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Complications of immunotherapy in advanced hepatocellular carcinoma

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Immune checkpoint inhibitors (ICIs) are highly effective in cancer treatment. However, the risks associated with the treatment must be carefully balanced against the therapeutic benefits. Immune-related adverse events (irAEs) are generally unpredictable and may persist over an extended period. In this review, we analyzed common irAEs reported in highly cited original articles and systematic reviews. The prevalent adverse reactions include fatigue, pyrexia, rash, pruritus, diarrhea, decreased appetite, nausea, abdominal pain, constipation, hepatitis, and hypothyroidism. Therefore, it is crucial to conduct evaluations not only of gastrointestinal organs but also of cardiac, neurologic, endocrine (including the frequently affected thyroid), and ophthalmic systems before commencing ICIs. This review further explores commonly reported types of irAEs, specific irAEs associated with each ICI agent, rare yet potentially fatal irAEs, and available treatment options for managing them. **(J Liver Cancer 2024;24:9-16)**

Keywords: Immune checkpoint inhibitors; Immunotherapy; Carcinoma, hepatocellular; Side effect, drug

INTRODUCTION

Hepatocellular carcinoma (HCC) is a prevalent cancer worldwide and a leading cause of cancer-related mortality.[1] HCC primarily affects individuals with hepatitis or hepatitis-related cirrhosis, which may result from viral infections such as hepatitis B or C, excessive alcohol consumption, nonalcoholic steatohepatitis, or cirrhosis.[2,3] Early-stage HCC can be treated through resection, liver transplantation, or ablation. However, the majority of patients present with advanced HCC and face a grim prognosis.[4] Multikinase inhibitors, such as sorafenib and lenvatinib, have gained approval as first-line systemic treatments for unresectable advanced HCC, demonstrating improved survival rates compared with placebos.[5-7] However, these gains in survival are modest, considering the multiple adverse events (AEs).[8] Recently, the introduction of immunotherapy for unresectable advanced HCC has significantly transformed the treatment landscape. Studies have shown that immune checkpoint inhibitors (ICIs) lead to improved overall survival (OS) when compared with sorafenib.[9-12] The first-line ICIs approved for advanced HCC are atezolizumab/bevacizumab and tremeli-mumab/dervalumab. These ICIs demonstrate superior effectiveness compared with existing tyrosine kinase inhibitors in the IMbrave150[10] and HIMALAYA trials,[9] respectively. The second-line ICIs approved for advanced HCC include nivolumab monotherapy, nivolumab/ipilimumab, and pembrolizumab.

ICIs are antibodies designed to block crucial regulatory signals that dampen the immune response, enabling tumor-reactive T cells to mount an effective anti-cancer response in the face of immunosuppression within the tumor microenvironment. The primary classes of ICIs include those targeting programmed cell death protein 1 (PD-1) and programmed death-ligand 1

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(PD-L1), and those targeting the cytotoxic T lymphocyte antigen-4 (CTLA-4).[13] Although the complete mechanism of ICIs is unknown, several proposed mechanisms exist. Among them is the reduction and depletion of regulatory T cells (Treg cells), which are essential immune cells for maintaining resistance induced by ICI treatment, particularly CTLA-4 blockade. Depletion of Treg cells subsequently leads to a decrease in anti-inflammatory cytokines and triggers the proliferation of CD8+ T cells.[14] Moreover, early B cell changes, such as the elevation of the CD21lo subtype, can induce autoreactive B cells and lead to immune-related adverse events (irAEs).[14] Despite the high effectiveness of ICIs, the risks of treatment must be carefully balanced against their therapeutic benefits. AEs associated with the immunologic mechanism of action in immunotherapy are commonly referred to as irAEs. They present differently from conventional chemotherapy AEs, are less predictable in timing, and often exhibit a longer duration. In this review article, we focus on the adverse effects of representative ICIs approved for unresectable advanced HCC. We analyze the literature to determine the types and frequencies of various irAEs by ICI type. Additionally, we provide a summary of guidelines that outline the evaluations required before initiating ICI treatment, along with a discussion of symptoms that warrant careful examination and immediate treatment upon occurrence.

