 diarrhea (11.5%) when compared to the dose 3 mg/kg (all-grade colitis: 9.6%; grade 3–4 colitis: 7.1%; grade 3–4 diarrhea: 5.2%) [13].

The microbiota composition may also play a role in IMC. Based on a few studies, it was found that patients with a higher baseline microbiota of *Bacteroidetes* had no-colitis related phylotypes. On the other hand, colitis-associated phylotypes

were associated with those who have a higher baseline microbiota of *Firmicutes*. It was also found that patients with microbiota predominantly with *Faecalibacterium* and *Firmicutes* had longer progression-free survival and overall survival when compared to microbiota enriched with *Bacteroidetes* [17, 18].

Another study revealed that out of 73 melanoma patients receiving ipilimumab, those with a history of NSAIDs usage prior to ipilimumab therapy had a higher incidence of enterocolitis [19]. A cohort study by Grover *et al.* [20] reported that out of 213 patients, those who had vitamin D supplementation prior to ICI therapy had a lower incidence of colitis when compared to those who did not have vitamin D supplementation.

PATHOGENESIS

PD-1 is a receptor that plays an essential role in immunosuppression. It is naturally present on APCs, such as dendritic cells (DCs), macrophages, and B lymphocytes. This receptor is also expressed in high numbers in tumor-specific T cells [21]. When a ligand, such as PD-L1, binds to PD-1 receptor, the T cell receptor (TCR) – mediated pathway that controls cytokine secretion and lymphocyte proliferation will be inhibited [22]. Thus, PD-1 and PD-L1 are vital in helping tumor cells achieve immune escape [23]. PD-L1 also has pro-tumorigenic properties that may further promote tumor progression [24].

For T cells to activate, two signals are required: one by the T cell receptor complex and the second one via binding of a pair of co-stimulatory receptors, such as CTLA-4 and CD28. Both CTLA-4 and CD28 share the ligands CD80 and CD86 [25]. CTLA-4 functions by competing with CD28 and thus depriving a cell from receiving CD28 costimulation [26]. When TCR engagement occurs without CD28 costimulation, it will lead to apoptosis or anergy. Anergic T cells are incapable of producing IL-2 and proliferation. Thus, CTLA-4 suppresses T cell activation and proliferation [27].

The PD-1/PD-L1 pathway has also been known to play a vital role in maintaining self-antigen tolerance in many tissues, such as the digestive system, via suppression of CD4+ and CD8+ T cell proliferation. Hence, blockade of the PD-1/PD-L1 pathway may lead to intestinal toxicity. Mice with deficient CTLA-4 have been shown to express fatal autoimmune reactions [28]. Likewise, humans with CTLA-4 mutations present with immune dysregulation syndromes manifesting as diarrhea and colitis. CTLA-4 deficiency has been proposed to downregulate the function of Tregs, leading to downgraded inhibitory effects on CD4+ and CD8+ T cells. This leads to an increased number of CD4+ and CD8+ T cells [28]. In particular, increased CD8+ T cell infiltration has been proposed as a characteristic feature of IMC [29].

However, the exact pathogenesis of IMC is still unclear. It was postulated that a dysregulated immune system caused by the blockade of immune targets and host factors might play a significant role. Dysregulated immune system may lead to an increased number of activated T cells and other pro-inflammatory cytokines (CTL, Th17 cells, neutrophils) in the gut, as well as suppressing anti-inflammatory cytokines (Treg and IL-10). Activated T cells may have a reduced immune tolerance and thus become autoreactive T cells that target healthy tissues, such as the gut. Increased systemic and local pro-inflammatory cytokines lead to inflammation of the intestinal mucosa. The interaction between ICI and gut microbiome has also been studied. Higher amounts of *Firmicutes* and *Enterobacteriaceae* were associated with a higher number of IMC, while a higher load of *Bacteroides*, *Bidifobactriae*, and *Lactobacilli* were associated with a lower number of IMC [30, 31].

