Original Article

Liver-directed moderately hypo-fractionated radiotherapy combined with pembrolizumab and bevacizumab for advanced hepatocellular carcinoma: a retrospective observational study of 23 cases

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Background: Programmed cell death protein 1 (PD-1) or its ligand (PD-L1) monoclonal antibody combined with bevacizumab (a monoclonal antibody targeting vascular endothelial growth factor) has been established as first-line systemic treatment for advanced hepatocellular carcinoma (HCC). Radiotherapy is a crucial local treatment for HCC. Mutual efficacy enhancement has been reported between radiotherapy, anti-angiogenesis therapy and immunotherapy in preclinical researches, but not been validated in clinical practice. Whether radiotherapy can enhance efficacy of anti-PD-1 immunotherapy plus bevacizumab for HCC remains unclear. This retrospective observational study aimed to appraise efficacy and safety of the combination of radiotherapy with pembrolizumab (a PD-1 monoclonal antibody) and bevacizumab for advanced HCC for the first time.

Methods: Patients with advanced HCC treated by intrahepatic tumor-directed moderately hypo-fractionated radiotherapy combined with pembrolizumab and bevacizumab were consecutively included. Clinicopathological characteristics, therapeutic outcomes and treatment-related adverse events (TRAEs) were recorded and evaluated.

Results: A total of 23 patients were eventually enrolled. Median cycles of pembrolizumab and bevacizumab were 4 (median, 1–8) and 4 (median, 1–9) cycles. The objective response rates and disease control rates of irradiated intrahepatic HCC and non-irradiated extrahepatic HCC were 34.8% [95% confidence interval (CI), 16.4–57.3%] *vs.* 10.0% (95% CI, 1.2–31.7%), and 91.3% (95% CI, 72.0–98.9%) *vs.* 70.0% (95% CI, 45.7–88.1%), respectively. The median progression-free survival (PFS) and overall survival (OS) were 6.6 (95% CI, 4.7–8.5) and 18.3 (95% CI, 8.2–33.6) months, and 12-month PFS and OS rates were 17.5% (95% CI, 7.0–28.0%) and 60.9% (95% CI, 50.7–71.1%). Two patients (8.7%) with locally advanced, unresectable HCC eventually underwent curative resection of tumors after this trimodal treatment. Eighteen patients (78.3%) had ≥ grade 3 TRAEs, with myelosuppression and transaminase increase as the most common.

Conclusions: This study firstly reported that combining radiotherapy with pembrolizumab and bevacizumab was preliminarily a feasible and effective therapeutic choice for advanced HCC in despite of more TRAEs. This tri-modal regimen may be a potential conversion therapy for unresectable, locally advanced HCC. The limitations of this study are its retrospective nature and small sample size; therefore,

big-sample prospective studies are warranted to further investigate this tri-modal regimen.

Keywords: Hepatocellular carcinoma (HCC); radiotherapy; bevacizumab; pembrolizumab; real-world study

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Introduction

Worldwide, liver cancer is the sixth most common emerging tumor, and the third leading cause of cancer-related death. Hepatocellular carcinoma (HCC) is the main pathological type of primary liver cancer, comprising 75–85% of cases. Hepatitis B virus or hepatitis C virus infection is the predominant etiology (1). Prognosis of HCC is very poor, with 5-year overall survival (OS) approximately equal to 18% (2). Up to 30–35% of cases are diagnosed as advanced stage, to whom systemic treatment is recommended (2-3).

Programmed cell death protein 1 (PD-1) or its ligand (PD-L1) inhibitors have shown clinical benefits in various cancers, including HCC. Only 12.4–18.3% of HCC patients benefit from PD-1/PD-L1 inhibitor monotherapy regardless of in first-line or second-line setting. However, objective response rate (ORR) increased to 20.5–37% when PD-1/PD-L1 inhibitor was combined with anti-angiogenesis therapy (including small molecular tyrosine kinase inhibitors and bevacizumab) (4). Sintilimab, a PD-1 monoclonal antibody, and atezolizumab, a PD-L1 monoclonal antibody, have been approved in combination with bevacizumab as standard first-line systemic treatment for advanced HCC (4-6) in China mainland.