COMMON AES REPORTED IN LANDMARK CLINICAL TRIALS

Nivolumab

Nivolumab is an intravenous recombinant human immunoglobulin (Ig) G4 monoclonal antibody PD-1 inhibitor that binds to the PD-1 receptor on the surface of a patient's T cells, thereby restoring their ability to combat cancer cells. In a phase 3 multinational randomized controlled trial (CheckMate 459) comparing nivolumab with sorafenib in patients with advanced HCC, the total frequency of AEs was 257 (70%), with 82 (22%) of them categorized as grade 3 or higher. The most common treatment-related adverse events (trAEs) included fatigue (15%), pruritus (13%), rash (11%), increased aspartate aminotransferase (AST) level (11%), diarrhea (8%), decreased appetite (6%), nausea (5%), weight loss (1%), and hypertension (1%). Adverse reactions more severe than grade 3 were most often increased AST level (6%), diarrhea (<1%), and palmar-plantar erythrodysesthesia syndrome (<1%). The reported proportion of serious AEs (≥grade 3) was significantly higher in the sorafenib group (47%) than in the nivolumab group (18%). However, the proportion of less severe AE (grade 1-2) was similar between the two groups (48% vs. 44%). Hand-foot syndrome was typically more common in the sorafenib group.[15] In the CheckMate 040 study, a phase I/II study of nivolumab in HCC, the incidence of trAEs did not seem to be dose-related. Among the 48 patients (25%), 12 experienced grade 3 or 4 trAEs. Treatment-related serious AEs included pemphigoid, adrenal insufficiency, and liver disorders.[16]

Nivolumab/ipilimumab

Nivolumab can be administered in combination with ipilimumab, a CTLA-4 inhibitor expressed on T cells (CheckMate 040). Among the 49 patients, 35 (94%) experienced trAEs, with common trAEs including pruritus (45%), rash (29%), diarrhea (24%), hypothyroidism (20%), fatigue (18%), adrenal insufficiency (14%), and decreased appetite (12%). Notably, this study reported one treatment-related death attributed to grade 5 pneumonitis.[17]

Atezolizumab/bevacizumab

Atezolizumab and bevacizumab are intravenous human IgG1 monoclonal antibodies. Atezolizumab targets PD-L1 on the cancer cell surface, whereas bevacizumab acts by binding to vascular endothelial growth factor, which is a form of molecularly targeted therapy.[18] The combination of anti-vascular endothelial growth factor therapy with ICIs is designed to enhance drug delivery and potentially reduce the required ICI dose, thereby lowering the risk of toxicity.[19] The phase 3 randomized controlled study (IMbrave150) yielded favorable results, establishing atezolizumab/bevacizumab as the recommended first-line treatment for unresectable advanced HCC. Out of the 329 patients, 322 (98%) experienced trAEs, with 207 (63%) classified as grade 3 or 4 and 23 (7%) as grade 5. The most common trAEs in atezolizumab/bevacizumab treatment included hypertension (29.8%), fatigue (20.4%), proteinuria (20.1%), hepatitis (increased AST level) (19.5%), pruritus (19.5%), diarrhea (18.8%), decreased appetite (17.6%), rash (12.5%), and nausea (12.2%).[10] Notably, a higher frequency of upper gastrointestinal bleeding was found in the atezolizumab/bevacizumab combination arm than in the sorafenib arm, even after excluding patients with high-risk bleeding before the study. The atezolizumab plus bevacizumab group experienced

six grade 5 bleeding events (five upper gastrointestinal bleeding events, including three gastrointestinal hemorrhages and two esophageal variceal hemorrhages, and one subarachnoid hemorrhage), whereas the sorafenib group had one (peritoneal hemorrhage).[20] Therefore, prior to atezolizumab/bevacizumab combination therapy, endoscopic evaluation for gastroesophageal varices is essential. Variceal treatment is indicated for patients at high risk of bleeding, and reconsideration of bevacizumab usage may be warranted. Moreover, apart from the risk of bleeding, bevacizumab is associated with increased cardiac toxicity, thrombosis-related stroke, and gastrointestinal perforation.

