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Perspective

Management of gastrointestinal adverse events induced by immune-checkpoint inhibitors

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Abstract

Immune-checkpoint inhibitors (ICIs) have been proven promising for advanced cancers, and they are characterized by a unique treatment-related adverse event (AE) spectrum. Toxicity of the gastrointestinal (GI) tract is one of the most common AEs and often results in discontinuation of ICIs. Since most of the current studies have focused on the incidence, characteristics, and management of colitis, very little is known about other types of GI AEs. Herein, we review the available relevant literature on upper and lower GI toxicities, and present an algorithm for GI AE management based on the existing evidence and our clinical experience. Nausea and decreased appetite are the most common upper GI AEs, and gastric bleeding has been observed. 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 characterized by inflammation of the mucosa, and high-dose glucocorticoids with other immunomodulators are recommended as salvage treatments. Constipation and paralytic bowel obstruction caused by dysfunction of the GI tract are less frequent and respond well to medications promoting bowel movements. Severe GI AEs should be managed by a multidisciplinary team based on a comprehensive assessment of disease severity. Further clinical trials are warranted to investigate the optimal management of GI AEs.

Keywords: Immune-checkpoint inhibitors; Treatment-related adverse event; Gastrointestinal tract; Risk factor; Management

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 receptor (PD-1) 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-

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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.

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.[7] 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.[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

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