Radiotherapy has become an important local treatment for HCC. There are increasing evidences supporting complex cross-talk between radiotherapy, tumor vasculogenesis and anti-tumor immunity. Irradiation causes aging and apoptosis of vascular endothelial cells, collapse of blood vessels, and results in local hypoxia which stimulates the expression of angiogenesis molecules contributing to radioresistance in turn (7). Bevacizumab can reduce hypoxia and alleviate resistance to irradiation through blocking angiogenesis signaling and normalizing tumor vessels (8,9). Anti-angiogenesis treatment promotes macrophage M1 polarization, $CD8^+$ T cell infiltration and secretion of anti-tumor cytokine, including *CXCL9*, *CXCL10*, *CCL21* and *IFN*-γ (10,11). Local irradiation to a tumor lesion can result in a non-irradiated tumor shrink by enhancing anti-cancer immune response, which is called abscopal effect (12). The mechanism lies in that irradiation induces immunogenic death of tumor cells, releasing damage-associated molecular patterns (DAMPs), such as calreticulin, adenosine triphosphate, and high mobility group box 1, and tumor-associated antigens (TAAs) which increase the activity of antigen-presenting cells (APCs) and specific T cells (12,13). Radiation-induced damage also increases availability of double-stranded DNA in the cytoplasm, and activates the cyclic guanosine monophosphate-adenosine monophosphate synthase (cGAS)-stimulator of interferon genes (STING) pathway which promotes production and secretion of cytokines and chemokines, recruiting and activating immune cells (13). Based on the mechanism mentioned above, it is rational to integrate radiotherapy, anti-PD-1/PD-L1 immunotherapy and bevacizumab. And this combination therapy has benefited patients

Highlight box

Key findings

- Integrating radiotherapy into bevacizumab-pembrolizumab was preliminarily an effective regimen for advanced hepatocellular carcinoma (HCC). This tri-modal therapy brought about more treatment related adverse events (TAREs) which were expected and manageable.

What is known and what is new?

- Programmed cell death protein 1 (PD-1) or its ligand (PD-L1) monoclonal antibody combined with bevacizumab has been established as first-line systemic treatment for advanced HCC. Radiotherapy is a crucial local treatment for HCC. However, whether radiotherapy can enhance efficacy of anti-PD-1 immunotherapy plus bevacizumab for HCC remains unclear.
- Combining radiotherapy with bevacizumab and pembrolizumab was a viable and effective therapeutic choice for advanced HCC.

What is the implication, and what should change now?

- Patients with advanced HCC may benefit from the combination therapy of radiotherapy, bevacizumab and pembrolizumab. This tri-modal regimen may be a potential conversion therapy for unresectable, locally advanced HCC.

with recurrent high-grade glioma in a prospective phase I clinical trial where tri-modal therapy of radiotherapy plus bevacizumab plus pembrolizumab achieved an ORR of 78%, even in patients with negative PD-L1 expression and/or resistance to bevacizumab. The median OS was 13.5 and 9.3 months for bevacizumab-naïve patients and bevacizumab-resistant patients, respectively (14). Zhong *et al.* retrospectively reported ORR of 40% and disease control rate (DCR) of 86.7% in a combination treatment consisting of palliative radiotherapy, anti-angiogenesis therapy and PD-1/PD-L1 inhibitors for advanced HCC with expected and manageable safety profiles (15). However, it is still uncertain whether adding intrahepatic tumor-directed radiotherapy to the combination of bevacizumab plus PD-1/PD-L1 inhibitor could further improve treatment outcome of advanced HCC. We conducted this retrospective observational study to provide data on efficacy and safety of liver-directed external beam moderately hypo-fractionated radiotherapy combined with bevacizumab (a monoclonal antibody targeting vascular endothelial growth factor) and pembrolizumab (a *PD-1* monoclonal antibody) for advanced HCC. We present this article in accordance with the STROBE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1333/rc).

Methods

Patients' eligibility

We retrospectively reviewed medical records of advanced HCC patients treated in the Fifth Affiliated Hospital of Sun Yat-sen University from January 2018 to December 2021. Patients with advanced HCC who met the following criteria were enrolled into this study: (I) age was 18–70 years old; (II) had received combined treatment including external beam hypo-fractionated radiotherapy to intra-hepatic tumor, bevacizumab and pembrolizumab; (III) radiation was started within 2 wteeks before or after the first administration of pembrolizumab; (IV) bevacizumab was initiated concurrently with pembrolizumab; (V) liver function was Child-Pugh A class. Patients who had received liver transplantation or had other malignancies were excluded. Anti-viral treatment was administered to patients with active hepatitis virus infection. This study was approved by Ethics Board of the Fifth Affiliated Hospital of Sun Yat-sen University (No. K47-1). The informed consent on treatment was taken from all patients. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Data collection and study objectives

Data on sex, age, hepatitis virus infection, Eastern Cooperative Oncology Group (ECOG) score, α-fetoprotein (AFP) level, Child-Pugh score, macrovascular invasion, extra-hepatic metastasis, number of tumor nodule, tumor size, previous treatment, pembrolizumab and its treatment cycles, bevacizumab and its treatment cycles, radiotherapy information, treatment-related adverse events (TRAEs), efficacy and survival were collected. TRAEs were graded according to the US National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE v4.03), with maximum grade recorded.

