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Retrospective Study

Correlation between immune-related adverse events and long-term outcomes in pembrolizumab-treated patients with unresectable hepatocellular carcinoma: A retrospective study

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Abstract

BACKGROUND

Although immune checkpoint inhibitor (ICI) therapy has improved the prognosis of unresectable hepatocellular carcinoma (HCC), it has also resulted in unique immune-related adverse events (irAEs). The relationship between irAE and treatment outcomes in ICI-treated unresectable HCC patients remains unknown.

AIM

To elucidate the correlation between immune-related toxic effects and prognosis in patients with unresectable HCC treated with pembrolizumab.

METHODS

From March 2019 to February 2021, a total of 190 unresectable HCC (Barcelona Clinic Liver Cancer C) patients receiving pembrolizumab treatment were retrospectively reviewed. Overall survival (OS) was the primary endpoint, while objective response rate (ORR), disease control rate (DCR), and time to progression (TTP) were secondary evaluation indexes. We assessed demographics, irAEs, and outcomes by retrospective review.

RESULTS

One hundred and forty-three males and 47 females were included in the study. The ORR and DCR were 12.1% (23/190) and 52.1% (99/190), respectively. The

median OS was 376 d [95% confidence interval (CI): 340-411 d] and the median TTP was 98 d (95%CI: 75-124 d). The overall incidence of treatment-related adverse events was 72.6% (138/190) and 10.0% of them were severe irAEs (grade ≥ 3). Child-Pugh B class, portal vein tumor thrombus, extrahepatic metastasis, and hypothyroidism were the independent risk factors for survival. Patients with hypothyroidism showed a longer OS [517 d (95%CI: 423-562) *vs* 431 d (95%CI: 412-485), $P = 0.011$] and TTP [125 d (95%CI: 89-154) *vs* 87 d (95%CI: 61-98), $P = 0.004$] than those without irAEs.

CONCLUSION

Pembrolizumab-treated patients with unresectable HCC who experienced hypothyroidism have promising ORR and durable response. Hypothyroidism, an irAE, may be used as a clinical evaluation parameter of response to ICIs in unresectable HCC.

Key Words: Hepatocellular carcinoma; Immune checkpoint inhibitors; Pembrolizumab; Immune-related adverse events; Overall survival; Retrospective study

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Core Tip: This is a retrospective study to elucidate the correlation between immune-related toxic effects and prognosis in patients with unresectable hepatocellular carcinoma (HCC) treated with pembrolizumab. One hundred and forty-three male patients and forty-seven female patients were included in the study. The overall incidence of treatment-related adverse events was 72.6% (138/190) and 10.0% of them were severe immune-related adverse events (irAEs) (grade ≥ 3). Patients with hypothyroidism were observed to have a longer overall survival and time to progression than those without irAEs. Unresectable HCC patients who experienced hypothyroidism had a better therapeutic effect.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death globally[1]. Because early-stage HCC is insidious and the tumors have a tendency to invade intrahepatic vessels and create distant metastases, 80% of patients are already in the advanced stage at diagnosis and lose the opportunity for hepatectomy. In addition, 70% of patients who receive radical liver resection will experience tumor recurrence[2]. Therefore, a large number of patients with unresectable HCC need comprehensive treatment. Locoregional therapy including transarterial chemoembolization or selective internal radiation therapy has been proven to prolong the median survival of patients with unresectable HCC[3]. Since sorafenib has been shown to improve the prognosis of unresectable HCC[4], tyrosine kinase inhibitors (TKIs) have become the first-line treatment for advanced HCC. However, the objective response rate (ORR) to TKIs is unsatisfactory, ranging from 6.5%-18.8%, and the prognosis improvement is not significant, with an average prolonged survival time of 2.8-5.8 mo[5,6]. Recent studies have shown that immune checkpoint inhibitors (ICIs) represented by pembrolizumab have become the second-line treatment for unresectable HCC due to their safety and long duration of response. KEYNOTE-224, a non-randomized, multi-center, open-label, phase 2 trial, has proven that pembrolizumab was effective and tolerable in patients with unresectable HCC who had previously been treated with sorafenib[7].

