Efficacy and Safety of Radiotherapy Plus Anti-PD1 Versus Transcatheter Arterial Chemoembolization Plus Sorafenib For Advanced Hepatocellular Carcinoma: a Real-World Study

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Abstract

Background: The combination of transcatheter arterial chemoembolization (TACE) plus sorafenib prolonged progression-free survival (PFS) and overall survival (OS) than sorafenib or TACE monotherapy for patients with hepatocellular carcinoma (HCC). This study assessed the efficacy and safety of radiotherapy (RT) plus monoclonal antibody against programmed cell death 1 (anti-PD1) versus TACE plus sorafenib for patients with advanced HCC.

Methods: Patients with advanced HCC who treated with RT plus anti-PD1 and TACE plus sorafenib were enrolled. Objective response rate (ORR), PFS, disease control rate (DCR) and OS were calculated to assess the antitumor response and the treatment-related adverse events to the safety.

Results: Between January 2018 to March 2021, 37 patients underwent RT plus anti-PD1 and 41 patients underwent TACE plus sorafenib. The baseline characteristics between the two groups were comparable. The ORR and DCR were significantly higher in the RT+PD1 group than the TACE plus sorafenib group according to RECIST 1.1 (54.05% vs 12.20%, $P < 0.001$; 70.27% vs 46.37%, $P = 0.041$; respectively) and according to mRECIST (56.76% vs 31.71%, $P = 0.039$; 70.27% vs 46.37%, $P = 0.041$; respectively). RT plus anti-PD1 provided significantly better PFS (HR, 0.51; 95% CI 0.30-0.86; $p=0.017$) than TACE plus sorafenib. Moreover, patients with RT plus anti-PD1 had significantly higher 3-, 6-, and 9-month OS rates than those with TACE plus sorafenib (97.3% vs 92.30%, $P < 0.001$; 91.89% vs 68.60%, $P < 0.001$; 75.5% vs 60.60%, $P < 0.001$; respectively). The median OS was more favorable 17.4 months for the RT+PD1 group and 11.9 months for the TACE plus sorafenib group. No treatment-related death was observed. Grade 3 or more treatment-related adverse events (TRAEs) occurred significantly less in patients in the RT+PD1 group than the TACE plus sorafenib group (29.7% vs 75.6%, $p < 0.001$), and all TRAEs were manageable.

Conclusions: In this real-world study, RT plus anti-PD1 showed significantly promising efficacy and manageable safety than TACE plus sorafenib in patients with advanced HCC. Toxicities were manageable, with no unexpected safety signals. The study provides evidence on a new therapeutic method in the treatment of advanced HCC.

Background

Hepatocellular carcinoma (HCC) is the most common type of liver cancer, which is the 6th most common cancer worldwide and the 3rd leading cause of cancer-related death [1]. Most patients are found at an advanced stage having a poor prognosis [2, 3]. TACE, RT and sorafenib are recommended as standard treatments for the patients with advanced HCC by The National Comprehensive Cancer Network (NCCN) guideline [4]. The new treatment strategies, combination of TACE with sorafenib, is proved to be a well-tolerated and feasible treatment [5, 6]. The combination of TACE and sorafenib prolonged progression-free and overall survival times than sorafenib or TACE monotherapy, and was indicated to be a promising treatment in patients with unresectable HCC [7–9].

With the rapid improvement of RT technology and equipment, the curative effect of RT for HCC has been significantly improved in recent years. Hypofractionated RT has also been shown to be effective in patients with HCC through excellent local control, downstaging, conversion from unresectable to resectable status, and treatments of unresectable HCC with vessel invasion or multiple intrahepatic metastases [10–12].

The anti-PD1 has emerged to play a promising role in the treatment of HCC over the last few years [13]. RT can undergo a so-called immunogenic death inducing in situ vaccination and render the tumor microenvironment conducive to effector T-cell recruitment and function to produce a synergistic anti-tumor immunity with anti-PD1 for durable disease control [14]. Early clinical trials combining RT with anti-PD1 showed clinical activity in several cancers including non-small cell lung cancer [15], malignant pigmented tumor [16], and pancreatic adenocarcinoma [17]. A case report including 5 cases showed the impressive tumor control in patients with advanced HCC treated by the combination of RT and anti-PD1 [18].

To the best of our knowledge, there has been rare study to directly compare the efficacy and safety of anti-PD1 plus RT versus other strategies in the treatment of advanced HCC. Therefore, we performed this real-world study to evaluate the efficacy and safety of anti-PD1 plus RT versus TACE plus sorafenib in the treatment of advanced HCC, and seek a new approach for the treatment of advanced HCC.