The primary endpoint was ORR. The secondary endpoints were progression-free survival (PFS), OS, DCR, duration of overall response (DOR) and toxicity profile. Treatment response evaluation was according to Response Evaluation Criteria in Solid Tumor (RECIST) v 1.1 (16). The definition of endpoints was as follow: (I) ORR, the proportion of patients with complete or partial response that was maintained for at least four weeks from the first radiological confirmation; (II) PFS, the time from the commencement of treatment to progression or death; (III) OS, the time from the commencement of treatment to death from any cause; (IV) DCR, the proportion of patients with objective response or stable disease; (V) DOR, the time from the first radiology-confirmed overall response to progression.

Treatment

Radiotherapy

Irradiation plan was calculated by intensity-modulated radiotherapy (IMRT) technique. Totally, 45 Gy was prescribed to tumor in a moderately hypo-fractionated scheme, with 3.0 Gy per fraction. The biological equivalent dose (BED) was 54–58.5 Gy (tumorous α/β =10–15 Gy). Patients were irradiated once a day from Monday to Friday.

Pembrolizumab and bevacizumab

Pembrolizumab was infused intravenously at a dose of 200 mg, every 3 weeks, according to KEYNOTE-240 trial (17). Bevacizumab was administered intravenously over 90 minutes by 15 mg/kg bodyweight every 3 weeks (5). Pembrolizumab and bevacizumab were infused within 2 weeks before or after the start of radiotherapy.

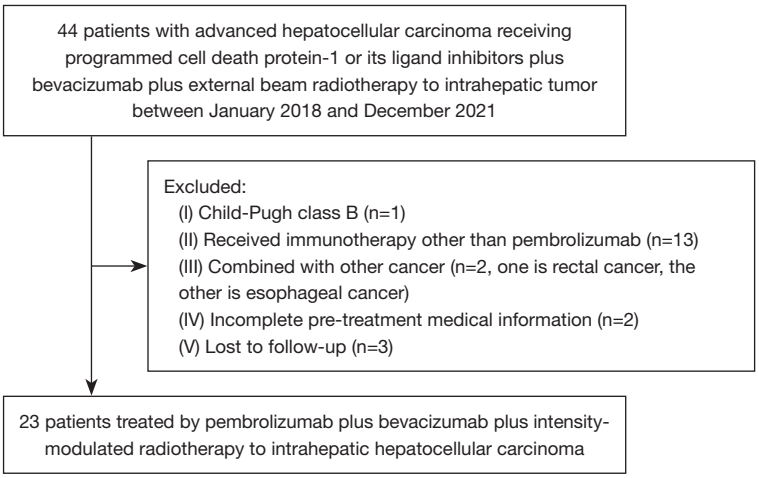

Figure 1 Summary of patient enrollment.

Statistical analysis

All statistical analysis were performed by SPSS Statistics, Version 25.0 (SPSS Inc., Chicago, IL, USA). ORR and DCR were calculated with 95% confidence interval (CI) by Clopper-Pearson method. Survival outcomes were estimated by Kaplan-Meier method. Double-tailed P value <0.05 was considered significant.

Results

Patients and treatment information

Twenty-three patients were eligibly enrolled into this study (*Figure 1*). The clinicopathological characteristics and treatment information are summarized in *Table 1*. Median age was 48 years (ranges, 24–67 years). The enrolled population was predominantly male (22/23, 95.7%). Twenty-two patients had Barcelona Clinic Liver Cancer (BCLC) staging C disease, with median and mean tumor diameters equal to 9.7 (range, 3.1–15.0) cm and 8.6 (95% CI, 5.2–12.1) cm, respectively. Twelve (52.2%) patients were diagnosed with intrahepatic macro-vascular invasion, and 20 (87.0%) patients had extrahepatic metastasis. The main etiology was hepatitis virus B infection (22/23, 95.7%), and all patients received antiviral therapy before radiotherapy. Fifteen patients had prior treatment, including hepatectomy, transhepatic arterial chemoembolization, chemotherapy, radiofrequency ablation or small molecule tyrosine kinase inhibitors. Eight patients received radiotherapy combined with pembrolizumab and bevacizumab as first-line treatment.

