Original Article

Safety and efficacy of anti-PD-1 inhibitors in Chinese patients with advanced lung cancer and hepatitis B virus infection: a retrospective single-center study

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Background: Programmed death protein (ligand) 1 [PD-(L)1] inhibitors have provided new therapeutic options for advanced lung cancer. However, patients with hepatitis B virus (HBV) infection have been traditionally excluded from most registered trials of this form of treatment.

Methods: We performed a retrospective analysis of patients with HBV and advanced lung cancer who received anti-PD-1 immunotherapy from September 2018 to May 2020 in our department. Treatment-related hepatotoxicity was evaluated and recorded. Overall response rate and progression free survival were also assessed in the patients using iRECIST.

Results: Seventeen patients were evaluated in this analysis. Of these, six (35.3%) experienced hepatic transaminase elevation during immunotherapy. Three of these patients developed Grade 3 hepatic immune-related adverse events and received systemic corticosteroids, following which aminotransferase levels recovered to normal in all patients and no adverse events were observed in subsequent treatment. No patient experienced HBV reactivation or flare. One patient developed active pulmonary tuberculosis (TB). Other adverse events were mild, well tolerated and short term. The objective response rate (ORR) of the cohort was 62.5%, and the median progression-free survival (PFS) was 3 months.

Conclusions: Lung cancer patients can be treated safely with anti-PD-1 inhibitors in the context of HBV infection. Close monitoring for hepatotoxicity and prophylactic antiviral therapy is advised. Further studies on the use of anti-PD-1 inhibitors in HBV-infected patients are needed.

Keywords: Lung cancer; hepatitis B virus infection (HBV infection); anti-programmed cell death protein 1 (anti-PD-1); immunotherapy; immune related adverse events

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Introduction

Lung cancer is the most frequently diagnosed cancer and major cause of cancer-related deaths worldwide (1-3). Conventional chemotherapy and radiation therapy for patients in the advanced stage may help to provide palliation in the setting of widespread disease but can be difficult for patients to tolerate. Over the past few decades, molecularly targeted therapy has greatly improved the survival time and life quality of lung cancer patients with targetable driver mutations (4,5). However, tumor response is often not durable with drug resistance, leading to therapeutic failure (6). Immune checkpoint inhibitors, known as a switch for restoring antitumor immunity, have ushered in a new era of anti-cancer therapy (7-9). The programmed cell death protein 1 (PD-1)/programmed cell death protein ligand 1 (PD-L1) axis has been widely investigated and anti-PD-1/PD-L1 therapy approved as a standard treatment for advanced lung cancer (10). Clinical trials have indicated immunotherapy, in combination of chemotherapy, showed a significant overall survival (OS) benefit to patients with advanced stage lung cancer patients. Chronic hepatitis B virus (HBV) is a serious global public health problem and endemic in East Asia (11). Those either carrying or infected with HBV are defined as hepatitis B surface antigen positive (HBsAg-positive). According to the World Health Organization (WHO), approximately 250 million people are living with chronic hepatitis B infection worldwide (12), and China accounts for 10% of the global HBV carrier population (13).

Host immune responses play a critical role in HBV control (14,15). Impaired immunity leads to HBV reactivation, showing active virus replication or immune-mediated hepatic injury (16). HBV reactivation can be triggered by cancer chemotherapy (17,18) with an incidence as high as 20–50% in patients who are chronic HBV carriers, and infection has been reported in this setting (19). With the advent of cancer immunotherapy, anti-PD-1/PD-L1 immune checkpoint inhibitors have become an effective method for lung cancer treatment. In the context of the cancer immunoediting theory, however, immunotherapy-related HBV reactivation is a potential threat to this therapy. There are few studies investigating the risk of viral reactivation and hepatotoxicity of PD-1/PD-L1 inhibitors for HBsAg-positive patients because such patients are initially excluded from clinical trials. Previous retrospective studies evaluated the safety of immunotherapy mainly in Caucasian cancer populations (multiple tumor types, such as melanoma and hepatocellular carcinoma) with HBV surface antigen expression. As the prevalence of HBV infection in China is relatively higher than Western countries and the increasing incidence of lung cancer, the safety and efficacy of immunotherapy in these patients needs to be urgently explored. In addition, the question of immunotherapy in the setting of HBV presents an important safety dilemma regarding subsequent therapies for lung cancer patients with immune-related liver dysfunction in the setting of potentially prolonged survival outcomes. Unfortunately, there are limited published data. Therefore, we conducted a single-center retrospective analysis of Chinese lung cancer patients with HBV surface antigen expression to evaluate the safety and efficacy of PD-1 checkpoint inhibitor immunotherapy. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/tlcr-21-79).