Methods

Study design and patients

This is a real-world study that was conducted at Guangxi Medical University Cancer Hospital, Nanning, China. Consecutive patients were identified via the electronic medical records from January 2018 to March 2021. Of these patients, 99 patients with advanced HCC were screened and 78 patients were included based on the following chief eligibility criteria: (a) patients with advanced HCC not fit for radical cures such as hepatic resection or local ablation and Barcelona Clinic Liver Cancer (BCLC) B or C stage, (b) diagnosed according to histopathology, the European Association for the Study of the Liver (EASL) criteria [19] or American Association for the Study of Liver Diseases (AASLD) [20], (c) received RT plus at least one cycle synchronous, or sequential anti-PD1 or TACE plus synchronous or sequential oral sorafenib, (d) had at least one measurable lesion based on Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 [21] and an Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1, (e) aged between 18 and 70 years, (f) had Child-Pugh class A or B liver function, (g) an observation period of ≥ 1 months. The key exclusion criteria were patients combined intrahepatic cholangiocarcinoma, with incomplete medical information or lost to follow-up, treatment duration of sorafenib less than 1 month. A total of 78 patients were enrolled in this study with 37 in the RT + PD1 group and 41 in the TACE + sorafenib group.

The study was conducted with approval from the institutional ethics committee of Guangxi Medical University Tumor Hospital. The patient's informed consent was obtained from all participants.

Anti-PD1 therapy

In the RT + PD1 group, anti-PD1 included pembrolizumab (Merck Sharp & Dohme Co., Inc.), camrelizumab (Jiangsu HengRui Medicine Co., Ltd.), toripalimab (Shanghai Junshi Biosciences Co., Ltd), tislelizumab (BeiGene), and sintilimab (Innovent Biologics [Suzhou] Co. Ltd.). Dose, method of injection and duration of anti-PD1 were according to the manufacturers instructions. The anti-PD1 were recommended to be used continually every 2 or 3 weeks until disease progression, or intolerable toxicity.

Hypofractionated intensity modulated radiotherapy

All patients treated with RT + PD1 underwent enhanced CT scan at 2.5-5mm slice thickness for hypofractionated intensity modulated radiotherapy (hypo-IMRT) planning. Gross tumor volume (GTV) was defined as tumor focus that was visualized on contrast imaging. The clinical target volume (CTV) was defined as GTV plus a margin of 4 ~ 5 mm as described before [22]. The target volumes and organs at risk (OARs) were contour in the MIM 6.8 system (MIM, USA). Whenever conditions permitted, CT-positron emission tomography (PET-CT) fusion and CT-magnetic resonance imaging (MRI) fusion were performed. For patients with multiple metastases, 1-5 lesions were chosen for hypo-IMRT at the discretion of the radiation oncologists. The planned target volume (PTV) was defined as GTV or CTV plus asymmetrical dilation of 1 cm in craniocaudal direction and 5 mm in axial direction to set uncertainty and respiratory movement. The hypo-IMRT plans were designed using the Monaco treatment planning system (TPS) (version 5.1) or Pinnacle 3 system (Philips, Netherlands), and performed by volumetric-modulated arc therapy (VMAT) or intensity modulated radiotherapy (IMRT). The RT was delivered daily over five fractions per week, using a 6 MV X-ray linear accelerator (ELEKTA Versa-HD). Cone-beam computed tomographic (CBCT) images were used to correct the positions.

Sorafenib therapy

In the TACE + sorafenib group, patients treated with sorafenib were prescribed with two tablets of sorafenib (200 mg tablet) twice daily (800 mg/day). If unacceptable treatment-related toxicity or disease progression occurs, dose reduction and treatment termination are allowed.

Transarterial chemoembolization

TACE was performed as described before [23]. Briefly, all patients in the TACE + sorafenib group underwent selective arteriography of the hepatic artery to locate *the* tumors and the percutaneous femoral artery was punctured using the Seldinger technique. The combination of local chemotherapy drug solution (cisplatin 80 mg/m² or pirarubicin 60–80 mg) and drug carriers (lipiodol or ethiodized poppy seed oil 5–15 mL) was introduced into the tumor. And blank CalliSpheres R microspheres was used to embolize the feeding artery of tumors Complete embolization of the tumor supplying artery with no tumor staining observed by angiography at the end of procedure was defined as a technical success. TACE was performed 1 to 2 months before or after sorafenib and repeated one to six times (median,3) at 3–6-week intervals if the patient could tolerate and consent of further treatment.