Tremelimumab/durvalumab

Tremelimumab is an intravenous human IgG2 monoclonal antibody that functions by binding to CTLA-4 expressed on T cells, whereas durvalumab is an intravenous human IgG1 monoclonal antibody that targets PD-L1. In the STRIDE study, a multinational randomized controlled phase 3 trial (HIMALAYA), 294 out of the 388 patients (75.8%) reported trAEs, with 100 (25.8%) categorized as grade 3 or 4. The study reported nine deaths (2.3%). The most common trAEs included diarrhea (26.5%), pruritus (22.9%), rash (22.4%), decreased appetite (17.0%), fatigue (17.0%), pyrexia (12.9%), nausea (12.1%), increased AST level (12.4%), and hypothyroidism (10.3%).[9] In another study, 61 out of the 74 patients (82.4%) experienced trAEs, with 28 (37.8%) of them being grade 3 or higher. This study reported a high incidence of pruritus (32.4%) and rash (32.4%), along with relatively lower rates of diarrhea (9.5%) and fatigue (10.8%).[21] To summarize, we have compiled a list of commonly reported AEs of ICIs in highly cited original articles (Table 1).

FATAL AES IN LANDMARK CLINICAL TRIALS

In this summary, we highlight AEs resulting in grade 5 or higher severity or death observed in various clinical trials. For patients receiving atezolizumab/bevacizumab, 14 out of the 329 individuals (4.6%) experienced grade 5 adverse reactions. These reactions included gastrointestinal hemorrhage (3), pneumonia (2), empyema (1), gastric ulcer perforation (1), hepatitis (1), liver injury (1), multiple organ dysfunction (1), esophageal variceal hemorrhage (1), respiratory distress (1), sepsis (1), and cardiac arrest (1). In the case of tremelimumab/durvalumab, eight out of the 388 patients (2.3%) died, experiencing other severe AEs such as myasthenia gravis (1), nervous system disorder (1), myocarditis (1), pneumonitis (1), heart failure (1), hepatitis (1), and immune-mediated hepatitis (2). Notably, no grade 5 trAEs were reported in the nivolumab trial.[9,10,15]

INCIDENCE OF IRAES ANALYZED IN META-ANALYSES

A meta-analysis conducted by Tian et al.[22] reported that the incidence of AEs in patients with HCC did not show a significant difference when compared with other tumor types. In a systematic meta-analytic review of ICI therapy for HCC, involving 6,472 patients across 47 studies, 83.4% experienced trAEs of any grade (95% confidence interval [CI], 77.0-89.1), with 33% (95% CI, 26.9-39.5) classified as grade 3 or higher. For irAEs, the incidence of any grade was 34% (95% CI, 22-47), and grade 3 or higher irAEs was reported in 9% (95% CI, 5-14). Notably, increased AST level was the most frequently encountered trAE (38%; 95% CI, 35-40), and fatigue was the predominant irAE (14%; 95% CI, 7-23). Among patients experiencing these AEs, 18.8% (95% CI, 13.2-25.2) received steroids, and 6.6% (95% CI, 4.6-9.0) discontinued treatment due to AEs.[22]

UNCOMMON, BUT FATAL IRAES REPORTED IN CASE REPORTS

The uncommon yet severe AEs documented in case reports are summarized as follows. A 76-year-old man experienced confusion, somnolence, and emesis 2 weeks after receiving atezolizumab/bevacizumab and was diagnosed with encephalitis. High-dose steroid treatment led to a full recovery without neurological deterioration within 9 days of initiation.[23] A 73-year-old man reported fatigue one month after atezolizumab/bevacizumab treatment. An incidental computed tomography scan revealed an intratumoral hemorrhage in a rib metastasis. Hemostasis was successfully achieved through selective transarterial embolization, enabling the patient to resume atezolizumab/bevacizumab therapy without experiencing further bleeding.[24] A 75-year-old man experienced dizziness, numbness, and loss of consciousness with severe hypotension during an infusion of atezolizumab/bevacizumab. Diagnosed with anaphylactic shock, the infusion was immediately halted, and 5 mg of dexamethasone was administered. He improved but did not resume atezolizumab/bevacizumab therapy.[25] An 82-year-old man presented to the emergency department with dyspnea 3 days after receiving atezolizumab/bevacizumab.

