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Review Article

Gastrointestinal Toxicities of Immune-Checkpoint Inhibitors in Non-Small Cell Lung Cancer Patients. A Review

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Abstract

Immune-checkpoint inhibitor (ICI)-based immunotherapy is now one of the most effective and widely used treatments in the field of onco-hematology. Among the malignancies where immunotherapy is most frequently employed with excellent results, lung cancer stands out, from the adjuvant, neoadjuvant, and perioperative phases to the metastatic stage. However, relatively little is known about the mechanisms underlying the full spectrum of immune-related adverse events (irAEs), with gastrointestinal involvement being among the most common. Therefore, early management of these adverse events is crucial before they progress to difficult-to-reverse clinical conditions. Corticosteroids remain the cornerstone of irAE treatment, but promising new therapeutic agents are emerging. In this review, we will examine the main immune-related gastrointestinal toxicities, their management strategies, and their correlation with the use of ICIs in the treatment of non-small cell lung cancer (NSCLC).

Keywords: Immune-Checkpoint Inhibitors; Gastrointestinal Adverse Events; Non-Small Cell Lung Cancer.

Introduction

Oncology immunotherapy (IO) has become a cornerstone of cancer treatment, particularly in certain malignancies such as NSCLC, where, in non-oncogene-addicted forms, it has delivered remarkable results, either alone or in combination with chemotherapy. Over recent years, it has significantly modified the natural history of these tumors, leading to significative improvements in survival and cure rates. Currently, seven ICIs are approved for NSCLC treatment at various stages, including programmed death-1 (PD-1) inhibitors Pembrolizumab, Cemiplimab, and Nivolumab; programmed death-ligand 1 (PD-L1) inhibitors Atezolizumab, Durvalumab, and Avelumab; and the cytotoxic T-lymphocyte antigen 4 (CTLA-4) inhibitor Ipilimumab [1,49-51,53,68,69].

Although IO is usually better tolerated than chemotherapy or chemo-immunotherapy and associated with fewer adverse effects, it is not always safe and irAEs, sometimes severe and life-threatening, can occur. These toxicities are classified into five grades according to the most recent Common Terminology Criteria for Adverse Events (CTCAE) [2,3].

A retrospective study reported that the overall incidence of any grade irAEs in NSCLC patients is approximately 30%, with severe cases accounting for 6% [4]. A meta-analysis by Sun et al. reported

an overall incidence of immune-related adverse events (irAEs) of 22%, with 4% being severe, in patients with non-small cell lung cancer (NSCLC) treated with anti-PD-1 and anti-PD-L1 agents [100].

Among the most common and frequently observed irAEs are gastrointestinal toxicities (GI irAEs), particularly colitis, which is a leading cause of emergency department visits in NSCLC patients treated with ICIs [5]. Other less common GI toxicities include mucositis, esophagitis, gastritis, cholecystitis, appendicitis, and diverticulitis.

It has been observed that GI irAEs are often associated with improved overall survival (OS), making timely symptom management and, when feasible, the resumption of IO a key objective [6,7, 101-103].

However, the exact mechanisms underlying these ir toxicities remain not yet been fully elucidated, which hinders the implementation of effective preventive measures in clinical practice [104]. Summarily, most irAEs are thought to be related to autoimmune mechanisms in normal tissue triggered by the activation of CD8+ cytotoxic T cells by ICIs, with some involving activated B cells and the pathological production of antibodies [105-107]. Other intrinsic mechanisms may include pre-existing autoimmunity, genetic variants, and unbalanced inflammatory cytokines [108-110]. In patients with NSCLC treated with anti-CTLA-4 agents, the most common irAEs include skin rashes and gastrointestinal issues such as diarrhea, nausea, and colitis [52,53,68-70,111]. In the gastrointestinal system, CTLA-4 plays a crucial role in maintaining gut homeostasis. Therefore, anti-CTLA-4 monoclonal antibodies, by activating T cells in the gut, can lead to colitis characterized by elevated CD4+ effector cells and significant alterations in regulatory T cells (Tregs). Conversely, gastrointestinal toxicities are also among the most frequent irAEs in patients with NSCLC treated with anti-PD-1/PD-L1 agents, although they are generally less severe in intensity [86,112-117].