Evaluation of efficacy and safety

The on-study date was defined as the day of acceptance of informed consent of sorafenib or hypo-IMRT planning. All TRAEs were recorded from on-study date until 30 days after last anti-PD1 injection or sorafenib, last follow-up as appropriate according to the Common Terminology Criteria for Adverse Events of the National Cancer Institute v5.0 (CTCAE 5.0). To evaluate tumour responses, RECIST 1.1 and modified Response Evaluation Criteria in Solid Tumors (mRECIST) [24] were used, respectively. The OS was defined as the on-study date to death from any cause. PFS was defined as the on-study date until disease progression or death. the ORR was defined as the proportion of patients with complete response (CR) or partial response (PR). Disease control was defined as the sum rate of CR + PR + stable disease (SD). All patients received follow-up visits every month for progression and survival status.

Statistical analysis

The data of all patients was collected through electronic medical records and enter the data into Research Electronic Data Capture (REDCap) [25]. Through the normal distribution test by visualization on a histogram and with Kolmogorov-Smirnov tests, the continuous variables conforming to the normal distribution were expressed as the mean $\pm$ standard deviation and visualized on a histogram and with Kolmogorov-Smirnov tests. The categorical variables were expressed as number and percentage. The t-test was used for the continuous variables conforming to normal distributions, and the Pearson's chi-square tests was used for categorical variables. OS and PFS were calculated and median OS and PFS were estimated for both groups by using Kaplan-Meier methods with the values compared using the Breslow generalized Wilcoxon test [26]. HR and CI were estimated using univariate Cox proportional risk model, and statistical analysis and forest mapping were performed using R 4.0.5 for the subgroups. All statistical tests were two tailed. IBM SPSS software (ver. 26.0 SPSS Inc., Chicago, IL, USA) was used for the statistical analysis unless otherwise indicated.

Results

Patients

Of the 78 patients with advanced HCC enrolled, 37 (47.4%) were in the RT+PD1 group and 41 (52.6%) were in the TACE + sorafenib group (Fig. 1). The baseline characteristics of these patients were summarized and comparable between the two groups (Table 1). There were no significant differences in the distribution of gender, age, bodyweight, chronic hepatitis B/C virus infection, liver cirrhosis, alpha fetoprotein, albumin–bilirubin (ALBI) grade, maximum tumor diameter, macrovascular invasion, BCLC stage, hemoglobin, platelet count, white blood cell, and prior therapy between the two groups (Table 1). In the RT+PD1 group, 31 patients (83.78%) had underlying diseases of chronic hepatitis B virus infection (HBV), 18 (48.65%) with the alpha-fetoprotein (AFP) level ≥ 400 , 16 (43.24%) with the macrovascular invasion (MVI), 8 (21.62%) had HCC with the largest diameter ≥ 10 cm, and 33 (89.19%) were categorized as BCLC stage C. And in the TACE plus sorafenib group, 31 patients (73.80%) have HBV, 19 (45.24%) with

the alpha-fetoprotein (AFP) level ≥ 400 , 24 (57.14%) with MVI, 13 (30.95%) had HCC with the largest diameter ≥ 10 cm, and 32 (76.19%) were categorized as BCLC stage C. Patients with extrahepatic metastasis were more prevalent in the RT+PD1 group than in the TACE + sorafenib group (59.5% vs. 35.7%, respectively, $p=0.044$), while Albumin ($<35\text{g/L}$) were more common in the TACE plus sorafenib group than in the TACE plus RT group (76.2% vs 46.0%, respectively; $p=0.010$).

Table 1
Patient baseline demographic and clinical characteristics.

Variables	RT+PD1, N=37 (%)	TACE + Sorafenib, N=41(%)	P value
			RT+PD1 vs TACE + sorafenib
Gender, male	35(94.60%)	37(90.24%)	0.678
Age, year	54.16±10.68	51.71±9.571	0.288
Bodyweight, kg	63.58±9.96	65.06±10.84	0.534
Hepatitis B, present	31(83.78%)	30(73.17%)	0.286
Hepatitis C, present	1(2.70%)	5(12.2%)	0.204
Liver cirrhosis, present	17(45.95%)	26(63.41%)	0.171
Alpha fetoprotein, ≥400 ng/ml	18(48.65%)	18(43.90%)	0.820
ALBI grade, ≤ 2	36 (97.3%)	38 (93.7%)	0.617
blood bilirubin, ≥21umol/L	9(24.32%)	14(34.15%)	0.457
Albumin, <35g/L	17(45.95%)	31(75.61%)	0.010
hemoglobin, <131g/L	22(59.46%)	19(46.34%)	0.266
Platelet count, <100*10 ⁹ /L	7(18.92%)	6(14.63%)	0.763
white blood cell, <3.97*10 ⁹ /L	7(18.92%)	4(9.76%)	0.333
Maximum tumor diameter, cm	7.30(4.75-8.65)	6.20(4.15-10.80)	0.860
Maximum tumor diameter, ≥10cm	8(21.62%)	13(31.71%)	0.444
Macrovascular invasion, present	16(43.24%)	24(58.54%)	0.257
Extrahepatic metastasis, present	22(59.46%)	14(34.15%)	0.040
BCLC stage			0.147
B	4(10.81%)	10(24.39%)	
C	33(89.19%)	31(75.61%)	
Prior therapy			
TACE, present	11(29.73%)	10(24.39%)	0.619

Data are mean ± standard deviation, median (IQR) or N (%).