Table 1. Incidence of immune-related adverse events in HCC immunochemotherapy

Immune-related adverse events	Nivolumab		Nivolumab/ipilimumab		Pembrolizumab		Atezolizumab/bevacizumab		Tremelimumab/durvalumab	
	Any (%)	Grade 3 (%)	Any (%)	Grade 3 (%)	Any (%)	Grade 3 (%)	Any (%)	Grade 3 (%)	Any (%)	Grade 3 (%)
Fatigue	15	<1	10-18	0-2	18.6-22.1	2.5-4.0	20.4	2.4	17.0	2.1
Asthenia	N/A	N/A	N/A	N/A	7-9	0.4	6.7	0.3	10.1	1.8
Pyrexia	N/A	N/A	4-10	0	9.3	0.7	17.9	1.2	12.9	0.3
Hypertension	1	0	N/A	N/A	N/A	N/A	29.8	15.2	5.9	1.8
Rash	11	0	17-29	0-4	10-11.5	0.7	12.5	0	22.4	1.5
Pruritus	13	<1	29-45	0-4	12.0-18.3	0.4	19.5	0	22.9	0.0
Diarrhea	8	<1	12-24	2-4	11.0-17.2	1.4	18.8	1.8	26.5	4.4
Decreased appetite	6	0	6-12	0-2	6.0-17.2	1	17.6	1.2	17.0	1.3
Abdominal pain	N/A	N/A	N/A	N/A	14.3	1.4	12.2	1.2	11.9	1.3
Nausea	6	0	2-10	0	8.0-11.5	0.7	12.2	0.3	12.1	0.0
Constipation	N/A	N/A	N/A	N/A	9.3	0.4	13.4	0	9.3	0.0
Increased AST	11	6	13-20	4-16	13.4-22.6	7.0-13.3	19.5	7	12.4	5.2
Increased ALT	N/A	N/A	8-16	0-8	8.6-17.6	4.0-6.1	14	3.6	9.3	2.6
Increased bilirubin	N/A	N/A	N/A	N/A	4.8-18.6	2.0-7.5	13.1	2.4	5.2	0.8
Cough	N/A	N/A	N/A	N/A	8.6	0	11.9	0	7.7	0.0
Hypothyroidism	N/A	N/A	8-20	0	5-6	0.4	N/A	N/A	12.1	0.0
Proteinuria	N/A	N/A	N/A	N/A	N/A	N/A	20.1	3	N/A	N/A
Anemia	N/A	N/A	N/A	N/A	3.0-9.7	1.0-3.9	N/A	N/A	9.3	2.8
Decreased platelet	N/A	N/A	N/A	N/A	N/A	N/A	10.6	3.3	N/A	N/A