CLINICAL MANIFESTATION

The clinical manifestation of IMC may be varied. IMC patients may present with diarrhea, abdominal pain, bloody stool, weight loss, fever, fatigue, nausea, vomiting, and perforation. Due to the fact that IMC could rapidly progress from a non-severe to a severe condition, a prompt diagnosis is vital. Wang *et al.* [14] presented an analysis regarding 327 cancer patients who received ICI at MD Anderson Cancer Center. They found that 36% of the patients had diarrhea, and 24% (n=77) required immunosuppressive therapy. A study by Bonnano *et al.* [32] also showed that diarrhea was the most common manifestation of IMC, followed by abdominal pain (31%), nausea/vomiting (12.5%), bloody diarrhea (9.4%), weight loss (8.3%), epigastric pain (7.3%), and fever (2.4%). Severe IMC manifestations were rare but may present as ileus, toxic megacolon, bowel perforation, and death. Muscle guarding, rigidity, and abdominal tenderness may indicate the presence of toxic megacolon and bowel perforation [33]. ASCO defined enterocolitis

as the presence of abdominal pain, rectal bleeding, or mucoid stools with either clinical or radiologic evidence of entero-colonic inflammation [7]. As stated above, enterocolitis may quickly develop into severe complications. Enterocolitis is mostly seen in patients using anti-CTL4 (ipilimumab) compared to anti-PD-1 or PD-L1 [34].

The reported onset of IMC was variable. One study showed that IMC commonly occurred at 5–10 weeks after the second or third dose [35]. Bonano *et al.* [32] reported that the median onset of IMC was 3.3 months among non-small cell lung cancer patients treated with ICI. Further data showed that the onset of IMC also varied according to the type of ICI. Anti-CTL4-induced IMC was reported at 6–7 weeks after the first treatment. Meanwhile, anti-PD-1 or PDL-1 can cause IMC at 1–2 weeks after treatment [36]. Some data also showed that IMC may still occur even years after discontinuation of anti-PD 1/PD-L1 agents. Therefore, the onset of anti-PD-1 or PLD-1-induced IMC may be less predictable [37]. An analysis by Tang *et al.* [36] showed that using both anti-PD-1 and PD-L1 may result in earlier onset of IMC.

The severity of IMC can be graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 (Table 2) [38]. While CTCAE has been commonly used for reporting IMC severity, Wang *et al.* [14] showed that IMC grading based on CTCAE did not correlate well with the histopathological results. Geukes Foppen *et al.* [39] also showed that there was no significant correlation between the severity of diarrhea with the endoscopic severity score or histopathological features. This finding raises concern regarding the usage of the CTCAE grading system in clinical practice, thus implying the need for further workup. Despite this, both the guidelines from ASCO and AGA still use CTCAE for grading IMC to guide clinicians for further workup and treatment [6, 7].

Table 2

Grading of IMC severity according to CTCAE [38]

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Diarrhea	Increase of <4 stools/day over baseline; mild increase in ostomy output compared with baseline	Increase of 4–6 stools/day over baseline; moderate increase in ostomy output compared with baseline; limiting instrumental ADL	Increase of ≥7 stools/day over baseline; severe increase in ostomy output compared with baseline; limiting self-care ADL	Life threatening consequences; urgent intervention indicated	Death
Enterocolitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Abdominal pain; mucus or blood in stool	Severe or persistent abdominal pain; fever; ileus; peritoneal signs	Life threatening consequences; urgent intervention indicated	Death

ADL: Activities of daily living; CTACE: Common terminology criteria for adverse events; IMC: Immune-mediated colitis.

DIAGNOSTIC APPROACH

Manifestations of IMC may mimic other gastrointestinal diseases. Therefore, clinicians should consider IMC as a differential diagnosis in patients with ongoing or recently completed ICI treatment. Diarrhea may become the main symptom of IMC and should warrant attention from clinicians. The principle of diagnosing IMC is to correctly evaluate suspected cases, excluding other causes of IMC, and establish the diagnosis of IMC. Clinicians should exclude other conditions such as infection, IBD, radiation colitis, tumor metastasis, and other medication-induced diarrhea [6, 7].