RT, radiotherapy; PD1, the monoclonal antibody against programmed cell death 1;TACE, transcatheter arterial chemoembolization; ALBI, albumin–bilirubin; BCLC, Barcelona Clinic Liver Cancer.

Variables	RT+PD1, N=37 (%)	TACE + Sorafenib, N=41(%)	Pvalue
			RT+PD1 vs TACE + sorafenib
Hepatectomy, present	16(43.24%)	14(34.15%)	0.487
Systemic therapy, present	6(16.22%)	6(14.63%)	1.000
Data are mean ± standard deviation, median (IQR) or N (%).			
RT, radiotherapy; PD1, the monoclonal antibody against programmed cell death 1;TACE, transcatheter arterial chemoembolization; ALBI, albumin–bilirubin; BCLC, Barcelona Clinic Liver Cancer.			

In the RT+PD1 group, patients received median 5 (1-20) cycles anti-pd1 including 32 patients with camrelizumab (SHR-1210, Jiangsu HengRui Medicine Co., Ltd.) [27], 3 with sintilimab (IBI308, Innovent Biologics [Suzhou] Co. Ltd.) [28], 2 with tislelizumab (BGB-A317, BeiGene) [29]. All patients with much more lesions than hypo-IMRT targets received hypo-IMRT median dose 40 Gy (rang 30-60 Gy) with median 4 Gy per fractions (rang 3-5 Gy per fractions). The median duration of sorafenib therapy was 6.5 (rang 1-20) months and the median number of TACE sessions was 2 (rang 1-6) in the TACE + sorafenib group.

At data cutoff, 14 (37.8%) patients had received subsequent therapy including 1 received TACE plus hepatectomy, 2 received regorafenib, 2 received sorafenib, 2 received lenvatinib, 3 received TACE, and 4 received apatinib in the RT+PD1 group after disease progression. As to the TACE + sorafenib group, 16 (39.0%) patients had received subsequent therapy including one received radiofrequency ablation plus anti-PD1, 1 received hepatectomy plus anti-PD1, 1 received lenvatinib, 1 received lenvatinib plus anti-PD1, 1 received apatinib, 1 received regorafenib plus anti-PD1, 2 received hepatectomy, and 10 received anti-PD1.

Radiologic response after treatment

The median follow-up of the patients in the RT+PD1 group was 13.4 months (95% CI 12.1–14.6), and in the TACE plus sorafenib group was 16.6 months (95% CI 14.9–18.3), $p = 0.034$. The tumor responses are presented in Table 2. the PR rate, ORR and DCR were significantly higher in the RT+PD1 group than the TACE plus sorafenib group according to RECIST 1.1 (54.05% vs 12.20%, $P < 0.001$; 54.05% vs 12.20%, $P < 0.001$; 70.27% vs 46.34%, $P = 0.041$; respectively) and according to mRECIST (56.76% vs 31.71%, $P = 0.039$; 54.05% vs 12.20%, $P < 0.001$; 70.27% vs 46.34%, $P = 0.041$; respectively). Best percent change from baseline in sum of longest diameters for target lesions per patient in the two groups is shown in the waterfall plot (Fig. 2), where Fig. A, B, C, and D represent the results in the RT+PD1 group based on RECIST 1.1, the TACE plus sorafenib group based on RECIST 1.1, the RT+PD1 group based on mRECIST, and the TACE plus sorafenib group based on mRECIST, respectively.

Table 2
Summary of efficacy outcomes.

Variables	RT+PD1, N=37 (%)	TACE + Sorafenib, N=41(%)	P value
According to RECIST 1.1			
Confirmed objective response	20 (54.05%)	5(12.20%)	< 0.001
Time to response, months, (IQR)	1.80(1.57-2.00)	2.87(1.407-6.86)	0.467
Disease control	26(70.27%)	19(46.34%)	0.041
Best overall response			
CR	0(0)	0(0)	1.000
PR	20 (54.05%)	5(12.20%)	< 0.001
SD	6(16.22%)	14(34.15%)	0.118
PD	11(29.73%)	22(53.66%)	0.041
Progression-free survival, months, median, (95% CI)	5.86(3.19-8.53)	3.70(2.60-4.80)	0.017
According to mRECIST			
Confirmed objective response	21(56.76%)	13(31.71%)	0.039
Time to response, months, (IQR)	1.85(1.60-2.98)	1.47(0.80-2.60)	0.061
Disease control	26(70.27%)	19(46.34%)	0.041
Best overall response			
CR	1(2.70%)	1(2.44%)	1.000
PR	20 (54.05%)	12(29.27%)	0.038
SD	5(13.51%)	6(14.63%)	0.774
PD	11(29.73%)	22(53.66%)	0.041
Progression-free survival, months, median, (95% CI)	5.86(3.19-8.53)	3.70(2.60-4.80)	0.019
Overall survival			

Data are n (%; 95% CI), unless indicated.