To our knowledge, there are no articles in the literature that exclusively focused on the incidence and impact on outcomes of GI irAEs in patients with NSCLC.

This review will analyze the main GI irAEs and their respective treatments especially from a clinical point of view, with a particular focus on their correlation with NSCLC treatment.

Diarrhea And Colitis

Diarrhea is the most common manifestation among the various GI irAEs. The incidence and severity of diarrhea are higher in treatments combining an anti-PD-1/PD-L1 antibody with an anti-CTLA-4 agent compared to monotherapy with an anti-PD-1/PD-L1 antibody, as highlighted in a meta-analysis by Wang et al., which reviewed 34 studies with a total of 8,863 patients [8].

In other recent meta-analyses, the incidence of colitis of any grade was found to be between 10% and 15% in patients treated with the ipilimumab/nivolumab combination, slightly lower in those treated with ipilimumab as a single agent, and approximately 1% in patients receiving an anti-PD-1/PD-L1 agent alone [9-11]. There do not appear to be significant differences in incidence and severity based on the type of malignancy being treated [8].

The clinical presentation of colitis can be highly variable, ranging from mild abdominal bloating and increased frequency of soft or liquid stools to severe colitis with abdominal pain and the presence of mucus and/or blood in the stool. Symptoms can appear immediately after the initiation of ICI therapy up to one year after the last administration, though in most cases, they occur within 2–3 months of starting IO [6].

Colitis can be associated with symptoms involving the upper digestive tract, such as oral ulcers and epigastric pain, as well as perianal lesions [11].

From a laboratory perspective, patients with ICI-related colitis often present with elevated C-reactive protein levels and hypoalbuminemia. Fecal calprotectin levels may also be elevated, though non-specific, and can help differentiate between inflammatory and non-inflammatory colitis [12].

Computed Tomography (CT) imaging may reveal fluid distension of the colon, diffuse bowel wall thinning, and mesenteric vessel congestion [13]. Colonoscopy can detect inflammatory changes such as edema, hyperemia, erosions, and ulcers, but even a nearly normal endoscopic appearance does not exclude a clinical suspicion of ICI-related colitis. Lesions, when present, are more commonly found in the distal colon [14].

Regarding the management of immune-related diarrhea and colitis, guidelines recommend discontinuing treatment until symptom resolution in cases of grade 2–3 colitis/diarrhea caused by an anti-PD-1 or anti-PD-L1 agent. If an anti-CTLA-4 agent or a combination of anti-CTLA-4 and anti-PD-1 is responsible, the literature suggests temporary suspension of treatment until symptoms resolve and the early administration of corticosteroids (for example, prednisone 1-2 mg/kg) in cases of grade 2 diarrhea/colitis, with permanent discontinuation of IO for grade 3–4 toxicity [15-17].

At least six retrospective studies have compared outcomes between patients who permanently discontinued IO due to irAEs, including diarrhea/colitis, and it seemed that those patients who were able to resume IO did not have worse outcomes than those who continued to receive it without significant toxicities [18-23].

Immune-Related Hepatotoxicity

Immune-related hepatotoxicity (irH) typically manifests within the first three months of treatment, with symptoms appearing earlier in patients receiving an anti-CTLA-4 antibody. Similar to other GI irAEs, the frequency of irH is significantly higher (13%) when a combination of an anti-PD-1/PD-L1 agent and an anti-CTLA-4 antibody is used [24]. The clinical spectrum of irH varies widely, ranging from asymptomatic cases to a series of overt clinical manifestations, including fever, fatigue, loss of appetite, nausea and vomiting (N/V), and jaundice. Rare cases of fulminant hepatitis (0.1–0.2%) and mortality due to acute liver failure have been reported [24-27]. The differential diagnosis should include idiopathic autoimmune hepatitis, viral hepatitis, and alcoholic hepatitis [28,29]. The most commonly used imaging modalities for suspected irH include: Ultrasound (US), CT, and Magnetic Resonance Imaging (MRI) with hepatospecific contrast agents [30].

Immune-Related Pancreatic Toxicity

Immune-related pancreatic toxicity (irP) is a relatively rare occurrence, but its incidence can reach up to 4% across all grades when an anti-PD-1 agent is combined with an anti-CTLA-4 agent [31-33]. The clinical presentation of irP can range from a simple elevation in lipase and amylase levels to a clear case of acute pancreatitis. Rare cases of endocrine pancreatic damage have also been reported especially in patients treated with anti-PD-1/PD-L1 antibodies [34-36].

