Editorial

Management of gastrointestinal adverse events induced by immune-checkpoint inhibitors

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Introduction

Cancer cells can avoid being recognized and destroyed by the immune system by activating immune checkpoints, such as cytotoxic T lymphocyte-associated antigen 4 (CTLA4) and the programmed death-1 (PD-1) receptor and its ligand PD-L1. Immune-checkpoint inhibitors (ICIs) have been proven effective with a long response duration in an increasing number of indications, such as melanomas and non–small-cell lung cancer (NSCLC).1 Recently, pembrolizumab, an anti-PD-1 monoclonal antibody, has shown significant antitumor activity in microsatellite instability-high (MSI-H) or DNA mismatch repair deficient (dMMR) tumors.2 Pembrolizumab has also been approved for use in PD-L1-positive gastric cancer.3 Nivolumab, another anti-PD-1 monoclonal antibody, has been approved for the treatment of gastric cancer and hepatocellular carcinoma by the U.S. Food and Drug Administration (FDA) and the Japan Ministry of Health, Labor and Welfare, respectively.4,5 Meanwhile, an increasing number of clinical trials are ongoing to evaluate the efficacy of ICIs with the goal of expanding the application of ICIs in advanced cancers.

Along with potential benefits, clinical safety is another major concern when applying check-point blockade therapy. With more cancer patients being treated with ICIs, more adverse events (AEs) are being recognized. Treatment-related AEs may involve any organ or system, and some of them are considered to be caused by a dysfunctional immune system.6 Disorders of the gastrointestinal (GI) tract are some of the most common AEs, which may be difficult to deal with and lead to discontinuation of ICIs.1,7 GI toxicity involves both upper and lower GI AEs. Only colitis and diarrhea, two types of lower GI AEs, have been investigated, and we know little about the epidemiology, pathogenesis, clinical features, and management of other GI AEs. Herein, we have reviewed the currently available literature on GI toxicity induced by ICIs and have shared our experience in managing treatment-related GI AEs based on our immunotherapy clinical practice.

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Upper GI AEs

Incidence

The upper GI toxicity has drawn little attention from oncologists. The most common manifestations are decreased appetite and nausea. With anti-PD-1 antibody, the incidences of decreased appetite and nausea were 2.5%–13.6% and 7.0%–16.5%, respectively, in non-upper-GI cancers,8–21 4.8%–15.3% and 4.2%–16.4%, respectively, in the upper GI cancers.22–28. Following treatment with anti-CTLA4 antibody, 25.0%–26.7% and 35.1%–36.1% of patients with melanoma presented with loss of appetite and nausea/vomiting, respectively,29,30 while 16.7% of upper GI cancer patients presented with nausea.31 Compared to monotherapy, combination immunotherapy (blockade of both PD-1/PD-L1 and CTLA4) was associated with similar incidences of decreased appetite and nausea.

Table 1 summarized the incidence of ICI treatment-related AEs in GI cancer.21–28,31–34

Other reported upper GI AEs included stomatitis, esophagitis, dysphagia, gastritis, vomiting and gastro-esophageal reflux disease.21,26,32,33 Recently, gastric hemorrhage was reported in patients with GI stromal tumors (GIST) receiving dasatinib plus ipilimumab in a phase Ib study.35 The AE incidences might be underestimated for the upper GI cancer patients because some AEs are considered tumor-related rather than treatment-related.

Potential risk models

No risk factor has been identified for upper GI AEs. The primary tumor does not influence the occurrence of upper GI AEs of any grade as their incidences were comparable between the upper and non-upper-GI cancer patients.6 However, severe hemorrhage has not been described in non-upper-GI cancers, indicating that the primary tumor may be a predictive factor for severe AEs. Radiation exposure of the upper GI tract may be another potential risk factor, as hemorrhage was observed in one patient who received radiotherapy for the primary tumor in our center. Moreover, one gastric cancer patient treated with anti-CTLA4 plus anti-PD-1 antibody in our center and three GIST patients treated with dasatinib plus ipilimumab developed severe gastric bleeding,35 indicating that combination therapy can increase the incidence of severe AEs such as upper GI hemorrhage. Chronic inflammation and long-term use of non-steroidal anti-inflammatory drugs (NSAIDs) may also increase the susceptibility to upper GI toxicity.

Management

There are no available management guidelines for upper GI AEs. Literature review and our experience shows that most AEs are primarily mild and can be resolved with symptomatic treatments alone. For severe AEs, a comprehensive workup should be performed in order to clarify the etiology (treatment-related or tumor-related) and evaluate the AE severity, which should include a complete blood count, serum electrolyte profile, stool occult blood test, abdominal CT scan, gastroscopy, and histopathology examinations.