RT, radiotherapy; PD1, the monoclonal antibody against programmed cell death 1;TACE, transcatheter arterial chemoembolization; RECIST 1.1, Response Evaluation Criteria in Solid Tumors 1.1; mRECIST, modified Response Evaluation Criteria in Solid Tumors; CR, Complete response; PR, Partial response; SD, Stable disease; PD, Progressive disease.

Variables	RT+PD1, N=37 (%)	TACE + Sorafenib, N=41 (%)	P value
3-month, %	97.30%	92.30%	< 0.001
6-month, %	91.90%	68.60%	< 0.001
9-month, %	75.50%	60.60%	< 0.001
12-month, %	52.20%	47.5%	0.061
Overall survival, months, median, (95% CI)	11.90 (6.35-17.45)	17.40 (8.69-26.11)	0.146
Data are n (%; 95% CI), unless indicated.			
RT, radiotherapy; PD1, the monoclonal antibody against programmed cell death 1; TACE, transcatheter arterial chemoembolization; RECIST 1.1, Response Evaluation Criteria in Solid Tumors 1.1; mRECIST, modified Response Evaluation Criteria in Solid Tumors; CR, Complete response; PR, Partial response; SD, Stable disease; PD, Progressive disease.			

Progression-free survival analysis

Progression of the disease was observed in 37 of the patients (47.4%) who underwent RT+PD1 and 41 of the patients who underwent TACE plus sorafenib group (52.8%) during follow-up. Patients in the PD1+RT group had significant better PFS compared with those in the TACE + sorafenib group (5.86 vs 3.70 months; HR, 0.51; 95% CI 0.30-0.86; $p=0.017$; Table 2 and Fig. 3). The median PFS in the PD1+RT group had significant longer than TACE + sorafenib group across subgroups based on age ≥ 53 , infection of hepatitis B (HBV), the maximum tumor diameter <10 cm, MVI, without extrahepatic metastasis, BCLC stage C, no prior TACE, prior hepatectomy, and no prior systemic therapy ($p = 0.01, 0.04, 0.031, 0.024, 0.049, 0.0067, 0.044, 0.024$ and 0.016 ; respectively, Fig. 4A). The effect of the two groups on median PFS was consistent across subgroups based on other baseline characteristics (Fig. 4A).

Overall survival analysis

Among the 37 patients in the RT+PD1 group, 18 are still alive, 18 have died, and 1 is lost to follow-up by the end of this study. Among the 41 patients who received TACE plus sorafenib, 13 are still alive, 25 have died, and 3 are lost to follow-up. The 3-, 6-, and 9-month OS rates were significant better in the RT+PD1 group than that in the TACE plus sorafenib (97.3% vs 92.30%, $P < 0.001$; 91.89% vs 68.60%, $P < 0.001$; 75.5% vs 60.60%, $P < 0.001$; respectively, Table 2). The median OS was 17.4 months for the RT+PD1 group and 11.9 months for the TACE plus sorafenib group (HR: 0.70, 95% CI, 0.38-1.30, $P=0.146$; Table 2 and Fig. 3B). There were no significant differences for the median OS in the distribution of the two groups, but a trend toward a more favorable outcome in the RT+PD1 group.

Patients in the RT+PD1 group had statistically significant better OS than those in the TACE plus sorafenib group with AFP level ≥ 400 ng/ml, BCLC stage C and MVI (11.8 vs 9.7 months, $P = 0.026$; 11.8 vs 9.7 months, $P = 0.031$; 11.8 vs 9.7 months, $P = 0.026$; respectively, Fig. 5). Although, there had not significant better OS with BCLC stage C and MVI using univariate Cox proportional risk model and R 4.0.5. The effect of the two groups on median OS was consistent across subgroups based on other baseline characteristics (Fig. 4B).