However, the response rate to both TKIs and ICIs was less than 30%. Moreover, adverse effects of the drugs may interfere with the judgment of curative effect and decrease compliance to the best treatment available. Therefore, determining patients who are mostly likely to benefit from TKIs or ICIs is very important. Researchers have been trying to find biomarkers that predict patient survival or response to drugs[8]. Previous studies have reported that unresectable HCC patients who developed hand-foot skin reaction possessed a prolonged time to progression (TTP) and better disease-control rate (DCR)[9]. Studies have suggested that vascular endothelial growth factor inhibition may rely on a stronger recruitment of inflammatory cells to take a more pronounced antitumor effect that is accompanied by stronger treatment-related adverse events[10]. Whether similar adverse events can be found to evaluate

the response of tumor to ICIs remains to be investigated. Immune-related adverse events (irAEs) have been reported to include polymyalgia, colitis, skin lesions (rash, pruritus, and vitiligo), hypophysitis, hepatitis, thyroiditis, uveitis, Guillain-Barré syndrome, and immune-mediated cytopenia. It was reported that the overall incidence of all-grade irAEs was 60%-80% and the incidence of high-grade irAEs was 20%-30%[11,12]. Several studies have suggested that autoimmune-like toxic effects are thought to represent bystander effects from activated T-cells, accompanied with antitumor effects, and are consistent with the mechanism of action of ICIs[13,14]. Herein, we retrospectively studied whether immune-related toxic effects correlated with prognosis in patients with unresectable HCC treated with pembrolizumab.

MATERIALS AND METHODS

Terminology

Overall survival (OS) was defined as the time from the start of ICIs until death or until last follow-up. ORR was defined as the proportion of patients achieving complete response (CR) and partial response (PR). DCR was defined as the proportion of patients achieving CR, PR, and stable disease (SD). TTP was defined as the time from the start of ICIs to the radiological confirmation of tumor progression. Tumor

burden score (TBS) was calculated as $\sqrt{a^2 + b^2}$ [a = maximum tumor diameter (cm), measuring the area of arterial enhancement and excluding the area of internal necrosis[15]; b = tumor number, the lesion is at least 1 cm in size][16].

Patients

Between March 2019 and February 2021, a total of 190 patients who received ICI treatment were included in this retrospective study at Tongji Hospital of Tongji Medical College of Huazhong University of Science and Technology. All patients included in the study met the following criteria: (1) Child-Pugh A/B; (2) Advanced HCC [Barcelona Clinic Liver Cancer (BCLC) stage C]; and (3) Not receiving previous antitumor therapy. HCC was diagnosed by the European Association for the Study of Liver criteria and American Association for the Study of Liver Disease guidelines[17,18]. Demographics, including age, sex, *etc.* laboratory examination, including levels of alanine aminotransferase, aspartate aminotransferase, alpha fetoprotein (AFP), *etc.* imaging examination, and survival status were reviewed retrospectively. The study was approved by the Ethical Committee of Tongji Hospital of Tongji Medical College of Huazhong University of Science and Technology. All procedures performed in this study abided by the Declaration of Helsinki.

Usage of ICIs

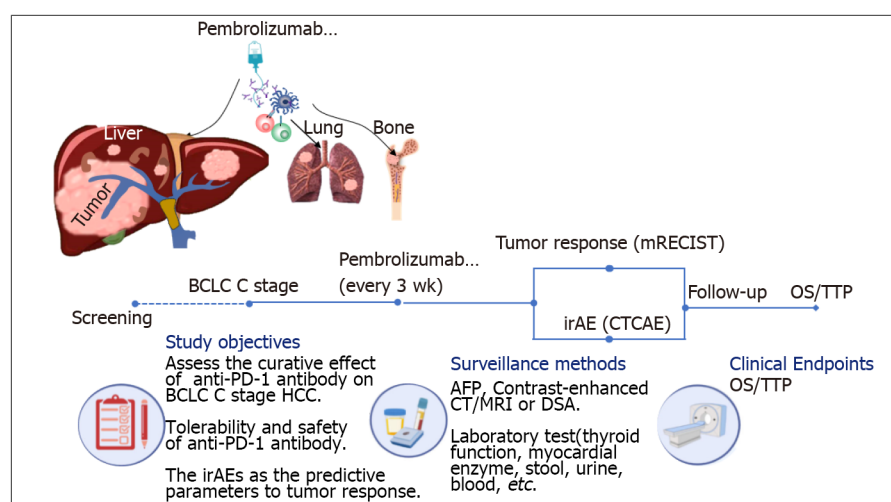
All of the patients received treatment with pembrolizumab (KEYTRUDA, Merck Sharp & Dohme Co., Inc.), 200 mg/time, every 3 wk, *via* intravenous infusion[7] according to the guidelines or expert consensus, with dose modification according to toxic effects, as needed.