Methods

Patients

Patients with histologically confirmed lung cancer who had been administered PD-1 immune therapy checkpoint inhibitors (ICIs) at the First Affiliated Hospital, College of Medicine, Zhejiang University between September 2018 and May 2020 were reviewed, with the final follow up occurring on August 14, 2020. Metastases in the porta hepatis or other causes of biliary obstruction or baseline liver cirrhosis were ruled out. Clinical and treatment information was collected from electronic medical records. Individual consent for our study was waived as the privacy of the patients has not been disclosed. This study was approved by the Ethics Committee of the First Affiliated Hospital, College of Medicine, Zhejiang University. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Response evaluation and statistical analysis

Adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. Management of immune-related AEs (irAEs) included discontinuation of treatment and administration of corticosteroids based on AE severity following standard protocol guidelines (20). The response evaluation of PD-1 antibody was based on the immune-related Response Evaluation Criteria in Solid Tumors (21). The objective

Table 1 Baseline characteristics of patients

Indices	n=17
Age, median (range), year	64 [41–76]
Gender, (male/female), n	16/1
Smoking/alcohol consumption, n	12/2
Clinical stage, n	
IIIA	3
IIIB	1
IV	13
Tumor types, n	
NSCLC	1
Adenocarcinoma	4
Squamous	10
SCLC	2
Tumor molecular mutation, n	
EGFR	1
KRAS	1
Other	1
WT	4
NA	10
Treatment line, n	
1	8
2	5
≥3	4
Treatment modality, n	
Anti-PD-1/PD-L1 monotherapy	7
Combination therapy	10
Brain/liver/pleural/bone/intrapulmonary metastases, n	2/1/3/4/3
Liver function before immunotherapy	
Normal	15
Abnormal	2
Antiviral prophylaxis, (yes/no) n	9/8

NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; EGFR, epidermal growth factor receptor; KARS, Kirsten rat sarcoma viral oncogene homolog; WT, wide type; NA, not available.

response rate (ORR) was defined as the proportion of patients who had achieved either complete response (CR) or partial response (PR). The disease control rate (DCR) was defined as CR, PR, or stable disease (SD). Progression-free survival (PFS) was calculated from the first day of treatment to the first radiological evidence of disease progression or death. The follow up interval was 3 months, at which time CT scan, MRI and bone scan were performed. OS was defined as the interval from the start of first line anti-cancer treatment to death from any cause. Censored data were defined as data from patients who were alive and had no evidence of disease progression at the last follow-up visit.

Baseline clinical characteristics, including age at diagnosis, gender, smoking/alcohol status, clinical stage, tumor histology, liver metastasis or not, baseline liver function test, history of anti-HBV therapy, the number of previous lines of treatment, adverse events, and abnormal changes of liver function were recorded during ICIs by retrospective chart review. Qualitative variables were reported as the frequency (percentage), and continuous variables were described as the median (range). The denominator for calculating ORR included all patients in our study who could be evaluated for response. Kaplan-Meier methodology was used to determine median PFS and all analyses were conducted using the SPSS software (ver. 13.0). The treating physician made all treatment strategy decisions.