Safety profile

The TRAEs, which occurred in $\geq 10\%$ of patients, are summarized in Table 3. No deaths were attributed to TRAEs in this study. The TRAEs in the RT+PD1 group show less than in the TACE plus sorafenib group, including increased AST (54.05% vs 92.68%, $p < 0.001$), increased AST (51.35% vs 80.49%, $p=0.008$), hand-foot skin reaction (HFSR) (0% vs 53.66%, $p < 0.001$). Decreased hemoglobin was more frequent in the RT+PD1 group than in the TACE plus sorafenib group (89.19% vs 68.29%, $p=0.031$). There were no differences in regard to other TRAEs such as decreased albumin, decreased white blood cell, increased blood bilirubin and decreased platelet count. Grade 3 or more TRAEs occurred significantly less in patients in the RT+PD1 group than the TACE plus sorafenib group (29.7% vs 75.6%, $p < 0.001$). The major grade 3 or more TRAEs were observed significantly milder in the RT+PD1 group than in the TACE plus sorafenib group, including increased aspartate aminotransferase (AST) (58.54%% vs 5.41%, $p=0.000$), increased alanine aminotransferase (ALT) (36.59% vs 5.41%, $p=0.001$) and hand-foot skin reaction (14.63% vs 0%, $p=0.027$). The two groups did not differ in terms of other grade 3 or more TRAEs including decreased hemoglobin, decreased albumin, decreased white blood cell, increased blood bilirubin and decreased platelet count.

Table 3. Treatment-related adverse events based on CTCAE 5.0.

Adverse events	RT+PD1, n=37 (%)		TACE + sorafenib, n=41 (%)		P value	
	Any grade (%)	Grade 3-4 (%)	Any grade (%)	Grade 3-4 (%)	Any grade	Grade 3-4
Increased AST	20(54.05%)	2(5.41%)	38(92.68%)	24(58.54%)	< 0.001	< 0.001
Increased ALT	19(51.35%)	2(5.41%)	33(80.49%)	15(36.59%)	0.008	0.001
Hand-foot skin reaction	0(0)	0(0)	22(53.66%)	6(14.63%)	< 0.001	0.027
Decreased hemoglobin	33(89.19%)	5(13.51%)	28(68.29%)	2(4.88%)	0.031	0.247
Decreased albumin	30(81.08%)	0(0)	37(90.24%)	1(2.44%)	0.333	1.000
Decreased white blood cell	28(75.68%)	3(8.11%)	12(29.27%)	1(2.44%)	< 0.001	0.341
Increased blood bilirubin	20(54.05%)	1(2.70%)	16(39.02%)	1(2.44%)	0.256	1.000
Decreased platelet count	19(51.35%)	8(21.62%)	14(34.115%)	5(12.20%)	0.169	0.364

Data are n (%).

CTCAE 5.0, the Common Terminology Criteria for Adverse Events of the National Cancer Institute v5.0; RT, radiotherapy; PD1, the monoclonal antibody against programmed cell death 1; TACE, transcatheter arterial chemoembolization; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Discussion

Few studies have investigated the efficacy and safety of combination RT plus anti-PD1 versus TACE plus sorafenib in the treatment of advanced HCC in the real-world study. The present observational study showed significantly better PFS and ORR with combining RT plus anti-PD1 than TACE plus sorafenib in patients with advanced HCC. The TRAEs were acceptable and milder in patients treated with RT plus anti-PD1 than with TACE plus sorafenib. Combining anti-PD1 with RT might be a potential beneficial strategy to efficiently and safely treat the patients with advanced HCC.

Sorafenib is recommended as the first-line treatment for the patients with advance HCC [4]. The outcome of patients who received sorafenib in our study are better than previous studies with consistent baseline. Patients with advanced HCC reached the median OS to 6.5 months, DCR to 35.3%, and the ORR to 3.3% in Asia Pacific patients with sorafenib [30], and 10.4 months, 64%, 4% in patients with sorafenib respectively in ORIENT-32 study [28]. Both treatments of our study achieved better outcome. Similarly, the recent

studies of combined TACE plus sorafenib have been conducted in patients with unresectable HCC, and combined treatments show an enhanced efficacy as compared to TACE or sorafenib alone [6, 8, 9, 31]. In the GIDEON study, the median OS was 12.7 months in prior-TACE group, 9.2 months in non-prior-TACE, 21.6 months in concomitant-TACE, and 9.7 months in non-concomitant-TACE one for patients treated with sorafenib, respectively. the median OS of combined TACE plus sorafenib in our study was 11.9 months (95% CI, 6.35-17.45) and was similar to the prior-TACE group but shorter than concomitant-TACE group in the GIDEON study. Notably, the tumor stage of BCLC and the rate of chronic HBV present were much higher in our study than the GIDEON study (A, 0 vs 10.5%; B, 24.39% vs 30.2%, for stage respectively; 73.17% vs 43.1% for the rate of HBV), meaning more prone to develop progressive disease and have poorer prognoses [32]. These findings suggest that combining TACE plus sorafenib contribute to the overall treatment benefit in patients with HCC.