Structured history-taking is crucial for diagnosing IMC. Clinicians should evaluate the symptoms in detail, including the severity, onset, duration, precipitating factor, and alleviating factor. Establishing a temporal relationship between ICI use and the onset of diarrhea is important. A review of past history, cancer management, current medication, and quality of life impairment are also important. Physical examination should be focused on hemodynamic stability as well as signs that may indicate severe IMC. Fever, severe abdominal pain, abdominal muscle guarding, and abdominal distention may indicate toxic megacolon or perforation and warrant urgent intervention [6, 7].

Laboratory examinations may include blood and stool tests. Blood tests, such as elevated C-reactive protein, erythrocyte sedimentation test, and white blood count may be used to evaluate the degree of systemic inflammation. Additional tests to evaluate include the metabolic panel and the celiac disease panel (tissue transglutaminase IgA and total IgA). Even though infection only accounted for less than 5% of diarrhea in ICI, AGA still recommends screening for enteric pathogens using stool cultures and *Clostridium difficile* tests. A stool analysis, including investigating for the presence of ova and parasites, may also be included. Evaluation of tuberculosis, HIV, hepatitis B, and hepatitis should also be performed. Causes of non-infectious diarrhea, such as Celiac disease and malabsorption, should also be considered. Specific gut inflammation markers, such as fecal calprotectin and lactoferrin, may be useful. Fecal calprotectin can be used as a screening modality to differentiate IBD from IBS as well as to monitor IBD disease activity. Due to the good correlation between fecal calprotectin and the degree of gut inflammation, fecal calprotectin can also help diagnose IBD. Furthermore, fecal calprotectin has a good sensitivity for detecting microscopic colitis and significant colitis. Recent evidence also suggests that fecal calprotectin strongly correlates with endoscopic severity in patients with IMC and can serve as a noninvasive marker of endoscopic and histologic remission. However, prospective data are needed to confirm whether fecal calprotectin can guide treatment decisions and help determine the necessity for further endoscopic evaluation [40].

Several studies have found that endoscopic findings may not correlate with the severity of clinical symptoms. However, endoscopy and histopathological examination are still regarded as the gold standard for diagnosing IMC, evaluating the disease severity, and determining the appropriate treatment [41]. The British Society of Gastroenterology (BSG) recommends performing colonoscopy for every patient with gastrointestinal immune-related adverse events (GI irAEs). Meanwhile, AGA suggests endoscopic evaluation to be performed for patients with grade $\geq$2 IMC [42].

There are no specific endoscopic findings for IMC. It can range from normal to various abnormalities such as mucosal edema, erythema, erosions, loss of vascular pattern, and superficial or deep mucosal ulcerations [43]. High-risk endoscopic findings, such as deep and large ulcers, may indicate a worse prognosis and require more aggressive treatment. Colonic ulcers are the only factor that can predict treatment response and the requirement for biologic therapy. The severity of endoscopic inflammation for IMC can be assessed using the MD Anderson Cancer Center Endoscopic Inflammation Grading and the Mayo Endoscopic Score. MD Anderson Cancer Center Endoscopic Inflammation Grading classifies patients into three categories based on the extent and severity of inflammation observed during endoscopy: mild severity, moderate severity, and high severity [44]. The Mayo Endoscopic Score categorizes patients into four groups, reflecting normal, mild, moderate, or severe disease activity based on endoscopic findings [45].

One-third of IMC patients may have normal colonoscopy results, and almost 20% of them may have normal biopsy results. Thus, microscopic colitis should be ruled out using routine biopsy. Re-evaluation endoscopy is essential to monitor treatment response and determine when to resume ICI [46].

The histological characteristics of IMC encompass acute colitis, chronic colitis, a combination of both, and microscopic colitis. In most cases, patients exhibit acute inflammatory changes with infiltration of neutrophils, lymphocytes, plasma cells, and eosinophils in lamina propria [41]. About 50% of patients present with chronic inflammation characterized by submucosal infiltration. In IMC caused by anti–PD-1, the histological findings typically indicate active colitis with crypt neutrophil infiltration and crypt distortion [47]. Conversely, IMC patients caused by anti–CTLA-4 often exhibit lymphocytic, plasma cell, and eosinophilic infiltration in the lamina propria, with rare reports of granulomas. In most cases, the inflammatory involvement is widespread [40].