Follow-up and irAE assessment

An experienced radiologist blinded to patient information assessed tumor response according to modified response evaluation criteria in solid tumor criteria every 6 wk by contrast-enhanced computed tomography or magnetic resonance imaging examination. Common Terminology Criteria for Adverse Events (CTCAE) were used by two experienced hepatologists to independently assess irAEs. Corresponding examinations or imaging examinations were performed to diagnose irAEs and assess the grades according to CTCAE. Follow-up was terminated on April 24, 2022. The survival status was confirmed by governmental death registration or telephone. The flow diagram of the study is displayed in Figure 1.

Statistics analysis

Continuous variables are presented as the median and interquartile range (IQR) and categorical data as numbers and percentages. Survival analysis was carried out using the Kaplan-Meier method and log-rank test. Univariate and multivariate Cox proportional regression analyses were used to evaluate risk factors for OS or TTP. A two-sided *P* value < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 19.0 for Windows (SPSS, Chicago, Illinois, United States). GraphPad Prism 7 software was used for all graphical drawings.



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Figure 1 Flow diagram of the study. mRECIST: Modified response evaluation criteria in solid tumors criteria; CTCAE: Common Terminology Criteria for Adverse Events; HCC: Hepatocellular carcinoma; AFP: Alpha fetoprotein; DSA: Digital subtraction angiography; OS: Overall survival; TTP: Time to progression; BCLC: Barcelona Clinic Liver Cancer; PD-1: Programmed death 1; CT: Computed tomography; MRI: Magnetic resonance imaging; irAE: Immune-related adverse event.

RESULTS

Demographics

The baseline characteristics of 190 unresectable HCC (BCLC stage C) patients receiving pembrolizumab as an initial treatment are summarized in Table 1. One hundred and fifty-four (81.1%) of the patients were male, and the primary cause of disease was chronic hepatitis B virus infection (75.8%). One hundred and forty-six (76.8%) of the patients had Child-Pugh class A and 44 (23.2%) had Child-Pugh class B. All of the patients were at BCLC stage C.

Tumor response

Follow-up was terminated on April 24, 2022. The mean follow-up time was 814 d (median, 748 d; range, 438-1146 d). No patients achieved CR. Twelve percent (23/190) of the patients achieved PR and 40% (76/190) had SD. The DCR was 52.1% (99/190), and 47.9% (91/190) of the patients had progressive disease (PD). All patients who experienced disease progression permanently discontinued ICI treatment; none of the patients discontinued ICIs because of adverse effects. At the end of the follow-up, 130 patients (68.4%) died. The median OS was 376 d [95% confidence interval (CI): 340-411 d] and the median TTP was 98 d (95% CI: 75-124 d) (Figure 2).

Incidence of irAEs

The overall incidence of irAEs was 72.6% (138/190) and 10.0% of them were severe irAEs (grade ≥ 3). Table 2 summarizes the observed representative irAEs. Elevated transaminase (> 3 times upper limit of normal) was the most common adverse reaction to ICIs seen in 69 (36.3%) patients, followed by diarrhea in 40 (21.1%), cutaneous toxic effects in 37 (19.5%), hypothyroidism in 25 (13.2%), and proteinuria in 24 (12.6%). Relatively rare adverse events were myocarditis in 3 (1.6%) patients and hypoadrenocorticism in 5 (2.6%). The elevated transaminase was the earliest irAE, and the median (IQR) time to onset was 4.8 (3.5-7.2) wk, followed by cutaneous toxic effects [5.9 (3.8-7.9) wk], proteinuria [6.8 (4.3-8.1) wk], diarrhea [7.1 (5.2-8.9) wk], hypoadrenocorticism [7.9 (6.7-9.5) wk], hypothyroidism [8.7 (6.9-10.9) wk], and myocarditis [10.2 (8.6-11.9) wk]. Figure 3A shows that the percentage of tumor burden score (TBS) changed from baseline by treatment of 91 patients who had PD. Figure 3B shows that the percentage of TBS changed from baseline by treatment of 99 patients who achieved CR, PR, or SD. We found that those patients who developed myocarditis or hypothyroidism tended to achieve PR and have a more significant decrease in tumor burden. In addition, patients without irAEs were more likely to enter a PD status. Figure 4 shows a spider plot which depicts the percentage change in TBS of 25 hypothyroidism patients from baseline by treatment over time. We observed substantial reductions in tumor burden and several responders exhibited deep responses.