Diagnosis relies not only on laboratory findings indicative of pancreatic damage but also on more advanced imaging techniques beyond US, such as CT and MRI. FDG-PET-CT has also shown some potential utility in the diagnostic process [25,30,31,33,37].

GI irAEs and NSCLC

As previously mentioned, diarrhea is the most common GI irAEs, and patients with NSCLC are no exception, particularly those treated with an anti-CTLA-4 agent alone or in combination with an anti-PD-1 or anti-PD-L1 antibody. Table 1 presents the main GI irAEs reported in NSCLC studies [Table 1].

irAEs	Anti-CTLA-4	Anti-PD-1	Anti-PD-L1	Other ICIs	Combined IO
Nausea/Vomiting	8-18% after ipilimumab (43,44)	2%-17.2% after pembrolizumab (46,47)	7.7%-14.2% after atezolizumab (52,53)	15% after vibostolimab (anti-TIGIT) (56)	42.9% after cobolimab (anti-TIM-3) plus nivolumab (54)
	10% after tremelimumab (45)	5%-17% after nivolumab (48-50)	8.7% nausea after Cobolimab (54)		1.2%-18% after durvalumab plus tremelimumab (45,57)
		3% after cemiplimab (51)	5% nausea after avelumab (55)		

Diarrhea	27%-30% after ipilimumab (43,44)	8.9%-24% after nivolumab (48,49,59-61)	0.5%-7% after avelumab (55,66,67)		57.1% after cobolimab (anti-TIM-3) plus nivolumab (74)
	8.4%-41% diarrhea after tremelimumab (45,58)	48% after pembrolizumab (62)	6.2%-20.6% after atezolizumab (53,68-70)		25% after eftilagimod (anti-LAG-3) plus pembrolizumab (75)
		5%-24% after cemiplimab (63-65)	4%-20% durvalumab (45,71-73)		1.9% after monalizumab (anti-NKG2A) plus durvalumab (76)
					6.4%-20% after ipilimumab plus nivolumab (77-79)
					10%-26% colitis after durvalumab plus tremelimumab (45,57,80)
Colitis	8.8%-19% after tremelimumab (45,58)	2%-4% after nivolumab (61,81)	2.1% after atezolizumab (68)	3% after vibostolimab (anti-TIGIT) (56)	4% after tiragolumab (anti-TIGIT) plus atezolizumab (84)
	4% after ipilimumab (43)	1%-3.9% after pembrolizumab (46,82,83)	0.3%-0.6% after avelumab (66,67)		1%-6% ipilimumab plus nivolumab (77,85)
		<4% after cemiplimab (51)	1.6%-4% after durvalumab (45,72)		1.8% after durvalumab plus tremelimumab (45)
Hepatic injury	8.3%-30% after tremelimumab (45,58)	2%-10% after nivolumab (81,86-89)	1%-23% after atezolizumab (52,70,98)		5% after tiragolumab (anti-TIGIT) plus atezolizumab (84)
	5%-42% after ipilimumab (43,44)	0.6%-2.1% after pembrolizumab (47,82,83,89)	0.8%-2% after avelumab (55,66)		11.3%-12.8% after ipilimumab plus pembrolizumab (90)
		<2% after cemiplimab (51)	13% after durvalumab (73)		1%-6% after ipilimumab plus nivolumab (77,91,92)
					3.5%-9% after durvalumab plus tremelimumab (45,93)

Autoimmune Hepatitis		2% after pembrolizumab (94)	2% after durvalumab (73)		1.7% durvalumab plus tremelimumab (45)
		<2% after cemiplimab (51)			3% after eftilagimod (anti-LAG-3) plus pembrolizumab (75)
					<1% after ipilimumab plus nivolumab (77)
Pancreatic toxicity	1.5% after ipilimumab (95)	0.5%-0.6% lipase elevation after nivolumab (46,48,81,87)	12.1% amylase elevation after durvalumab (76)		6.8% amylase elevation after monalizumab (anti-NKG2A) plus durvalumab (76)
	7% pancreatitis after tremelimumab (58)	1%-6% amylase elevation after nivolumab (50,81,87)	2% lipase elevation after durvalumab (73)		2%-10.4% pancreatic toxicity after ipilimumab plus nivolumab (96,97)
		<2% lipase elevation and <4% amylase elevation after cemiplimab (51)	2%-3% amylase/ lipase elevation after avelumab (55)		1.2% pancreatitis after durvalumab plus tremelimumab (45)
		<1.2% pancreatitis after pembrolizumab (47,89,94)	0.5%-1.3% pancreatitis after atezolizumab (69)		