Cross-sectional imaging findings for IMC are not specific and commonly include thickening of the bowel wall, colon distension, and congestion of mesenteric vessels. Imaging is typically recommended when there are suspicions of colitis-related complications. Patients experiencing these complications often present with abdominal pain, fever, or rectal bleeding [8].

MANAGEMENT APPROACH

There are two guidelines that clinicians may use to guide their management of IMC patients. The first is from ASCO, and the second is from AGA. Both guidelines used the CTCAE grading

system as a basis for the initial management, followed by endoscopy to guide further treatment [6, 7].

GRADE 1 IMC

For grade 1 IMC, both ASCO and AGA recommend continuing ICI and giving supportive treatment, such as anti-diarrheal agents [6, 7]. Unlike AGA, ASCO allows clinicians to consider withholding ICI temporarily until the symptoms resolve. In addition to giving anti-diarrheal agents, ASCO also suggests diet modification, monitoring for dehydration, and follow-up on the patient's condition. If the symptoms are prolonged, ASCO suggests consulting with a gastroenterologist for endoscopy and biopsy [7]. Conversely, AGA recommends endoscopy for those with IMC of grade 2 or higher [6].

GRADE ≥2 IMC MANAGEMENT ACCORDING TO AGA GUIDELINE

AGA recommends discontinuing the ICI and planning further management based on the endoscopic findings. Patients with microscopic colitis can be given mesalamine or budesonide as an initial treatment. For patients with mild endoscopic findings (erythema, decreased vascular pattern, mild friability), oral corticosteroid may be given. If there is no improvement after 72 hours, a trial of intravenous corticosteroid for 3 days should be given. If the patients remain unresponsive or do not achieve complete remission, then second-line immunosuppression biologic agents, such as infliximab or vedolizumab, should be employed. If there is only partial improvement on follow-up, then infliximab/vedolizumab may be continued for longer terms and consider repeating colonoscopy. If the patient had clinical remission, then ICI may be resumed after the steroid has been tapered off.

In patients with grade ≥ 2 IMC with moderate or severe endoscopic findings, high-dose intravenous corticosteroid and biologic agents (vedolizumab/infliximab) should be given. If there is no clinical improvement, workup to exclude infectious agents should be repeated. Clinicians may also consider fecal microbiota transplantation and surgical consultation. If there is clinical improvement, re-evaluation with endoscopy should be made after three doses of the biologic agents. If the re-evaluation showed complete endoscopic remission, then clinicians may safely discontinue infliximab/vedolizumab. Concurrent use of vedolizumab should be considered in patients planning to resume ICI. If the re-evaluation showed partial endoscopic remission and clinical remission, then infliximab/vedolizumab should be continued and only anti-PDL-1 agents may be resumed.

There is no data available that directly compared the usage of infliximab against vedolizumab for initial treatment. Infliximab is contraindicated in patients with moderate or severe heart failure, and hematologic malignancies. Vedolizumab may influence the effectiveness of immunotherapy if administered in patients with gastrointestinal tumors or metastases [6].

GRADE ≥2 IMC MANAGEMENT ACCORDING TO ASCO GUIDELINE AND COMPARISON WITH AGA GUIDELINE

Grade 2 IMC

Both ASCO and AGA agree on discontinuing ICI and performing endoscopy in patients presenting with grade 2 IMC [6, 7]. ASCO recommends starting steroids promptly at an initial dosage of 1 mg/kg/day until there are clinical improvements and then taper off for over 4–6 weeks. Patients who do not improve by 1 grade within 72 hours of treatment of corticosteroids, or are dependent on corticosteroids, or have high-risk endoscopic features (large deep ulceration, multiple ulcers, and extensive colitis beyond left colon) may be given an additional biologic agent in combination with corticosteroids [7]. Unlike ASCO, AGA recommends a trial of steroids for patients with mild endoscopic findings for 6 days (oral then intravenous) before adding biologic agents [6].