A total of 100 cycles of pembrolizumab were given to 23 patients, and the median was 4 (range, 1–8) cycles. Totally, 91 cycles of bevacizumab were administered to all patients, and the median was 4 (range, 1–9) cycles. All patients received moderately hypo-fractionated IMRT to intrahepatic tumor. The median and mean dose of irradiation was 45.0 (range, 36.0–48.0) Gy and 42.9 (95% CI, 40.1–45.8) Gy, respectively.

Efficacy

Median follow-up duration was 15.8 (range: 5.4–43.5) months. According to RECIST v1.1 criteria, no patients achieved complete response (CR) (*Figure 2* and *Table 2*). There were 8 partial response (PR), 13 stable disease (SD) and 2 progressive disease (PD) when irradiated intrahepatic tumor was assessed. There were 2 PR, 12 SD and 6 PD when non-irradiated extrahepatic tumor was evaluated. The ORRs and DCRs of irradiated intrahepatic tumor and non-irradiated extrahepatic tumor were 34.8% (95% CI, 16.4–57.3%) and 10.0% (95% CI, 1.2–31.7%), 91.3% (95% CI, 72.0–98.9%) and 70.0% (95% CI, 45.7–88.1%), respectively. Patients of No. 15 (before, *Figure 3A,3B*; after, *Figure 3C,3D*) and No. 19 (before, *Figure 3E,3F*; after, *Figure 3G,3H*) who had locally advanced, unresectable HCC both achieved PR after 3 Gy*15 f IMRT combined with 4 cycles of bevacizumab and 5 cycles of pembrolizumab as first-line treatment, and finally underwent curative surgical resection. Thirteen patients

Table 1 Clinicopathological characteristics and treatments

Characteristic	Statistic results (n=23)
Age, year, median [range]	48 [24–67]
Gender, n (%)	
Female	1 (4.3)
Male	22 (95.7)
ECOG score, n (%)	
0	14 (60.9)
1	9 (39.1)
Maximum tumor size (cm)	
Median [range]	9.7 [3.1–15.0]
Mean (95% CI)	8.6 (5.2–12.1)
<5.0, n (%)	7 (30.4)
≥5.0, n (%)	16 (69.6)
Number of nodules	
Median [range]	3 [1–3]
<3, n (%)	10 (43.5)
≥3, n (%)	13 (56.5)
BCLC staging, n (%)	
B	1 (4.3)
C	22 (95.7)
Serum AFP level, n (%)	
<400 ng/mL	11 (47.8)
≥400 ng/mL	12 (52.2)
Cirrhosis, n (%)	21 (91.3)
Hepatitis virus infection, n (%)	
HBV	22 (95.7)
HCV	2 (8.7)
HDV	1 (4.3)
Macro-vascular invasion, n (%)	12 (52.2)
Portal vein	12 (52.2)
Hepatic vein	6 (26.1)
Inferior vena cava	5 (21.7)
Hepatic artery	1 (4.3)
Extrahepatic metastasis, n (%)	20 (87.0)
Lymph node	13 (56.5)
Bone	6 (26.1)
Lung	8 (34.8)
Peritoneum	3 (13.0)
Adrenal gland	2 (8.7)
Kidney	1 (4.3)
Cycles of pembrolizumab, median [range]	4 [1–8]
Cycles of bevacizumab, median [range]	4 [1–9]
Radiotherapy dose (Gray)	
Median [range]	45.0 [36.0–48.0]
Mean (95% CI)	42.9 (40.1–45.8)
Prior treatment, n (%)	
No	8 (34.8)
Hepatectomy	7 (30.4)
Radiofrequency ablation	3 (13.0)
TACE	9 (39.1)
Target therapy	6 (26.1)
Chemotherapy	1 (4.3)

ECOG, Eastern Cooperative Oncology Group; CI, confidence interval; BCLC, Barcelona Clinic Liver Cancer; AFP, α-fetoprotein; HBV, hepatitis virus B; HCV, hepatitis virus C; HDV, hepatitis virus D; TACE, transhepatic arterial chemoembolization.

died from tumor progression. The estimated median PFS was 6.6 (95% CI: 4.7–8.5) months, and estimated median OS was 18.3 (95% CI, 8.2–33.6) months (*Figure 4*). The estimated 12-month PFS and OS rates were 17.5% (95% CI, 7.0–28%) and 60.9% (95% CI, 50.7–71.1%), respectively. Median DORs of irradiated intrahepatic tumor and non-irradiated extrahepatic tumor were 4.6 and 4.2 months, respectively.