For upper GI bleeding caused by gastritis (including positive fecal occult blood), which is potentially immune-mediated, we do not advocate glucocorticoids to be used due to their potential to result in upper GI ulcerations and aggravate hemorrhage. In our center, all cases of upper GI bleeding were resolved with routine non-surgical approaches, including proton pump inhibitors (PPI), octreotide, and hemostatic drugs. Elective resection of the primary tumor should also be considered to avoid hemorrhage recurrence in upper GI cancer patients.

For severe AEs except for bleeding, best supportive care and symptomatic treatments can offer great benefit. If dysfunction of the immune system is suspected to be the etiology, high-dose glucocorticoids should be used according to the principles of the current guidelines.1 However, it should be noted that glucocorticoids are not recommended for autoimmune gastritis and have not yet been investigated in ICI-induced upper GI AEs.36 Therefore, a multidisciplinary team (MDT) should determine whether to initiate treatment with glucocorticoids. PPIs and gastric mucosa protectants should be used along with glucocorticoids to prevent the occurrence of upper GI bleeding.

Lower GI AEs

Incidence

Clinical manifestations of lower GI complications mainly involve colitis and diarrhea. A meta-analysis involving 10 clinical trials showed that ICIs were more likely to induce colitis and diarrhea compared to the control.37 Patients treated with CTLA4 blockade therapy had higher rates of lower GI AEs than those treated with PD-1 blockade therapy.16 In GI cancers, colitis occurred in 0.6%–5.6% of the patients receiving monotherapy (anti-PD-1 or anti-CTLA4 antibody). The incidences of diarrhea were 6.6%–27.8% among patients receiving monotherapy and
Table 1
The incidence of ICI treatment-related AEs in GI cancers.

| Study | ICIs | Cancer type | Decreased appetite (%) | Nausea (%) | Diarrhea (%) | Colitis (%) | Others (%) |
|-------|------|-------------|------------------------|------------|-------------|------------|------------|
| CheckMate 032 | Nivo (3)a, n = 74 | CRC | – | 9.5 | 21.6 | 1.4 | 4.1 (Stomatitis) |
| KEYNOTE-012 | Pembrolizumab, n = 39 | GC | 12.8 | – | – | – | – |
| KEYNOTE-059 cohort 1 | Pembrolizumab, n = 259 | GC | 7.3 | 6.9 | 6.6 | 2.3 | – |
| ATTRACTION-2 | Pembrolizumab, n = 163 | GC, EGJ | 4.3 | 2.5 | 1.9 | 0.0 | – |
| CheckMate 032 | Nivo (3)a, n = 59 | GC, EC, EGJ | 15.3 | – | 15.3 | – | – |
| Desai et al 2017 | BGB-A317, n = 55 | GC, EC | – | 16.4 | – | 1.8 | 14.5 (Dysphagia) |
| KEYNOTE-028 | Pembrolizumab, n = 23 | EC | 13.0 | – | – | – | – |
| Kudo et al 2017 | Pembrolizumab, n = 65 | SCC | 9.2 | – | 13.8 | – | 1.5 (Constipation) |
| Ralph et al 2010 | Pembrolizumab, n = 18 | GC, EAC | – | 16.7 | 27.8 | 5.6 | – |
| KEYNOTE-059 cohort 2 | Pembrolizumab + 5-FU/Cape + CDDP, n = 25 | GC | – | – | – | 4.0 | – |
| Moehler et al 2016 | Pembrolizumab, n = 30 | CRC | – | 20.0 | 43.3 | – | – |
| CheckMate 142 | Pembrolizumab, n = 10 | CRC | – | 20.0 | 40.0 | – | 10.0 (Vomiting) |
| Moehler et al 2016 | Pembrolizumab, n = 10 | CRC | – | 30.0 | 40.0 | – | 30.0 (Vomiting) |

ICI: immune-checkpoint inhibitor; AE: adverse event; GI: gastrointestinal; Pembrolizumab; Nivo: nivolumab; Ipi: ipilimumab; Treme: tremelimumab; 5-FU: 5-fluorouracil; CAPE: capecitabine; CDDP: cisplatin; CRC: colorectal cancer; GC: gastric cancer; EGJ: esophagogastric junction; EC: esophageal carcinoma; EAC: esophageal adenocarcinoma; ESCC: esophageal squamous-cell carcinoma; –: not applicable.

a The number in the parenthesis indicated the dose of Nivo or Ipi: “3” represented “3 mg/kg” and “1” represented “1 mg/kg”.