Results

In total, 330 consecutive lung cancer patients who received PD-1 ICIs were reviewed, 17 of whom had a history of HBV. The clinical characteristics of the 17 HBV patients are summarized in *Table 1*. The median age of patients was 64 (range, 41–76) years old, and 47.1% [8/17] were ≥65 years old. The majority of patients (94.1%, 16/17) were male and reported a history of current or prior smoking (70.1%, 12/17). Metastases were present in 13 patients with advanced lung cancer (Figure S1). Extrapulmonary metastases were most commonly found in the bone (23.5%, 4/17), followed by pleura (17.6%, 3/17), brain (11.8%, 2/17) and liver (6.0%, 1/17). Ten patients were diagnosed squamous carcinoma, whilst four had adenocarcinoma and two had small cell lung cancer (SCLC). The one left was classified as non-small cell lung cancer (NSCLC) due to low tumor differentiation. Molecular testing, including *EGFR/KRAS/NRAS/BRAF/HER-2/MET/PI3KCA* mutation and

ALK/ROS1/RET fusion were performed in seven patients. Among four adenocarcinoma patients, one patient harbored *EGFR* 19 deletion combined with T790M mutation, another one harbored *HER2* mutation, and the other two had no known positive genetic mutation. One NSCLC patient harbored *KRAS*. Two squamous carcinoma patients were wild type (*Table 2*). Routine tumor staining for PD-L1 was not performed. All patients were treated with PD-1 inhibitors monotherapy or combination therapy, including 2 Tislelizumab, 2 Sintilimab 2 Nivolumab, 3 Camrelizumab, 3 Triprizumab, and 5 Pembrolizumab. Eight patients received anti-PD-1 immunotherapy as first-line treatment, and the other nine patients received it as second or later line immunotherapy. Ten patients received anti-PD-1 in combination with chemotherapy. Seven patients were treated with single anti-PD-1 agent, and nine patients received anti-HBV treatment when anti-PD-1 immunotherapy started according to infectious disease consultation, due to the lack of specific antiviral strategy for cancer immunotherapy.

Baseline liver function test abnormalities were seen in 11.8% [2/17] of patients before immunotherapy. One patient had grade 2 ALT elevation before anti-PD-1 immunotherapy and developed grade 3 elevation of ALT after immunotherapy, while another one with grade 1 baseline ALT elevation also experienced a mild rise in ALT.

Treatment

Single agent anti-PD-1 immunotherapy was given to 41.2% of patients (7/17). Only one patient received single agent anti-PD-1 immunotherapy as first line therapy, because of their poor ECOG status. Six patients received single agent anti-PD-1 immunotherapy as subsequent treatment (*Table 1*) and seven received chemotherapy combined with anti-PD-1 immunotherapy as first-line treatment. Of these, five patients diagnosed as having lung squamous cell carcinoma received nano-albumin bound paclitaxel plus carboplatin and two lung adenocarcinoma patients received pemetrexed plus carboplatin.

Effectiveness

Among the 17 patients, 16 were available for anti-PD-1 immunotherapy response evaluation (*Table 2*), and one was lost to follow-up. The median number of cycles of immunotherapy used was 5 (range, 1–28). PR was achieved in 10 of 16 patients (62.5%), and five patients (31.2%) had SD. The ORR of the cohort was 62.5%, and DCR was 93.7%.

At the end of the last follow-up, eight patients were still receiving anti-PD-1 immunotherapy, six patients discontinued anti-PD-1 immunotherapy for various reasons including treatment-related adverse events, three had disease progression and two had died (*Figure 1*). The median PFS was 3 (range, 1 to 16.5) months and the median OS was 7.5 (range, 1.2 to 46.0) months.

Safety

Generally, anti-PD-1 immunotherapy was well tolerated in lung cancer patients with HBV infection. There was no treatment related death in our study. The most prevalent side-effect was hepatic transaminase elevation in six patients (35.3%). Other treatment related AEs were neutropenia, seen in patients who received chemotherapy combined with ICIs, and which was considered a chemotherapy related AE as well as fatigue and rash. One patient developed active pulmonary tuberculosis (TB) after 12 cycles of anti-PD-1 immunotherapy. The patient then ceased anti-PD-1 immunotherapy and is receiving anti-TB treatment (*Table 2*). Liver function abnormalities were specifically analyzed (*Table 3*). Among six patients who were observed to have hepatic transaminase elevation, three patients developed grade 3 elevation transaminase and in all patients, anti-PD-1 agent was withheld and systemic corticosteroid therapy initiated. Aminotransferase reverted to normal in all patients and no adverse events were observed in subsequent treatment. The remaining three patients exhibited grade 1-2 aminotransferase elevation, with or without a concomitant increase in bilirubin levels. One patient developed grade 1 aminotransferase elevation after 2 cycles of neoadjuvant chemotherapy combined with immunotherapy; however aminotransferase levels slowly returned to baseline without intervention or treatment breaks. The patient received single agent mono-chemotherapy as postoperative adjuvant therapy and no aminotransferase abnormalities were observed.