Safety

TRAEs are shown in *Table 3*. All patients suffered from TRAEs of different grade. The most common TRAEs were anemia (65.2%), thrombocytopenia (52.2%), lymphocytopenia (47.8%), neutropenia (39.1%), leukopenia (34.8%), appetite loss (34.8%), aspartate aminotransferase increase (30.4%) and alanine aminotransferase increase (30.4%), serum bilirubin increase (30.4%), and weight loss (21.7%). Myelosuppression was probably related

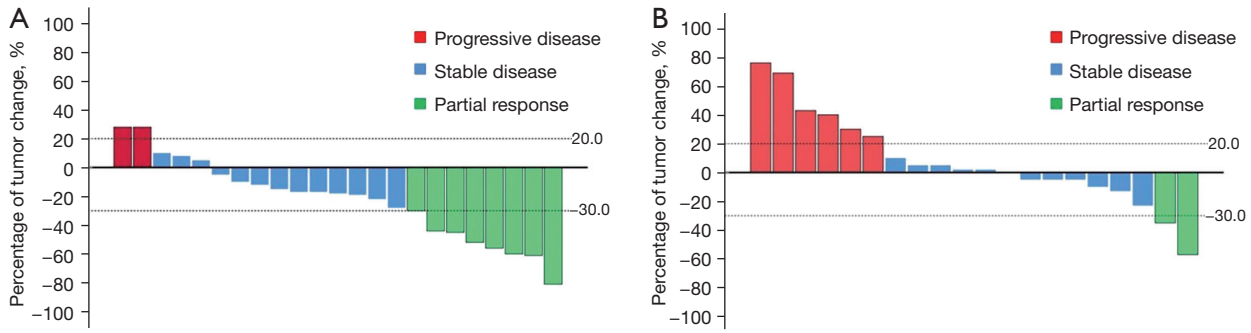

Figure 2 Tumor diameter changes of intrahepatic hepatocellular carcinoma (A) and extrahepatic hepatocellular carcinoma (B) after liver-directed radiotherapy combined with pembrolizumab and bevacizumab.

Table 2 Efficacy evaluation*

Response	Intrahepatic irradiated tumor	Extrahepatic non-irradiated tumor
CR, n (%)	0	0
PR, n (%)	8 (34.8)	2 (10.0)
SD, n (%)	13 (56.5)	12 (60.0)
PD, n (%)	2 (8.7)	6 (30.0)
ORR, n (%, 95% CI)	8 (34.8, 16.4–57.3)	2 (10.0, 1.2–31.7)
DCR, n (%, 95% CI)	21 (91.3, 72.0–98.9)	14 (70.0, 45.7–88.1)
DOR (months)	4.6	4.2

*, according to RECIST v 1.1. CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate; DOR, duration of overall response; RECIST, Response Evaluation Criteria in Solid Tumor.