N/A, not available; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Despite receiving treatment with steroids and undergoing low tidal mechanical ventilation with high positive end-expiratory pressure, he was diagnosed with acute respiratory distress syndrome and unfortunately succumbed 31 hours later.[26] An 89-year-old man was diagnosed with grade 2 colitis after undergoing six cycles of atezolizumab/bevacizumab therapy. He exhibited improvement following 0.5 mg/kg/day prednisolone steroid therapy. Colitis did not recur upon the resumption of atezolizumab/bevacizumab therapy.[27] A 52-year-old man, who was receiving high-dose steroids for transverse myelitis after nivolumab administration, did not initially respond to the treatment. However, he showed improvement after receiving intravenous immunoglobulin and plasmapheresis.[28] A 67-year-old man experienced hematemesis following atezolizumab/bevacizumab administration, and endoscopy failed to locate the bleeding source. Angiography revealed a gastric artery pseud oaneurysm, which was successfully treated with embolization.[29] A 73-year-old man was diagnosed with a pyogenic liver abscess after undergoing two cycles of atezolizumab/bevacizumab therapy. He received treatment with percutaneous catheter drainage insertion and antibiotics. However, despite 37 days of intensive care unit treatment, he showed no improvement in sepsis and experienced worsening renal function.[30] An 80-year-old man was admitted to the hospital on the 22nd day following treatment with tremelimumab and durvalumab, presenting with dyspnea and myalgia. He was diagnosed with torsade de pointes. Subsequently, his ejection fraction decreased to 20%, leading to the administration of immunosuppressive treatment with amiodarone, but he died on the 14th day due to septic shock.[31] A 64-year-old man was hospitalized due to abdominal pain and was diagnosed with primary sclerosing cholangitis after nivolumab treatment. He was treated with steroids and mycophenolate mofetil but succumbed to liver failure 8 months later.[32] In another case, a 55-year-old man was diagnosed with Graves disease after undergoing tremelimumab and ipilimumab treatment. Following the diagnosis, he initiated treatment with carbimazole, resulting in subsequent improvement in his thyroid function.[33] A 86-year-old man developed petechial purpura on his extremities and trunk following the third cycle of atezolizumab/bevacizumab therapy. He was diagnosed with immune thrombocytopenic purpura (ITP) and received high-dose immunoglobulin and *Helicobacter pylori* eradication therapy. Although an improvement in thrombocytopenia was observed, hemolytic anemia was detected 20 days after the onset of ITP. Both direct and indirect Coombs tests were positive, leading to a diagnosis of autoimmune hemolytic anemia induced by an

Table 2. Uncommon, but fatal irAEs reported in case reports

Study	Age	Sex	ICI	AE	Treatment for AE	Prognosis
Song et al.[41] (2023)	76	M	Ate/beva	Encephalitis	Steroid	Full recovery
Mitsuyama et al.[24] (2023)	73	M	Ate/beva	Intramural hemorrhage in rib metastasis	Selective transarterial embolization	No further bleeding
Bian et al.[25] (2021)	75	M	Ate/beva	Anaphylactic shock	Immediately stop ICI therapy, dexamethasone	Improved
Cho et al.[26] (2023)	82	M	Ate/beva	ARDS	Steroid, mechanical ventilation	Expire
Fuji et al.[27] (2022)	89	M	Ate/beva	Colitis	Steroid	Improved
Chatterton et al.[28] (2023)	52	M	Nivolumab	Transverse myelitis	Steroid	Improved
Pang et al.[29] (2023)	67	M	Ate/beva	Gastric artery pseudoaneurysm	Selective transarterial embolization	No further bleeding
Uchida et al.[30] (2022)	73	M	Ate/beva	Pyogenic liver abscess	Percutaneous catheter drainage, antibiotics	Expire
Diaz-Rodriguez et al.[31] (2023)	80	M	Tre/durva	Myocarditis	Steroid, mycophenolate mofetil, amiodarone	Expire
Hirasawa et al.[32] (2021)	64	M	Nivolumab	Primary sclerosing cholangitis	Steroid, mycophenolate mofetil	Expire
Gan et al.[33] (2017)	55	M	Tremelimumab	Graves disease	Carbimazole	Improved
Fukushima et al.[34] (2023)	86	M	Ate/beva	Evans syndrome	Steroid, IVIG, *H. pylori* eradication	Improved

irAE, immune-related adverse events; ICI, immune checkpoint inhibitors; AE, adverse events; M, male; Ate/beva, atezolizumab with bevacizumab; Tre/durva, tremelimumab with durvalumab; ARDS, acute respiratory distress syndrome; IVIG, intravenous immunoglobulin; *H. pylori*, *Helicobacter pylori*.

irAE and combined Evans syndrome due to ITP. After treatment with prednisolone, hemoglobin levels improved, and hemolytic findings were normalized in blood tests.[34] Finally, numerous case reports have documented variceal bleeding following the combination of atezolizumab and bevacizumab treatment.[35-38] To summarize, we prepared a table of uncommon and fatal irAEs that were reported in the aforementioned case reports (Table 2).