ASCO suggests resuming ICI if symptoms have improved to ≤ grade 1, steroid taper has been completed, and/or endoscopic and histologic remission have been achieved. When endoscopy and/or histologic examination is not possible, fecal calprotectin ≤ 116 μg/g may be used instead as an alternative [7]. AGA guideline had a slightly different recommendation. For those with mild inflammation, ICI may be continued if there is clinical remission and steroid taper has been completed. If there is only partial improvement, continue biologic agent, and repeat colonoscopy is recommended. If there is partial endoscopic remission, the biologic agent should be continued, and PD-1/PD-L1 agent may be resumed [6]. ASCO also recommends resuming PD-1/PD-L1 agent,

but CTLA-4 inhibitor agent may still be considered in those who have not responded or have inadequate response [7].

Grade 3 IMC

Based on the ASCO guideline, those with grade 3 IMC without high-risk endoscopic features should be given corticosteroids with an initial dose of 1–2 mg/kg/day prednisone until the severity is downgraded to grade 1 [7].

For those who have high-risk endoscopic features, ASCO recommends starting with a combination of corticosteroid and biologic agent. AGA also had a similar recommendation for those with moderate or severe inflammation [6, 7].

ASCO recommends considering hospitalization in patients with dehydration or electrolyte imbalance, while AGA has no recommendation for inpatient management. Both ASCO and AGA prefer resuming PD-1/PD-L1 agents over CTLA-4 inhibitor [6, 7].

Grade 4 IMC

ASCO suggests starting with 1–2 mg/kg/day methylprednisolone until improvement to grade 1, then tapered down over 4–6 weeks. A biologic agent may be administered when there is an inadequate response after 3 days of treatment. Lower gastrointestinal endoscopy is recommended if symptoms continue to be refractory or there is concern for a new infection [7].

ASCO recommends permanently discontinuing ICI [7]. Meanwhile, AGA allows resuming ICI as long as there is complete endoscopic remission, with or without concurrent vedolizumab. When there is partial endoscopic remission, AGA recommends resuming PD-1/PD-L1 agent along with the continuation of biologic agent [6]. ASCO also suggests inpatient management for all patients with grade 4 IMC. Meanwhile, AGA did not have any recommendations for inpatient management [6, 7]. The full comparison of the recommendations of ASCO and AGA can be seen in Table 3.

Table 3

Comparison of Recommendations of ASCO and AGA on Management of IMC [6, 7]

	ASCO	**AGA**
CTCAE Grade 1	Continue ICI or temporarily discontinue ICI until symptoms resolve.	Continue ICI.
	Supportive treatment: - Loperamide in patients with diarrhea only without colitis and infection - Monitor dehydration - Diet modification	Supportive treatment: - Anti-diarrheal agents
	Monitor patient's symptoms every 3 days or more frequently as needed until stabilization.	
	If prolonged, consider consulting a gastroenterologist for endoscopy and biopsy.	
CTCAE Grade 2	Discontinue ICI	Discontinue ICI
	Endoscopic examination is highly recommended to determine patients that require early treatment with biologic agent.	Endoscopic examination is recommended to confirm diagnosis and severity of IMC.
	Give corticosteroids with an initial dose of 1 mg/kg/day prednisone or equivalent until symptoms improve to grade 1, and then taper off over 4–6 weeks.	If there is mild inflammation[a] on endoscopy: - Give mesalamine, or budesonide for microscopic colitis. - If refractory, give oral corticosteroids 0.5–2 mg/kg/day prednisolone or equivalent. - If refractory to 3 days of oral corticosteroids, give intravenous corticosteroids. - If there is no improvement within 3 days, add 1 dose of infliximab (5 mg/kg IV) or vedolizumab (300 mg IV). - If there is clinical remission, ICI may be resumed after steroid taper. - If there is partial improvement, continue biologics (infliximab or vedolizumab) and consider repeat colonoscopy.