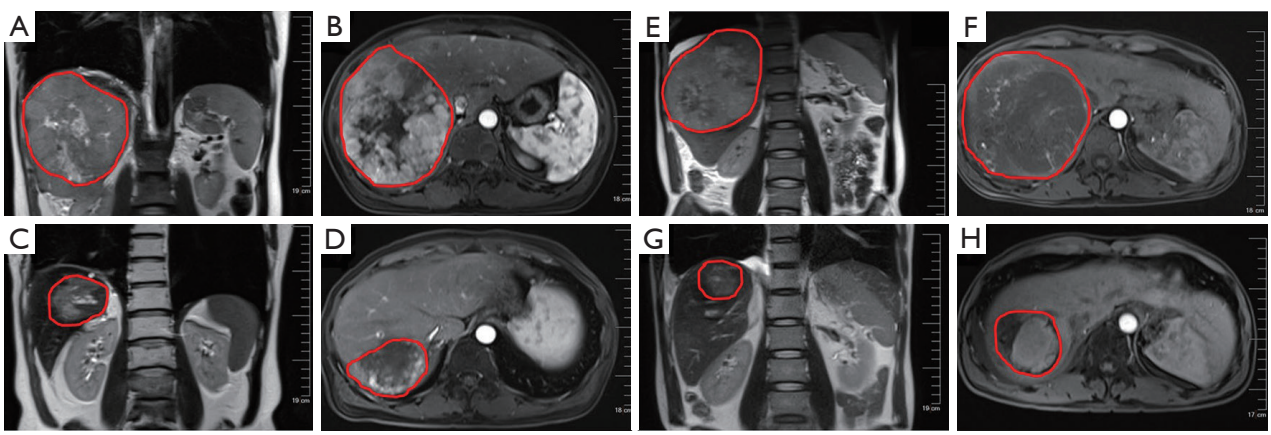

Figure 3 Patients of No. 15 (A,B: before treatment; C,D: after treatment) and No. 19 (E,F: before treatment; G,H: after treatment) with locally advanced, unresectable hepatocellular carcinoma received 3.0 Gy*15 f intensity-modulated radiotherapy plus 4 cycles of bevacizumab plus 5 cycles of pembrolizumab, and both achieved partial response, and finally underwent curative surgical resection of residual tumor. The red circles indicated the boundaries of tumor nodules.

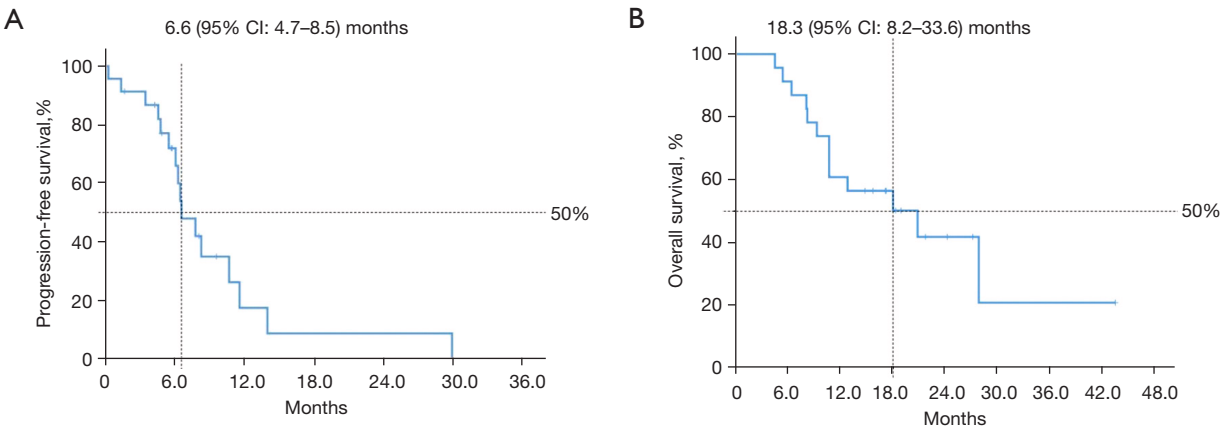

Figure 4 Kaplan-Meier curves of progression-free survival (A) and overall survival (B) of advanced hepatocellular carcinoma receiving combination treatment of pembrolizumab plus bevacizumab plus intrahepatic hepatocellular carcinoma-directed external beam moderately hypo-fractionated radiotherapy. CI, confidence interval.

Table 3 Treatment related adverse events*

Toxicities	Any grade, n (%)	Grade 3/4, n (%)
Anemia	15 (65.2)	2 (8.7)
Thrombocytopenia	12 (52.2)	3 (13.0)
Lymphocytopenia	11 (47.8)	11 (47.8)
Neutropenia	9 (39.1)	2 (8.7)
Leukopenia	8 (34.8)	3 (13.0)
Appetite loss	8 (34.8)	0
Aspartate aminotransferase increase	7 (30.4)	6 (26.1)
Alanine aminotransferase increase	7 (30.4)	3 (13.0)
Serum bilirubin increase	7 (30.4)	0
Weight loss	5 (21.7)	0
Epulis	2 (8.7)	2 (8.7)
Fatigue	2 (8.7)	0
Gastrointestinal hemorrhage	1 (4.3)	1 (4.3)
Dental ulcer	1 (4.3)	1 (4.3)
Allergy	1 (4.3)	1 (4.3)
Rash	1 (4.3)	1 (4.3)
Nausea	1 (4.3)	0

*, toxicity grading was according to the US NCI CTCAE v4.03. NCI, National Cancer Institute; CTCAE, Common Terminology Criteria for Adverse Events.

to radiotherapy. Loss of appetite and weight, and increase of liver enzymes and bilirubin were supposed to result from both radiotherapy and pembrolizumab-bevacizumab. Totally, 18 patients (78.3%) had ≥ grade 3 TRAEs. The most frequent TRAEs of ≥ grade 3 were lymphocytopenia (47.8%), thrombocytopenia (13.0%), aspartate aminotransferase increase (26.1%), alanine aminotransferase increase (13.0%), and leukopenia (13.0%). Decrease of peripheral blood lymphocyte did not affect radiotherapy or systemic treatment. There were no patients who developed classical radiation-induced liver disease or Child-Pugh score progression ≥2. Two patients discontinued radiotherapy for more than one week due to ≥ grade 3 TRAEs (one with grade 3 leukocytopenia, thrombocytopenia, and neutropenia; and the other with grade 3 alanine transaminase increase and gastro-intestinal bleeding). The latter patient also discontinued bevacizumab and pembrolizumab due to bleeding of sigmoid and rectum.