In our real-word study, the PR rate, ORR and DCR were significantly higher in the RT+PD1 group than the TACE plus sorafenib group according to RECIST 1.1 (54.05% vs 12.20%, $P < 0.001$; 54.05% vs 12.20%, $P < 0.001$; 70.27% vs 46.34%, $P = 0.041$; respectively) and according to mRECIST (56.76% vs 31.71%, $P = 0.039$; 54.05% vs 12.20%, $P < 0.001$; 70.27% vs 46.34%, $P = 0.041$; respectively). The ORR was better than in the IMbrave150 trial (27.3%) [33] and in the REFLECT trial (24.1%) [34]. Significantly better PFS was showed in this study for patients with advanced HCC with combining RT plus anti-PD1 than TACE plus sorafenib (5.86 vs 3.70 months, HR, 0.51, $p=0.017$). The 3-, 6-, and 9-month OS rates were significant better in the RT+PD1 group than that in the TACE plus sorafenib group (97.3% vs 92.30%, $P < 0.001$; 91.89% vs 68.60%, $P < 0.001$; 75.5% vs 60.60%, $P < 0.001$; respectively). The 6-month OS rates was better in the RT+PD1 group than in the IMbrave150 trial (84.8%) [33]. There is a trend toward a more favorable median OS in the RT+PD1 group than TACE plus sorafenib (17.4 months vs 11.9 months; HR, 0.70, 95% CI, 0.38-1.30). It is worth noting that the median follow-up of the patients in the RT+PD1 group was significantly shorter than the TACE plus sorafenib group (13.4 months, 95% CI, 12.1–14.6 vs 16.6 months, 95% CI, 14.9–18.3; $p = 0.034$). These may account for no significantly better OS in the present study. Considering the statistically significant shorter in median follow-up in the RT+PD1 group than that in the TACE plus sorafenib group, the median OS and PFS were estimated for both groups by using Kaplan-Meier methods with the values compared using the Breslow generalized Wilcoxon test giving more weight to earlier events [35]. These findings suggest that both combining RT plus anti-PD1 and TACE plus sorafenib contribute to the overall treatment benefit in patients with advanced HCC.

Meanwhile, subgroup analysis for PFS and OS was done. The median PFS in the PD1+RT group had significant longer than TACE + sorafenib group across subgroups based on age ≥ 53 , infection of hepatitis B (HBV), the maximum tumor diameter ≤ 10 cm, MVI, without extrahepatic metastasis, BCLC stage C, no prior TACE, prior hepatectomy, and no prior systemic therapy ($p = 0.01, 0.04, 0.031, 0.024, 0.049, 0.0067, 0.044, 0.024$ and 0.016 ; respectively). Patients in the RT+PD1 group had statistically significant better OS than those in the TACE + sorafenib group with AFP level ≥ 400 ng/ml, BCLC stage C and MVI (11.8 vs 9.7 months, $P = 0.026$; 11.8 vs 9.7 months, $P = 0.031$; 11.8 vs 9.7 months, $P = 0.026$). Although, there had not significant better OS with BCLC stage C and MVI using univariate Cox proportional risk model and $R^2 4.0.5$. The shorter follow-up may account for no significantly better OS.

Together, these findings may help to select patients with advanced HCC who would derive an OS and PFS benefit from combining RT plus anti-PD1 and TACE plus sorafenib. However, further investigation and confirmation are needed.

The spectrum, incidence, and severity of adverse events in the TACE plus sorafenib group were consistent with the known safety profile observed in other studies[5, 7–9, 36]. The TRAEs in the RT+PD1 group were less than in the TACE plus sorafenib group, including increased AST (54.05% vs 92.68%, $p < 0.001$), increased ALT (51.35% vs 80.49%, $p=0.008$), hand-foot skin reaction (HFSR) (0% vs 53.66%, $p < 0.001$). Grade 3 or more TRAEs occurred significantly less in patients in the RT+PD1 group than the TACE plus sorafenib group (29.7% vs 75.6%, $p < 0.001$). The major grade 3 or more TRAEs were increased AST (58.54% vs 5.41%, $p=0.000$), increased ALT (36.59% vs 5.41%, $p=0.001$) and hand-foot skin reaction (14.63% vs 0%, $p=0.027$).

This study had several limitations. First, the nature of this retrospective design study was the main drawback and vulnerable to other potential biases, such as adherence and different socioeconomic status among patients. Second, the follow-up period was not long enough in the RT + PD1 group and significantly shorter than the TACE plus sorafenib group. However, the follow-up duration was sufficient to evaluate PFS and tumor response in the RT + PD1 group were better than the other group, which are more accurately reflect efficacy than OS [37]. Third, three types of anti-PD1 were used in this study and may also be a confounding factor. There have no clinical studies to compare for anti-PD1 to provide evidence of which one works best. Finally, some adverse events, such as cardiotoxicity, could not obtain in some patients due to the absence of standard hematological tests.