Discussion

The results of the Chinese National Hepatitis seroepidemiological survey of 2019 (22) indicate the overall prevalence of HBV infection in the general population to be 5–6% with around 70 million people chronically infected. HBV infection represents a significant public

Table 2 Safety and efficacy of PD-1/PD-L1 inhibitors in patients with HBV infection

Patient	Age	Gender	Smoking consumption	Clinical stage	Tumor types	Tumor molecular mutation	Treatment line	Distant metastases	Cycles of immunotherapy	Any iAE ≥ G2	Best response
1	72	M	Y	IVA	NSCLC	KRAS	1	Pleural	5	Neutropenia (G4)	PR
2	66	M	Y	IVB	Squamous	NA	1	Bone	2	–	PR
3	72	M	Y	IVA	Squamous	WT	3	Intrapulmonary	5	Fatigue	PR
4	60	M	Y	IVB	SCLC	NA	2	Liver	2	Rash	SD
5	53	M	N	IVA	Adenocarcinoma	WT	2	Brain	28	Fatigue, Pruritus	PR
6	76	M	Y	IIIA	Squamous	NA	2	–	9	Fatigue	PR
7	64	M	Y	IVA	SCLC	NA	3	Pleural	15	ALT/AST↑, Bilirubin↑ (G2)	PR
8	60	F	N	IVA	Adenocarcinoma	Ex19-Del+T790M	4	Pleural	8	–	SD
9	56	M	Y	IVA	Squamous	NA	2	Intrapulmonary	5	–	PR
10	59	M	Y	IIIA	Squamous	NA	1	–	2	Neutropenia, Creatinine↑	PR
11	64	M	N	IIIA	Adenocarcinoma	WT	1	–	2	ALT/AST↑	PR
12	69	M	Y	IVA	Squamous	WT	1	Bone	2	ALT/AST↑ (G3)	SD
13	67	M	Y	IVA	Squamous	NA	2	Intrapulmonary	17	Pulmonary tuberculosis	SD
14	41	M	N	IVB	Adenocarcinoma	HER2	1	Bone	3	ALT/AST↑	PR
15	71	M	N	IVA	Squamous	NA	1	Bone	1	ALT/AST↑ (G3)	NE
16	66	M	Y	IIIB	Squamous	NA	3	–	16	Fatigue	SD
17	62	M	Y	IVA	Squamous	NA	1	Brain	1	ALT/AST↑ (G3)	PD

M, male; F, female; NA, not available; WT, wide type; PR, partial response; SD, stable disease; NE, not evaluable; PD, disease progression.