Discussion

This is the first reported study that combined intrahepatic tumor-directed external beam moderately hypo-fractionated radiotherapy, pembrolizumab and bevacizumab for advanced HCC with poor prognosis. This study preliminarily showed that the tri-modality treatment was an effective regimen, without unmanageable or unexpected toxicity.

Former studies indicated that tumor diameter >5 cm, ECOG >0, macroscopic vascular invasion, lymph node

involvement, advanced BCLC staging, multiple tumor nodules, extrahepatic invasion or metastasis, viral hepatitis and cirrhosis were adverse prognostic factors for HCC (18-21). In our study, the majority of patients had the inferior prognostic factors mentioned above, especially in aspects of large tumor diameter and high percents of BCLC C stage, macrovascular involvement and extrahepatic metastasis. More than half of patients failed previous treatment. Therefore, treatment for these patients was palliative. The reason of less cycles of pembrolizumab and bevacizumab was partially due to economic burden.

Systemic treatment is recommended for advanced HCC (2). However, efficacy of PD-1/PD-L1 inhibitor or anti-angiogenesis monotherapy was unsatisfactory. The ORR of PD-1/PD-L1 inhibitor monotherapy were 12.4–18.3% (4). ORRs of sorafenib, lenvatinib, regorafenib, ramucirumab, bevacizumab and cabozantinib were 4.0–11.0% (4,22), 18.2–18.8% (23,24), 3.0–10.0% (22,25,26), 7.0–7.3% (27,28), 13.0–14.0% (29,30), and 4.0–4.9% (31,32), respectively. PD-1/PD-L1 inhibitors combined with anti-angiogenesis therapy achieved higher ORRs of 20.5–37%, and improved median PFS of 4.6–9.3 months and OS of 17.1–22.0 months than monotherapy (4). Anti-PD-1/PD-L1 immunotherapy combined with bevacizumab or lenvatinib has been recommended as first-line systemic treatment for advanced HCC. There was growing evidence that intrahepatic tumor-directed local therapy (for example, radiotherapy, trans-arterial chemoembolization, radiofrequency ablation, etc.) alone or combined with target therapy exhibited potential of triggering antitumor immune response (33-35). Radiotherapy is an immune response modifier for immune-oncology. Irradiation to tumor cells leads to immunogenic cell death, releasing DAMPs, and activates *cGAS/STING/interferon-I* signaling, which promotes the production and release of cytokines and chemokines (36). *Interferon-I* and DAMPs (such as adenosine triphosphate and high mobility group box 1) stimulate the maturation of dendritic cells and promote the anticancer function of cytotoxic T lymphocytes and natural killer cells (13). Based on the mechanisms mentioned above, radiotherapy might improve the efficacy of immunotherapy plus anti-angiogenesis therapy. A retrospective analysis investigating PD-1/PD-L1 inhibitor plus anti-angiogenesis tyrosine kinase inhibitor plus palliative radiotherapy for advanced HCC reported an ORR of 40%, median PFS of 4.6 months and OS of 21.2 months (15). Recently, START-FIT trial reported that sequential transhepatic arterial chemoembolization and stereotactic body radiation therapy followed by avelumab as conversion therapy for patients with locally advanced, unresectable HCC achieved radiological CR rate of 42%, and 12% of patients had curative surgery (37). Herein, the ORR of irradiated tumor was 34.8% in our cohort, slightly higher than ORR of 20.4% in ORIENT-32 trial investigating an anti-PD-1 monoclonal antibody (sintilimab) plus bevacizumab biosimilar IBI305 (6), and similar to ORR of 27.3% in IMbrave150 trial evaluating atezolizumab plus bevacizumab for advanced HCC (5). The median PFS was 6.6 months, higher than that of 4.6 months in ORIENT-32 trial (6), similar to 6.8 months of PFS in IMbrave150 trial (5). The median OS was 18.3 months, similar to 19.2 months of OS in IMbrave150 trial. The 12-month OS rate was 60.9%, lower than those of 67.2% and approximately 65% in IMbrave150 and ORIENT-32 trials, respectively. When compared to a trial which investigated pembrolizumab plus lenvatinib for unresectable HCC (38), the ORR was similar, but PFS and OS of our cohort were inferior. Explanations for inferior survival here were possibly as follow. (I) Our cohort study had higher percentage of adverse prognostic factors, such as BCLC C stage, macroscopic vascular invasion, extrahepatic metastasis, cirrhosis, and hepatitis virus infection. (II) Our cohort had less treatment duration of pembrolizumab (median, 4 cycles) and bevacizumab (median, 4 cycles) due to unaffordable drug expense. Treatment durations of PD-1/PD-L1 inhibitor plus bevacizumab or lenvatinib in previous studies were more than half year (5,6,38). (III) Radiotherapy was primarily palliative in this study. Discretely distributed metastatic tumor in liver and/or extrahepatic organs could not be included in irradiation target due to dose constraints of organs at risk. For non-irradiated tumor, ORR was only 10%, lower than those of previous studies, possibly due to less duration of systemic treatment; but our DCR was 70%, similar to those of previous studies (5,6). For irradiated tumor, DCR was 91.3%, higher than previous studies (5,6). Therefore, palliative radiotherapy combined with pembrolizumab and bevacizumab predominantly helped to improved local control of tumor. To improve prognosis of advanced HCC, longer duration of anti-PD-1 immunotherapy plus bevacizumab and irradiation to all tumors should be warranted. A single-arm, phase 2, prospective trial reported sequential transhepatic arterial chemoembolization and stereotactic body radiotherapy followed by anti-PD-L1 immunotherapy as conversion therapy for locally advanced unresectable HCC and found that 55% patients were amenable to curative treatment (37).