irAEs and prognosis

In order to determine independent risk factors affecting OS, the clinical parameters including demographics, laboratory results, and adverse events were included in the univariate and multivariate Cox proportional regression analyses. We found that Child-Pugh class B [hazard ratio (HR) = 1.321;

Table 1 Clinical characteristics of 190 patients

Clinical characteristic	No. of patients
Age (yr), median (IQR)	51 (42-58)
Sex	
Male, <i>n</i> (%)	154 (81.1)
Etiology	
Hepatitis B	144 (75.8)
Hepatitis C	4 (2.1)
Hepatitis B & C	2 (1.1)
Non-hepatitis B, non-hepatitis C	40 (21.0)
ALT (U/L), median (IQR)	75 (51-254)
AST (U/L), median (IQR)	57 (47-302)
TbIL (μ mol/L), median (IQR)	20.1 (11.2-31.2)
AFP (ng/mL), median (IQR)	205 (19.2-4692)
Child-Pugh class	
A	146 (76.8)
B	44 (23.2)
Portal vein tumor thrombosis	131 (68.9)
Extrahepatic metastasis	
Lung	64 (33.7)
Bone	31 (16.3)
Peritoneum	25 (13.1)
Multiple locations	15 (7.9)
BCLC stage	
C	190 (100)
Tumor response	
Complete response	0 (0)
Partial response	23 (12.1)
Stable disease	76 (40.0)
Progressive disease	91 (47.9)
Follow-up time, median (range)	748 (438-1146) d
TTP, median (95%CI)	98 (75-124) d
OS, median (95%CI)	376 (340-411) d

IQR: Interquartile range; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; TbIL: Total bilirubin; AFP: Alpha fetoprotein; TTP: Time to progression; OS: Overall survival; BCLC: Barcelona Clinic Liver Cancer; CI: Confidence interval.

95%CI: 1.112-1.711], portal vein tumor thrombus (PVTT) (HR = 3.125; 95%CI: 3.021-3.568), extrahepatic metastasis (HR = 2.871; 95%CI: 2.579-3.052), and hypothyroidism (HR = 0.641; 95%CI: 0.489-0.901) were the independent risk factors for survival. Similarly, AFP > 400 ng/mL (HR = 1.872; 95%CI: 1.357-2.135), PVTT (HR = 2.472; 95%CI: 2.243-2.891), extrahepatic metastasis (HR = 1.489; 95%CI: 1.246-1.574), and irAE of hypothyroidism (HR = 0.613; 95%CI: 0.362-0.886) were the independent risk factors for TTP (Table 3). The OS and TTP of patients who developed hypothyroidism (*n* = 25) were compared with those patients without irAE using the Kaplan-Meier method and a log-rank test. We found that the median OS was 517 d (95%CI: 423-562 d) in patients with hypothyroidism, which was longer than that of patients without irAE [431 d (95%CI: 412-485 d), *P* = 0.011] (Figure 5A). Similarly, the median TTP was 125 d (95%CI: 89-154) in patients with hypothyroidism, which was longer than that of patients without irAE [87 d (95%CI: 61-98 d), *P* = 0.004] (Figure 5B).

Table 2 Incidence of treatment-related adverse events

Adverse event	Any grade	Grade 3	Grade 4
Cutaneous toxic effects	25 (13.2)	3 (1.6)	2 (1.1)
Mucositis	8 (4.2)	2 (1.1)	1 (< 1)
Rash	7 (3.7)	1 (< 1)	1 (< 1)
Pruritus	10 (5.3)	2 (1.1)	0 (0)
Diarrhea	27 (14.2)	4 (2.1)	1 (< 1)
Elevated transaminases	35 (18.4)	10 (5.3)	2 (1.1)
Hypothyroidism	25 (13.2)	4 (2.1)	2 (1.1)
Myocarditis	3 (1.6)	1 (< 1)	2 (1.1)
Hypoadrenocorticism	5 (2.6)	1 (< 1)	0 (0)
Proteinuria	18 (9.5)	5 (2.6)	0 (0)
Overall incidence	138 (72.6)	12 (6.3)	7 (3.7)