9.6%—43.3% among those receiving combination therapy (Table 1).21–28,31–33 These data were comparable to those from non-GI cancers.6,38 Panenteritis,39 celiac disease,40 and constipation15 have also been reported, and paralytic bowel obstruction has been observed in our center.

Potential risk models

Identifying patients prone to treatment-related AEs before starting ICI therapy can help optimize the follow-up strategy and determine the treatment intensity. Underlying diseases, previous treatments, positive baseline biomarkers and intensive treatment of ICIs may favor the emergence of colitis.41–52 However, we know little about risk factors for other lower GI AEs.

Whether underlying immune disorders increase the likelihood of colitis, is controversial.41 Among patients with prior ipilimumab-induced colitis, recurrence of colitis following anti-PD-1 therapy was rare.42,43 However, 3 out of 13 patients (23.1%) with preexisting Crohn’s disease or ulcerative colitis experienced disease flares or newly emerged colitis (Table 2),42–44 which was much higher than the rate of 5%—8% reported in melanoma patients in another study.38 Larger studies are warranted to clarify the impact of underlying immune disorders on the development of colitis. Some previous treatments increased the likelihood of lower GI AEs. Prescribed NSAIDs were associated with a higher susceptibility to enterocolitis.41 Existing evidence shows that previous thoracic and brain radiotherapy is associated with increased incidences of pulmonary toxicity and hypophysitis, respectively.53,54 We presume that radiation exposure of the colorectum can increase the possibility of developing colitis as well. One patient with severe colitis in our center was rectally exposed to radiation. Similarly, in prostate cancer, the incidence of diarrhea was numerically higher in patients who received pelvic radiotherapy before ICI therapy than those who did not.45 The relationship between radiation exposure of the colorectum and colitis should be investigated in prospective clinical trials.

The presence of baseline gut microbiota enriched with Firmicutes was associated with the more frequent occurrence of colitis, whereas patients with Bacteroidetes bacteria enrichment were resistant to colitis.46,47 The use of antibiotics can alter the gut
microbiota. However, it did not influence the occurrence of colitis.41 Pretreatment serum IL-17 levels were significantly associated with the development of grade 3 diarrhea or colitis, but not with all grades of colitis.38 Increase in expression of two neutrophil-activation markers, CD177 and carcino-embryonic antigen related cellular adhesion molecule1 (CEA-CAM1),49 and any abnormal histologic finding after ICI initiation50 predicted the emergence of lower GI AEs. However, these biomarkers need further verification in clinical practice and are not recommended to predict lower GI AEs currently.

In terms of treatment intensity, the incidence of colitis did not increase in the patients receiving high doses of ipilimumab only.41 However, it was much higher in patients receiving combination immunotherapy compared to those receiving monotherapy,6,51 and combining immunotherapy with conventional therapies may induce more treatment-related AEs.52

Management

Once treatment with an ICI is started, patients should be followed up regularly as the majority of any-grade AEs and all grades 3–5 AEs occurred within the first 12–16 weeks.7,55 Patients should be told to report any discomfort and oncologists should always keep treatment-related AEs in mind. The proposal of prophylactic approaches to prevent treatment-related AEs is attractive. Nevertheless, prophylactic budesonide did not reduce the incidence of colitis.50,56

Most cases of mild diarrhea and colitis (grade 1–2) were treated successfully under the guidance of detailed algorithms.1 However, for severe lower GI AEs, most of them are graded only based on symptoms, which might lead to an inaccurate evaluation of the condition and inappropriate treatment. Radiological and histopathologic examinations should be integrated into a comprehensive assessment plan for severe colitis.57,58 Kim et al58 reviewed radiological images of 16 patients with ipilimumab-associated colitis and identified two distinct CT patterns: the diffuse colitis pattern and the segmental colitis associated with diverticulosis (SCAD) pattern. The diffuse colitis pattern was characterized by mesenteric vessel engorgement, mild diffuse bowel wall thickening, and fluid-filled distended colon, and the SCAD pattern had the features of segmental moderate wall thickening and pericolic fat stranding in a segment of preexisting diverticulosis. Patients with the SCAD pattern presented with more severe symptoms such as mixed watery and bloody diarrhea and cramping pain and were recommended to be treated with both glucocorticoids and antibiotics. Endoscopy and histopathological evaluation should be performed if there is no contradiction. Oncologists should confirm the etiology of diarrhea (ICI-induced colitis or inflammatory bowel disease) and evaluate the severity of colitis.59 One patient with grade 3 colitis in our center was treated with low dosage of methylprednisolone (0.5–1 mg·kg⁻¹·d⁻¹) mainly because only mild inflammation was observed pathologically, and he responded well. Therefore, we need to investigate the additional role of radiological and histopathological findings in guiding treatments. Glucocorticoids are the first-line therapy for severe colitis or diarrhea, with other immunosuppressive drugs as salvage therapies such as infliximab.1 It should be kept in mind that approximately 50% of the colitis patients undergoing upper GI endoscopy had gastritis or duodenitis.59,60 Therefore, oncologists must pay more attention to potential upper GI bleeding, and prophylactic PPI may be beneficial.