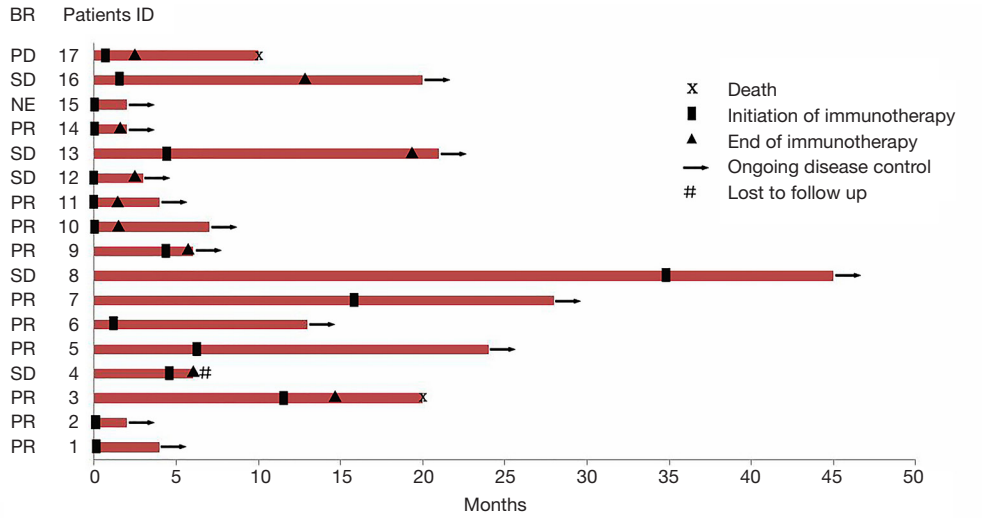

Figure 1 Overall survival follow-up of each patient from diagnosis.

health burden in China in spite of the success of HBV vaccination (23). Due to the immunocompromised status, patients with hematological malignancies and lymphomas are at high risk for reactivation of HBV (24,25). Previous studies report HBV reactivation and subsequent liver function impairment in lung cancer patients who received chemotherapy and targeted therapy. In the case report of Qin *et al.*, fulminant viral hepatitis occurred in a patient with SCLC during chemotherapy and the patient succumbed to liver failure (26). In the study by Yao *et al.* 16 of 171 patients developed HBV reactivation during EGFR TKI treatment, with an annual incidence of 7.86% (27). It is generally assumed that HBV mediates chronic liver injury through abnormal immune attack. HBsAg seropositive patients are considered to have impaired baseline liver function and are more prone to trigger immune reconstitution inflammatory syndrome, although the initial ALT/AST are within the normal range.

Recently, anti-PD-(L)1 therapy has provided new therapeutic options for patients with various cancer types, including lung cancer. Limited evidence exists on the incidence of high-grade immune-related adverse events in patients with advanced lung cancer and HBV infection. In clinical trials, the reported incidence of immune-related hepatitis in lung cancer patients ranges from 5–10% with monotherapy to 25–30% with combined chemotherapy (28-30). A case series (31) reported 5 patients developing liver injury, 1 suffering from grade 2 ALT increase and 4 showing grade 1 ALT increase (28). In the retrospective study of Byeon *et al.*, 5 of the 9 NSCLC patients who were treated with PD-1 inhibitors and shown to have severe AST/ALT elevation (grade 3 or higher) were infected with HBV (32). In our study, 6 of 17 patients developed ALT/AST abnormality and 3 experienced severe hepatitis (grade 3). Of the 3 patients, 1 whose HBV-DNA was undetectable and had normal liver function before treatment and had received preventative antiviral drugs. However, that patient showed a higher HBV-DNA copy number and grade 3 liver injury during PD-1 inhibition. Another patient, not receiving antiviral medication, had a HBV DNA copy number of 3.02×10^2 IU/mL and grade 2 hepatic dysfunction before treatment. After 1 cycle of immunotherapy, ALT elevated to 6-fold from its baseline level while no increase of the DNA load was seen. The remaining 1 patient, whose HBV DNA copy number was 3.26×10^3 IU/mL and liver metabolism was normal, experienced grade 3 transaminase elevation and higher DNA copy number 2 cycles later. This suggests the incidence of immune-related hepatitis is unpredictable due to different treatment regimens, cycles and individual difference. HBV-positive patients, receiving chemotherapy and immunotherapy, are at high risk of hepatitis reactivation. Antiviral prophylaxis should be considered while HBsAg seropositivity has been confirmed.