Table 3 Univariate and multivariate analyses of prognostic factors for predicting overall survival and time to progression

Variable	Univariate analysis		Multivariate analysis	
	HR (95%CI)	P value	HR (95%CI)	P value
OS				
Child-Pugh, class B	1.446 (1.044-1.547)	0.039	1.321 (1.112-1.711)	0.021
AFP > 400 ng/mL	1.651 (1.351-1.782)	0.021	1.446 (0.875-1.836)	0.239
PIVKA > 40 mAU/mL	1.324 (1.023-1.472)	0.043	1.568 (0.411-1.687)	0.085
PVTT, yes	2.145 (1.897-3.587)	0.003	3.125 (3.015-3.568)	0.008
Extrahepatic metastasis, yes	1.784 (1.254-2.571)	0.013	2.871 (2.581-3.052)	0.028
Cutaneous toxic effects, yes	0.741 (0.654-0.968)	0.025	0.845 (0.425-1.751)	0.129
Hypothyroidism, yes	0.623 (0.487-0.912)	0.034	0.641 (0.489-0.901)	0.017
TTP				
AFP > 400 ng/mL	1.757 (1.271-1.972)	0.023	1.872 (1.357-2.135)	0.017
PVTT, yes	2.595 (1.377-3.889)	0.003	2.472 (2.243-2.891)	0.008
Extrahepatic metastasis, yes	1.536 (1.296-1.765)	0.031	1.489 (1.246-1.574)	0.012
Cutaneous toxic effects, yes	0.874 (0.621-0.925)	0.036	0.785 (0.358-1.258)	0.157
Hypothyroidism, yes	0.741 (0.514-0.870)	0.024	0.613 (0.362-0.886)	0.018

AFP: Alpha fetalprotein; PIVKA: Protein induced by vitamin K absence or antagonist-II; OS: Overall survival; PVTT: Portal vein tumor thrombus; HR: Hazard rate; TTP: Time to progression; CI: Confidence interval.

DISCUSSION

Previous study has reported that among the irAEs manifesting as endocrine dysfunctions, hypothyroidism (6.07%) and hyperthyroidism (2.82%) were most common[19]. Thyroid events occur in approximately 10% of patients treated with anti-programmed death 1 (PD-1)/programmed death-ligand 1 (PD-L1) monotherapy[20,21]. The median time to onset of thyroid dysfunction, most of which is hypothyroidism, is 6 wk after ICI initiation[22]. In our study, we found that patients who developed hypothyroidism had a longer OS and TTP than those without irAE. Multivariate analysis showed that hypothyroidism was an independent prognostic factor. In addition, we found that patients with hypothyroidism had a significant reduction in TBS from baseline by treatment, which was an intuitive manifestation of the effectiveness of immunotherapy. Many previous studies have also shown that patients who experienced irAEs had a superior progression free survival and OS compared to those who did not experience irAEs[23-25]. A study of 270 non-small cell lung cancer (NSCLC) patients