Conclusion

Treatment with RT plus anti-PD1 was associated with significantly better PFS, PR rate, ORR and DCR outcomes than TACE plus sorafenib in patients with advanced HCC, and better OS than TACE plus sorafenib in patients with BCLC stage C, macrovascular invasion, or AFP level ≥ 400 ng/ml. The adverse events treated with RT plus anti-PD1 were acceptable and milder than TACE plus sorafenib. Combining anti-PD1 with RT might be a novel potential beneficial strategy to treat the patients with advanced HCC. Additional follow-up and larger sample sizes are needed to draw more accurate conclusions.

Abbreviations

TACE, transcatheter arterial chemoembolization; PFS, progression-free survival; OS, overall survival; HCC, hepatocellular carcinoma; RT, radiotherapy; anti-PD1, monoclonal antibody against programmed cell death 1; ORR; objective response rate; DCR, disease control rate; HR, hazard ratio; TRAE, treatment-related adverse events; NCCN, The National Comprehensive Cancer Network; BCLC, Barcelona Clinic Liver Cancer; EASL, European Association for the Study of the Liver; AASLD, American Association for the Study of Liver Diseases; RECIST, Response Evaluation Criteria in Solid Tumors; ECOG, Eastern Cooperative Oncology Group; hypo-IMRT, hypofractionated intensity modulated radiotherapy; CTCAE 5.0, Common

Terminology Criteria for Adverse Events of the National Cancer Institute v5.0; mRECIST, modified Response Evaluation Criteria in Solid Tumors; CR, complete response; PR, partial response; SD, stable disease; ALBI, albumin–bilirubin; MVI, macrovascular invasion; HBV, chronic hepatitis B virus infection; AFP, alpha-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Declarations

Ethics approval and consent to participate:

All the procedures were carried out in accordance with the Helsinki Declaration of 1975. This study was approved by the institutional review board of Guangxi Medical University Cancer Hospital (number LW20211104). Patient consent was waived due to the retrospective nature of the study.

Consent for publication:

Not applicable.

Data availability:

The data underlying this article will be shared on reasonable request to the corresponding author.

Competing interests:

The authors have no conflict of interest to declare that are relevant to the content of this article.

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Author contributions:

XBD conceived the study; all authors participated in the acquisition of the data; LJX and DWX analyzed data; LJX, HST and LXF assessed tumor response; LJX drafted and revised the manuscript. All authors read and approved the final manuscript.

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Figures

Figure 1

Patient selection flow. HCC, hepatocellular carcinoma; TACE, transcatheter arterial chemoembolization; ICC, intrahepatic cholangiocarcinoma; RT, radiotherapy; PD1, monoclonal antibody against programmed cell death.

Figure 2

Best percentage change from baseline in sums of diameters of target lesions. (A) In the RT+PD1 group based on RECIST 1.1, (B) In the TACE plus sorafenib group based on RECIST 1.1, (C) In the RT+PD1 group based on mRECIST, (D) In the TACE plus sorafenib group based on mRECIST. RT, radiotherapy; PD1,

monoclonal antibody against programmed cell death; TACE, transcatheter arterial chemoembolization; RECIST 1.1, Response Evaluation Criteria in Solid Tumors 1.1; mRECIST, modified Response Evaluation Criteria in Solid Tumors; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Figure 3

Kaplan–Meier analysis of overall and progression free survival. (A) PFS and (B) OS for all patients. HR, hazard ratio; RT, radiotherapy; PD1, monoclonal antibody against programmed cell death; TACE, transcatheter arterial chemoembolization; OS, overall survival; PFS, progression-free survival.

Figure 4

Forest plot of PFS (A) and OS (B) in subgroups of patients. RT, radiotherapy; PD1, monoclonal antibody against programmed cell death; TACE, transcatheter arterial chemoembolization; OS, overall survival; PFS, progression-free survival; HBV, Hepatitis B; BCLC, Barcelona Clinic Liver Cancer; AFP, alpha-fetoprotein.

Figure 5

Kaplan–Meier analysis of overall and progression free survival in patient subgroups. (A) OS among patients with BCLC-C; (B) OS among patients with MVI; RT, radiotherapy; PD1, monoclonal antibody

against programmed cell death; TACE, transcatheter arterial chemoembolization; OS, overall survival; PFS, progression-free survival; BCLC-C, Barcelona Clinic Liver Cancer C stage; MVI, macrovascular invasion; AFP, alpha-fetoprotein.