In our study, two patients (2/3) with locally advanced, unresectable HCC achieved PR after 3.0 Gy*15 f IMRT combined with 5 cycles of pembrolizumab and 4 cycles of bevacizumab, and then had curative resection of residual tumors. This trimodal treatment might be a potential conversion therapy for selective locally advanced HCC.

Combining radiotherapy with anti-PD-1/PD-L1 inhibitor and anti-angiogenesis therapy has aroused much interest of clinicians. Regarding to HCC, there are several on-going prospective trials investigating this triple treatment (ChiCTR1900027102, NCT05010434, NCT05096715, NCT04857684, NCT05137899, ChiCTR2200056068). No prospective clinical studies have reported the toxicity profile of this trimodal therapy in advanced HCC. Consistent with results from a retrospective study comparing PD-1 inhibitor plus anti-angiogenic therapy with or without IMRT for advanced HCC (39), in our study adding intrahepatic HCC-directed external beam radiotherapy led to more hepato-toxicities, such as increase of aspartate transaminase, alanine transaminase and serum bilirubin, and more hematologic toxicities, such as anemia, thrombocytopenia, neutropenia and leukopenia. Combining radiotherapy with pembrolizumab and bevacizumab increased incidence of ≥ grade 3 toxicity, which was 78.3% in our study, comparing to 56.0% and 38.0% in ORIENT-32 trial (6) and IMbrave150 trial (5), respectively. The most common ≥ grade 3 toxicities, such as platelet decrease, leukopenia, aspartate transaminase increase and alanine transaminase increase, were probably related to intrahepatic HCC-directed radiotherapy. These could be relieved by thrombopoietin, recombinant human granulocyte stimulating factor, and hepato-protective enzyme-reducing therapy. The spectrums of adverse events observed with intrahepatic HCC radiotherapy plus pembrolizumab plus bevacizumab were consistent with the known toxicity profile of each monotherapy and manageable.

This study is limited by its small sample size and retrospective design. So far, there are no prospective trials reporting efficacy and toxicities of radiotherapy plus pembrolizumab plus bevacizumab for advanced HCC. This real-world study could shed some light on the dosing, sequencing, efficacy and toxicity profile of the tri-modal therapy.

Conclusions

Combining intrahepatic HCC-directed moderately hypo-fractionated radiotherapy with pembrolizumab and bevacizumab was shown to be an effective regimen for advanced HCC. A palliative radiotherapy did not bring unexpected and unmanageable adverse effects. This study offered a potential conversion therapy approach for advanced HCC.

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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 Ethics Board of the Fifth Affiliated Hospital of Sun Yat-sen University (No. K47-1) and informed consent was taken from all patients.

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