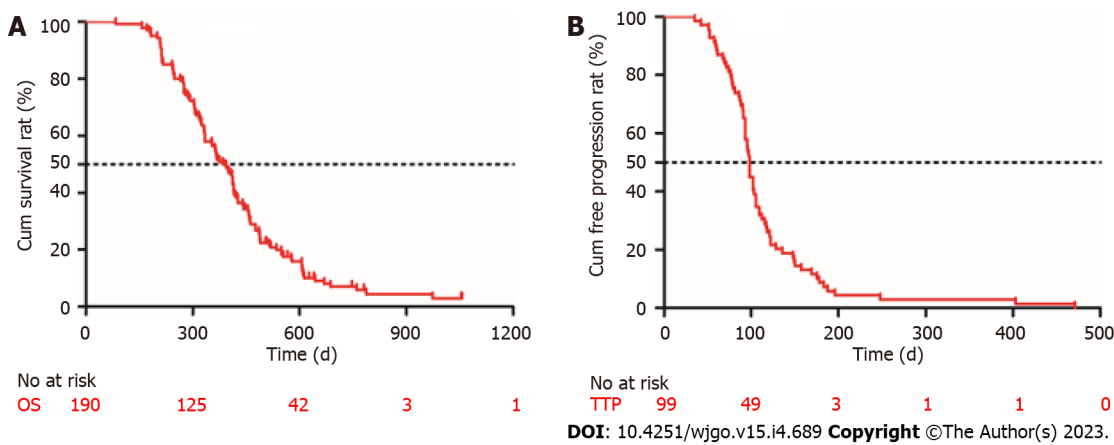


Figure 2 Kaplan-Meier curves describing the overall survival of all patients ($n = 190$) and the time to progression of patients who achieved disease control ($n = 99$). A: Survival curve; B: Time to progression curve. OS: Overall survival; TTP: Time to progression.

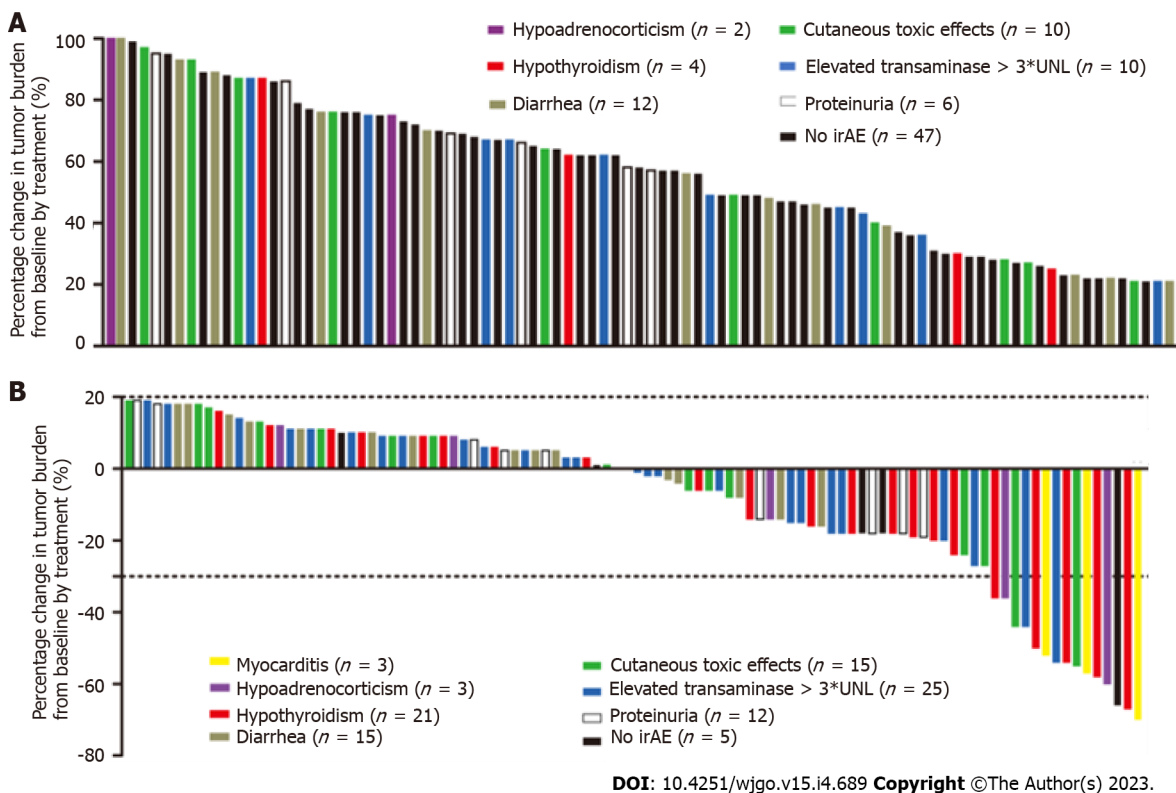


Figure 3 Waterfall plots of percentage change in tumor burden from baseline ($n = 190$). The “y” axis represents the percentage change in tumor burden from baseline by treatment. The immune-related adverse events are distinguished by different colors. Negative/positive values represent maximum tumor reduction or minimum tumor increase, respectively. A: 91 patients had progressive disease; B: 99 patients achieved complete response, partial response, or stable disease. irAE: Immune-related adverse event.

treated with at least one dose of anti-PD-L1 or anti-PD-1 antibodies showed that patients who experienced thyroiditis had statistically significant improvements in OS compared to patients who did not ($P = 0.01$)[26]. A meta-analysis of 12 randomized controlled trials identified 3815 metastatic head & neck and lung cancer patients treated with ICIs and showed a significant correlation between endocrine irAEs and OS was observed ($P = 0.019$)[27]. In addition, a retrospective study reviewed 318 advanced melanoma patients and found that patients who experienced irAEs had a superior OS compared to those who did not[13].