ASSOCIATION BETWEEN IRAES AND PROGNOSIS

Studies have reported varying results regarding the association between irAEs and prognosis. Patients who experienced irAEs showed improved progression-free survival (PFS), but no significant difference in OS.[22] In a meta-analysis of 48 clinical trials involving 7,936 patients, the incidence of skin irAEs (r=0.79; P<0.001), gastrointestinal irAEs (r=0.56; P=0.006), and endocrine system irAEs (r=0.44; P=0.05) was positively correlated with increased objective response rates (ORRs) following nivolumab treatment. Nevertheless, no analogous correlation was observed with liver, lung, and kidney irAEs. Similarly, the ORR of nivolumab/ipilimumab therapy was positively associated with the incidence of skin irAEs (r=0.54; P=0.04) and gastrointestinal system irAEs (r=0.60; P=0.02), but not with that of endocrine, liver, lung, and kidney irAEs.[39] Enhanced OS was also reported in patients with HCC receiving anti-PD-(L)1 monotherapy or combinations when patients developed grade 2 or higher trAEs. TrAEs of grade 2 or higher were identified as a predictor of improved OS (hazard ratio [HR], 0.55; 95% CI, 0.34-0.88) and PFS (HR, 0.51; 95% CI, 0.35-0.74) and were associated with a higher ORR of ICI (27% vs. 16%).[40] According to Song et al.,[41] patients with thyroid AEs demonstrated significantly better PFS, OS, and ORR than those without thyroid AEs, even after adjusting for confounding factors. This finding suggests that the development of thyroiditis may be associated with improved outcomes following atezolizumab/bevacizumab therapy in patients with HCC.[41] In the study by Pinato et al.,[42] the steroid dose or duration of use did not significantly affect the survival time or PFS of patients with HCC undergoing immunotherapy.

TREATMENT OF IRAES

IrAEs are speculated to result from ICIs suppressing immune checkpoints, leading to uncontrolled self-reactive T cells attacking the body as if exerting antitumor effects. Therefore, irAE treatment is primarily aimed at immune system suppression. The initial step involves discontinuation of ICI, whenever possible, with particular emphasis on discontinuation for severe irAEs of grade 3 or higher.[43-48] Determining the grade of toxicity is crucial, as the treatment approach varies based on the grading system. Patients with grade 1 symptoms who experience a swift recovery may have the option to retry ICIs. For irAEs of grade 2 or higher, dose reduction may be considered. However, irAEs might still occur after dose reduction. In a study focusing patients who experienced grade 2 or higher irAEs, re-dosing resulted in 43% experiencing the same irAEs as before and 13% developing new irAEs.[49] Should irAEs persist even after ICI discontinuation or dose reduction, corticosteroid therapy may become necessary.[50,51] If no response to steroids is observed, immunosuppressive agents can be considered. Although rare, plasmapheresis has been shown to improve survival in cases of fatal irAE.[52]

CONCLUSION

Immunotherapy is widely used in the treatment of unresectable HCC. Given that ICIs can induce irAEs in multiple organs, having knowledge of the anticipated irAEs and conducting organ evaluations before initiating immunotherapy are essential. Comprehensive assessments should include the evaluation of gastrointestinal organs, as well as the cardiac, neurologic, endocrine, and ophthalmic systems. In advanced HCC, ICIs are increasingly used in combination therapy rather than as standalone treatments. Nevertheless, in some cases, adverse effects may occur due to the synergistic effect of the combination, rather than being solely attributed to the adverse effects of the ICI itself. Particularly in the case of atezolizumab/bevacizumab therapy, adverse effects caused by bevacizumab rather than the ICI often led to dangerous situations. Although irAEs manifest at varying times following ICI treatment and are challenging to predict, early detection by healthcare professionals holds paramount importance. Managing irAEs fundamentally involves discontinuing ICIs, administering corticosteroids or other immunosuppressive agents, and considering specific treatments tailored to the type of irAEs.

Conflicts of Interest

Jeong-Ju Yoo is an editorial board member of Journal of Liver Cancer, and was not involved in the review process of this article. Otherwise, the authors have no conflicts of interest to

disclose.

Ethics Statement

This review article is fully based on articles which have already been published and did not involve additional patient participants. Therefore, IRB approval is not necessary.

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Data Availability

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