Besides diarrhea and colitis, constipation may occur in a small number of patients and paralytic bowel obstruction in rare cases. These AEs may represent another type of lower GI disorders, namely dysfunction of bowel movements probably mediated by enteric neuropathy. These symptoms can be considered ICI-induced only after excluding mechanical obstruction due to the primary tumor, peritoneal metastasis, and weak bowel movements caused by decreased appetite or poor performance status, which were rather common in advanced cancers, especially GI cancers. Medications facilitating the digestive tract force, such as
anticholinesterase drugs and mosapride, may be sufficient. The therapeutic value of glucocorticoids needs to be further clarified.

**Future directions**

Immunotherapy has been proven promising in a wide range of cancers. Combining immunotherapy with conventional treatments often offers a therapeutic advantage, but it can increase the incidence of rare and severe AEs. Currently, our knowledge of these AEs is rather limited.

Identifying risk factors can help select high-risk patients to be followed up intensively and be given prophylactic treatments. For treatment-related GI AEs, although oral budesonide failed to decrease the frequency of colitis, it remained unclear whether budesonide was beneficial in a high-risk population. PPI or histamine H2-receptor antagonists may be used for preventing gastritis and upper GI hemorrhage, but this needs further confirmation in clinical trials.

When GI symptoms appear in advanced cancer patients, especially in patients with GI cancers, one major challenge is to identify whether these symptoms are manifestations of the ICI-associated AEs, primary or metastatic tumor or a potential infection. However, the clinical, radiological and pathological characteristics have not been well described for most GI AEs, thus making differential diagnosis difficult. If patients who had tumor progression or an infection were misdiagnosed with GI AEs and treated with glucocorticoids, the symptoms could worsen or even turn fatal. Therefore, further studies should investigate the characteristics of GI AEs.

Another challenge lies in finding appropriate treatments for severe GI AEs. Overall, there is no high-level evidence supporting the current recommendations from guidelines. Well-designed prospective randomized clinical trials need to be conducted to investigate the most optimal treatments. According to the current guidelines, glucocorticoids are recommended for severe colitis and diarrhea, but one-third to two-thirds of the patients either do not respond to standard glucocorticoids or have a relapse during glucocorticoid tapering, indicating that glucocorticoids are not the best choice in some cases, where infliximab seems to be more appropriate. Moreover, the role of other immunomodulators (e.g., tacrolimus, cyclosporine, and mycophenolate mofetil) has not been clarified. Further studies are warranted to predict glucocorticoid resistance and to evaluate the efficacy of non-glucocorticoid regimens in colitis patients. In addition, an increasing number of rare GI AEs have been observed with no available treatment recommendations, such as upper GI bleeding and paralytic bowel obstruction. Our experiences described here have been helpful and should be considered in clinical trials. A multidisciplinary team (MDT) involving oncologists, rheumatologists, gastroenterologists, radiologists, and pathologists should be built to evaluate all aspects of the AEs and provide personalized treatments. Oncologists worldwide are encouraged to share their experiences in dealing with these challenging situations.

**Conclusions**

Immunotherapy has shown great promise for advanced cancers, and a growing number of new ICIs targeting PD-1/PD-L1 and CTLA4 are being evaluated in early-phase clinical trials. However, these drugs are associated with AEs affecting almost every system. Upper GI AEs have been poorly investigated, and gastric bleeding has been observed in GI cancer patients. Glucocorticoids are not recommended for upper GI bleeding and should be carefully used for cases without bleeding. Diarrhea and colitis are the most common lower GI AEs, where high dosage of glucocorticoids and timely addition of other immunomodulators are important. Constipation and paralytic bowel obstruction, caused by GI tract dysfunction, represent other types of lower GI AEs and can be resolved with medications promoting bowel movements. The MDT approach should be considered in every severe or rare case of AEs. Further research is warranted to establish risk models for the development of GI AEs and to investigate the radiological and pathological characteristics to optimize treatments for severe cases.

**Conflicts of interest**

No potential conflicts of interest were disclosed.

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