Although the precise mechanisms by which irAEs occur have not been fully uncovered, they are thought to represent bystander effects from activated T-cells and are consistent with the mechanism of action of ICIs[14,28]. It is now generally accepted that the pathogenesis of ICI-induced dysthyroidism involves both immune and non-immune mechanisms[29]. It is traditionally believed that thyroperoxidase (TPO) and thyroglobulin (Tg) antibodies may play an important role in mediating thyroiditis.

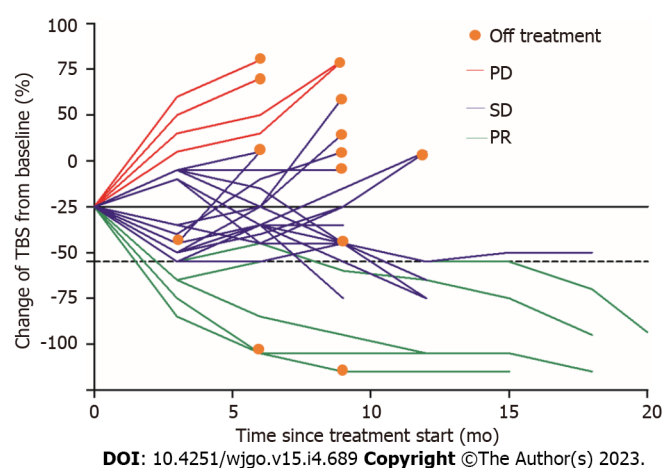


Figure 4 Spider plot displaying tumor response in 25 patients with hypothyroidism. PD: Progressive disease; SD: Stable disease; PR: Partial response; TBS: Tumor burden score.

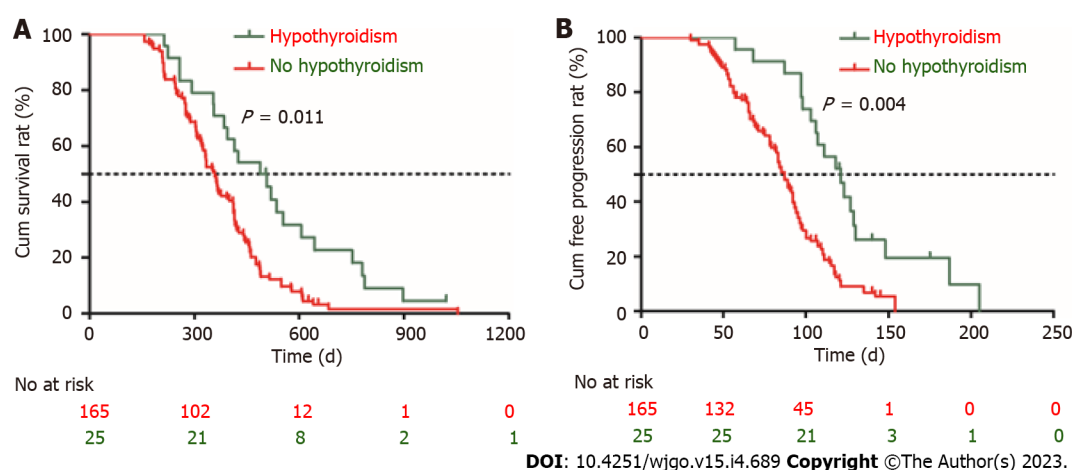


Figure 5 Prognosis comparison between hypothyroidism group and non-hypothyroidism group. A: Survival curve; B: Time to progression curve.