Table 3 (continued)

	ASCO	AGA
	If refractory to corticosteroid (i.e: did not improve by one grade ≤ 72 hours) or has high-risk endoscopic features (large deep ulceration, multiple ulcers, extensive colitis beyond left colon), consider adding anti-TNF (infliximab) or anti-integrin (vedolizumab) antibody.	If there is moderate[b]/severe[c] inflammation on endoscopy: - Give a combination of intravenous corticosteroid with vedolizumab/infliximab. - If there is microscopic colitis, give budesonide. - If refractory, repeat workup for infections, consider fecal microbiota transplantation, or consult surgery. - If there is clinical improvement, repeat endoscopy after 3 doses of add-on therapy. - If there is complete endoscopic remission, stop infliximab/vedolizumab. Concurrent vedolizumab may be considered if resuming ICI. - If there is partial endoscopic remission and clinical remission, continue infliximab/vedolizumab. PD-1/PD-L1 agent may be resumed.
	Resuming ICI may be considered if symptoms have improved to ≤ grade 1, steroid taper is completed, and/or endoscopic and histologic remissions are achieved. Fecal calprotectin ≤ 116 μg/g may be considered as surrogate for endoscopic and histologic remission.	
	If patient is maintained on biologics, resuming ICI may be considered based on evaluation of the risks and benefits.	
	Resuming PD-1/PD-L1 agent has a lower risk of flare-up. However, CTLA-4 inhibitor can still be considered in patients who have inadequate respond or have not yet responded.	
CTCAE Grade 3	Similar to grade 2 with the additions of following: - Give corticosteroids with an initial dose of 1–2 mg/kg/day prednisone or equivalent until symptoms improve to grade 1, and then taper off over 4–6 weeks. Intravenous methylprednisolone may be considered if there is concern for upper GI inflammation. - If have high-risk endoscopic features or inadequate response to steroid (symptoms persist after 3 days), consider adding infliximab or vedolizumab. - Consider hospitalization for patients with dehydration or electrolyte imbalance. - Consider repeating colonoscopy in patients who are immunosuppression-refractory. - Should permanently discontinue CTLA-4 inhibitor.	Similar to grade 2.
CTCAE Grade 4	Similar to grade 2–3, with the addition of following: - Permanently discontinue ICI. - Hospitalize patient. - Give 1–2 mg/kg/day methylprednisolone or equivalent until symptoms improve to grade 1, and then taper off over 4–6 weeks. - Consider adding infliximab or vedolizumab if there is inadequate response to steroids after 3 days. - Consider lower GI endoscopy if symptoms are refractory to treatment or there is concern for new infection.	Similar to grade 2.

[a] Mild: Erythema, decreased vascular pattern, mild friability.
[b] Moderate: Marked erythema, absent vascular pattern, friability, erosions.
[c] Severe: Spontaneous bleeding, ulceration.

AGA: American gastroenterological association; ASCO: American society of clinical oncology; CTCAE: Common terminology criteria for adverse events; CTLA-4: Cytotoxic T lymphocyte-associated antigen 4; GI: Gastrointestinal; ICI: Immune checkpoint inhibitor; IMC: Immune-mediated colitis; IV: Intravenous; PD-1: Programmed cell death 1; PD-L1: Programmed death ligand 1; TNF: Tumor necrosis factor.

CONCLUSION

IMC may become a rising issue due to the increased use of ICI in cancer management. Clinicians should have a high suspicion of IMC in patients with ongoing or post-treatment with ICI. Further studies should be employed to decipher the intricate mechanisms of IMC, the best therapeutic approach for IMC, and ways to prevent IMC. For now, clinicians may use the AGA and ASCO guidelines to guide their clinical practice.

Progresele cercetării în domeniul tratamentului oncologic au condus la utilizarea pe scară largă a imunoterapiei. Utilizarea terapiilor tip immune checkpoint inhibitor (ICI) a îmbunătățit supraviețuirea pacienților cu cancer cu metastaze. Acest lucru a dus, de asemenea, la creșterea rapidă a indicațiilor pentru utilizarea ICI. Cu toate acestea, utilizarea ICI poate duce la toxicitate imun mediată, în diferite organe. Evenimentele adverse immune (irAEs) ale ICI pot duce la creșterea morbidității, scăderea calității vieții și încetarea timpurie a tratamentului cu ICI. Manifestările clinice ale irAE în sistemul gastrointestinal sunt variabile, variind de la evenimente autolimitate până la evenimente care pun viața în pericol sau fatale. În acest articol, am dorit să ne concentrăm pe discutarea colitei induse de ICI, care este una dintre cele mai frecvente irAE ale ICI în tractul gastrointestinal.

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