Table 1: Clinical manifestations of common GI irAEs in NSCLC patients (modified from Hu X et al (99)).

A retrospective study found that the overall incidence of irAEs in NSCLC patients is approximately 30%, with severe cases accounting for about 6% [38]. In these patients, the incidence of diarrhea of any grade was approximately 30%, irH ranged from 5% to 40%, and enteritis occurred in 4% to 8% of cases. N/V were also relatively frequent, affecting about 15% of patients [Table 1].

Currently, the two most commonly used anti-CTLA-4 antibodies are Ipilimumab and Tremelimumab, which, despite belonging to the same drug class, exhibit slightly different toxicity profiles. Although no direct comparative studies exist, diarrhea appears to have a similar incidence with both agents, while irH, N/V, and irP (pancreatitis) seem to occur slightly less frequently with Tremelimumab compared to Ipilimumab [Table 1].

Combination IO regimens showed to have higher toxicity rates, particularly for diarrhea (6.4%–57%) and N/V (1.2%–42.9%). For instance, the combination of Ipilimumab and Nivolumab has been associated with diarrhea (6.4%–20%), pancreatitis (2%–10.4%), colitis (1%–6%), and irH (1%–6%). The combination of Durvalumab and Tremelimumab, however, has demonstrated a higher incidence of colitis (10%–26%) [Table 1].

The incidence of GI irAEs also varies significantly among different anti-PD-1/PD-L1 antibodies. Nivolumab is associated with diarrhea in 8.9%–24% of cases, while N/V appears to be more frequent with Pembrolizumab (2%–17.2%). Cemiplimab and Durvalumab have also been linked to significant rates of diarrhea (5%–24% and 4%–20%, respectively) [Table 1]. Durvalumab appears to cause any grade of irH in 13% of cases and pancreatitis in 2%–12.1%. For Atezolizumab, reported rates include diarrhea (6.2%–20.6%), irH (1%–23%), and N/V (7.7%–14.2%), whereas Avelumab appears to have a lower overall incidence of irAEs, including those affecting the gastrointestinal system [Table 1].

Other less common GI toxicities include mucositis, esophagitis, gastritis, cholecystitis, appendicitis, and diverticulitis.

Santini et al. reported a retrospective study of 482 NSCLC patients treated at MSKCC between 2011 and 2016 with anti-PD-1/PD-L1 agents, alone or in combination with an anti-CTLA-4 antibody. Among them, 68 patients (14%) discontinued treatment due to irAEs, but only 44% stopped permanently, while 56% resumed therapy after a temporary suspension. Among these 68 patients, only 12 (17%) discontinued treatment due to diarrhea/colitis, and 7 later resumed therapy without experiencing additional severe irAEs in about 50% of cases [18].

For mild to moderate irAEs, temporary or permanent disconetinuation of IO and treatment with corticosteroids represent the predominant approach [39]. However, for patients refractory to corticosteroid treatment, various second-line options have been evaluated with positive outcomes. For instance, Infliximab, a TNF antagonist, and Vedolizumab, an anti-integrin α4β7 antibody, have demonstrated good efficacy in improving GI irAEs, particularly when used early [40-42].

Conclusions

IO has radically changed the approach and outcomes of treatment for numerous tumors, and it is foreseeable that soon, it will be administered at increasingly earlier stages of the natural history of tumors. Complete understanding of the mechanisms underlying the various toxicities recorded remains quite limited. Therefore, early identification of NSCLC patients at potential higher risk of developing these irAEs is a priority. Efforts should thus be directed both towards deeper research into these mechanisms and towards the identification of predictive biomarkers of toxicity. Finally, the identification of new agents capable of rapidly counteracting irAEs without negatively impacting patient outcomes remains a challenge.

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