Maekura *et al*[30] considered that the presence of anti-thyroid antibodies such as TPO and Tg antibodies is a positive predictive factor for developing hypothyroidism in a Japanese cohort of 64 patients with advanced NSCLC treated with nivolumab. Recent study found that the mechanism of thyroid destruction by PD-1 antibodies may be mediated by T cells, natural killer (NK) cells, and monocytes[31-33]. Delivanis *et al*[31] showed that patients treated with anti-PD-1 therapy had an increasing circulating number of CD56⁺CD16⁺ NK cells and high HLA-DR surface expression in CD14⁺ CD16⁺ monocytes that mediate the inflammation. In addition, Das *et al*[34] considered that B lymphocytes also played a role in mediating dysthyroidism. They showed that patients with advanced melanoma treated by a combined checkpoint blockade who developed high-grade irAEs, compared to those who did not, had a decreased total peripheral B lymphocyte count with increased plasmablasts and a subset of B lymphocytes[34,35].

There are some limitations to our study. First, the study is retrospective and conducted only in one center; therefore, multiple centers should be evaluated in further studies. Second, the sample size was relatively small so that the sample of irAEs was small, resulting in large confidence intervals and imprecise results. Third, the effect of different ICI agents on adverse reactions and prognosis in patients was not strictly excluded in this study. Fourth, our study did not include those patients with autoimmune disease, meaning that the correlation between irAEs and prognosis in patients with autoimmune disease needs further exploration. Finally, some adverse events which tended to be ignored, such as fever, weakness, and anorexia, were not recorded, resulting in a lower incidence of irAEs than in previous studies.

CONCLUSION

In conclusion, dysthyroidism is the most common irAE related to a good prognosis and involves T and

B-lymphocytes, multiple cytokines, and diverse factors. Further clinical and laboratory studies should be conducted to clarify the mechanism of ICI-related dysthyroidism. Additionally, the clinical diagnosis and management of thyroid irAEs should be enhanced to avoid life-threatening complications. In addition, the long-term effects of ICIs on dysthyroidism should be further researched to better understand thyroid irAEs and autoimmune thyroid diseases.

ARTICLE HIGHLIGHTS

Research background

Unresectable hepatocellular carcinoma (HCC).

Research motivation

Immune-related adverse events (irAEs) have a high incidence in immune checkpoint inhibitor (ICI) treatment of unresectable HCC. The relationship between irAEs and treatment outcomes in ICI-treated unresectable HCC patients remains unknown.

Research objectives

A retrospective study was conducted to elucidate the correlation between immune-related toxic effects and prognosis in patients with unresectable HCC treated with pembrolizumab.

Research methods

A total of 190 unresectable HCC (Barcelona Clinic Liver Cancer stage C) patients receiving pembrolizumab treatment were retrospectively reviewed. All irAEs were reviewed and the relationship between irAEs and prognosis was analyzed.

Research results

In our study, we found that the overall incidence of irAEs was 72.6% (138/190) and 10.0% of them were severe irAEs (grade ≥ 3); elevated transaminase (> 3 times upper limit of normal) was the most common adverse reaction to ICIs. Patients who developed myocarditis or hypothyroidism tended to achieve partial response and have a more significant decrease in tumor burden. In addition, patients without irAEs were more likely to have progressive disease. It suggested that irAEs are indeed closely related to antitumor effects. In addition, hypothyroidism was the independent risk factors for time to progression and overall survival.

Research conclusions

irAEs, especially hypothyroidism, could be used as an indicator to evaluate the effect of immunotherapy.

Research perspectives

The study could help doctors in identifying patients who are responding to immunotherapy. In general, the response rate to both tyrosine kinase inhibitors and ICIs is less than 30%. Serious adverse events may put patients at risk of death. Therefore, timely identification of the right patients can not only reduce the side effects of immunotherapy but also improve the effectiveness of treatment.

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FOOTNOTES

Author contributions: Zhou JM and Xiong HF analyzed the data and wrote the manuscript; Zhu LP, Zhang ZW, and Chen XP designed the research; Wu B modified the manuscript; and all authors read and approved the final manuscript.

Institutional review board statement: The study was approved by the Ethical Committee of Tongji Hospital of Tongji Medical College of Huazhong University of Science and Technology. All procedures performed in this study abided by the Declaration of Helsinki.

Informed consent statement: All study participants or their legal guardian provided informed written consent about

personal and medical data collection prior to study enrolment.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: The datasets (data) for this study can be found in the (figure)

<https://figshare.com/s/ee63fa5271448d51104e>. The other datasets were available on request from the corresponding author at wuhanyywb@163.com.

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