It is interesting to note that that 1 patient was newly diagnosed with pulmonary TB during their anti-PD-1 treatment. Previous studies (33,34) have similarly reported patients subsequently infected with active TB, including

Table 3 Profile of patients with active virus replication or immune-mediated hepatic injury

Patient	HBsAg/anti-HBc	Baseline AST/ALT	Baseline HBV viral load, IU/mL	Antivirus therapy	Peak ALT/AST during therapy, U/L	Peak HBV viral load during therapy, IU/mL	Abnormal AST/ ALT and CTCAE grading (G)	Occurrence time after therapy	Outcome
1	+/+	Normal	5.04×10^{2}	Y	Normal	Undetectable	–	–	–
2	+/+	Normal	4.39×10^{4}	Y	Normal	Undetectable	–	–	–
3	+/+	Normal	Undetectable	N	Normal	Undetectable	–	–	–
4	+/+	Normal	1.28×10^{2}	Y	Normal	Undetectable	–	–	–
5	+/+	Normal	Undetectable	Y	Normal	Undetectable	–	–	–
6	+/+	Normal	Undetectable	Y	Normal	Undetectable	–	–	–
7	+/+	2×	Undetectable	N	3×	Undetectable	G1	15 Cycles	No delay
8	+/+	Normal	Undetectable	N	Normal	Undetectable	–	–	–
9	+/+	Normal	Undetectable	N	Normal	Undetectable	–	–	–
10	+/+	Normal	Undetectable	Y	Normal	Undetectable	–	–	–
11	+/+	Normal	1.78×10^{3}	N	2×	Undetectable	G1	2 cycles	Neoadjuvant therapy for 2 cycles and completed
12	+/+	Normal	3.26×10^{3}	Y	12×	4.3×10^{1}	G3	2 cycles	Premature termination and liver function normalised after GC administration
13	+/+	Normal	Undetectable	N	Normal	Undetectable	–	–	–
14	+/+	Normal	1.44×10^{3}	Y	1×	Undetectable	G1	3 cycles	No delay
15	+/+	Normal	Undetectable	Y	11×	1.33×10^{2}	G3	1 cycle	Premature termination and liver function normalised after GC administration
16	+/+	Normal	Undetectable	N	Normal	Undetectable	–	–	–
17	+/+	4×	3.02×10^{2}	N	6×	Undetectable	G3	1 cycle	Premature termination and liver function normalised after GC administration

A viral load of <30 IU /mL is considered undetectable. The normal range of ALT is 5–35 U/L and AST is 8–40 U/L. HBsAg, hepatitis B surface antigen; anti-HBc, antibodies to hepatitis B core; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GC, glucocorticoid; ×, n-fold compared to baseline.

TB-related fatalities when treated with anti-PD-1 ICIs. As patients with active TB infections are excluded from clinical trials, there is limited research assessing the risk of developing TB secondary to immunotherapy. On this basis, it may be necessary to screen closely for TB infection when initiating immunotherapy. Other possible irAEs, such as fatigue, rash, pruritus and creatinine elevation, appear to be well tolerated and short-lived in duration.

It is currently believed that PD-1 inhibitors exert anti-tumor effects by promoting T-cell activation, rather than through the suppression of T-cells. Patients with HBV infection, characterized by T-cell exhaustion and impaired T-cell function, may theoretically have a poor response to PD-1 blockade therapy. In addition, HBV-positive patients may be even more vulnerable to virus reactivation and immune-mediated liver injury as their baseline liver function is compromised. It should be noted that the anti-tumor efficacy of ICIs is promising with an ORR of 62.5% for lung cancer patients.

As our study included only HBsAg-positive lung cancer patients who received immunotherapy in our center and there is a risk factor for HBV reactivation, the sample sizes were relatively small. Considering this, the included patients may not accurately represent the population of HBV infections and bias may exist in the results of our study. Further, due to the application of multiple kinds of anti-PD-1 in our study, there may be adverse reaction differences caused by differences in the agents.

These results support the clinical observation that lung cancer patients can be treated safely with anti-PD-1 immunotherapy in the context of HBV infection. Treatment-related irAE's were found to be manageable. Close monitoring for hepatotoxicity, including HBV-DNA is advised and treatment with prophylactic antiviral therapy implemented when indicated. Further studies on the PD-1 ICIs in HBV-infected patients are required.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Clinical Research Ethics Committee of the First Affiliated Hospital, College of Medicine, Zhejiang University. The privacy of the patients has not been disclosed in our study and individual consent for this retrospective analysis was waived.

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