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ORIGINAL RESEARCH

PD-1 Inhibitors Combined with Tyrosine Kinase Inhibitors with or without Hepatic Artery Infusion Chemotherapy for the First-Line Treatment of HBV-Related Advanced Hepatocellular Carcinoma: A Retrospective Study

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Purpose: Comparing the efficacy and safety of programmed cell death protein-1 (PD-1) inhibitors combined with tyrosine kinase inhibitors (TKIs) with or without hepatic artery infusion chemotherapy (HAIC) in HBV-related advanced HCC and exploring prognostic predictors of the combined regimen.

Patients and Methods: A total of 194 patients diagnosed with HBV-related advanced HCC between 2020 and 2022 were included in the study, including 99 in the HAIC combined with PD-1 inhibitors plus TKIs (HPT group) and 95 in the PD-1 inhibitors plus TKIs (PT group). The efficacy was evaluated according to the tumor response rate and survival, and the safety was evaluated according to the adverse events.

Results: The HPT group showed higher overall response rate and disease control rate than the PT group. The median overall survival (OS) of the HPT group and the PT group were 18.10 months and 12.57 months, respectively, and the difference was statistically significant (hazard ratio (HR) = 0.519, 95% confidence interval (CI): 0.374–0.722, P < 0.001). The median progression-free survival (PFS) was 9.20 months in the HPT group and 6.33 months in the PT group (HR = 0.632, 95% CI: 0.470–0.851, P = 0.002). In addition, albumin bilirubin (ALBI) and systemic inflammatory response index (SIRI) are independent prognostic factors affecting HAIC combined with targeted immunotherapy and can be used as prognostic predictors. Almost all patients included in the study experienced treatment-related adverse events (TRAEs) of varying degrees of severity, with grade 1–2 adverse events predominating.

Conclusion: The HPT group had better OS and PFS than the PT group in patients with HBV-related advanced HCC. In addition, high ALBI and high SIRI were associated with poor prognosis in the HAIC combined group.

Keywords: hepatocellular carcinoma, hepatic artery infusion chemotherapy, programmed cell death protein-1, tyrosine kinase inhibitors, systemic inflammatory response index, albumin-bilirubin

Introduction

Hepatocellular carcinoma (HCC) is the sixth most commonly diagnosed cancer and the third leading cause of cancer death worldwide, and the fourth highest incidence of malignant tumors in greater China, accounting for about 50% of the total number of new cases in the world each year.[1] About 50%–80% of HCC cases globally are caused by HBV infection and the incidence of HBV-related HCC is higher in eastern Asian.[2] HBV-related HCC falls under the category of the proliferative subtype, distinguished by inadequate differentiation, aggressiveness, and the coexistence of macrovascular

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invasion or extrahepatic metastasis.[3] Although targeted and immune drugs have been used in patients with HBV-related advanced HCC, the 5-year survival rate is still less than 20%.[4]

Sorafenib is the first TKI drug approved for first-line treatment of advanced HCC, but it has been shown to be less effective in patients with HBV-related HCC than in patients without HBV infection.[5,6] Lenvatinib (REFLECT)[7] is non-inferior to sorafenib for the first-line treatment of primary unresectable HCC and has a longer time to progression and better tumor response in patients with chronic hepatitis B-associated HCC.[7,8] However, with targeted therapy alone, patients are prone to progression and drug resistance. PD-1/PD-L1 inhibitors are commonly used immune drugs in clinical practice. Nonetheless, single-agent PD-1/PD-L1 inhibitors did not show an advantage over sorafenib in prolonging the overall survival of patients with advanced HCC in the first line.[9,10]

In addition, the IMbrave150 study showed that PD-L1 inhibitor combined with VEGF inhibitor (atezolizumab-bevacizumab) had good efficacy and safety in the first-line treatment of patients with advanced HCC, but the HBV infection rate of the patients enrolled in this study was less than 50%.[11] And a large-scale study of first-line treatment for HBV-related HCC suggests that PD-1 inhibitor in combination with VEGF inhibitor (sintilimab-bevacizumab biosimilar) have superior long-term survival data for HBV-infected HCC patients than non-HBV-infected HCC patients.[12]

Hepatic artery infusion chemotherapy (HAIC), as a local treatment modality, allows chemotherapeutic drugs to directly enter the tumor supplied by the hepatic artery in a local concentration-increasing manner, and provides strong anti-tumor effect and low systemic toxicity through the first-pass effect of the liver.[13] At present, retrospective studies have pointed out the efficacy and safety of HAIC combined with PD-1 inhibitors plus TKIs in patients with advanced HCC, but there is still a lack of research on HBV-related HCC.[14–16] Moreover, there are deficiencies in the survival prediction indicators of the combined treatment method, which we analyzed the inflammatory indicators and liver function indicators.

Material and Methods

The Inclusion and Exclusion Criteria

Patients with HBV-related advanced HCC admitted to the Harbin Medical University Cancer Hospital from 2020 to 2022 were included in this study. The inclusion criteria were as follows: (1) Patients with HCC diagnosed by pathology and imaging; (2) No systemic therapy prior to HPT and PT treatment; (3) Received at least two cycles of HPT or PT with at least one efficacy evaluation; (4) Eastern Cooperative Oncology Group (ECOG) Score: 0–1; (5) Child-Pugh grade: A or B. Exclusion criteria were as follows: (1) Irregular treatment or lack of complete clinical information; (2) Combined with other primary tumors; (3) The absence of measurable target lesions; (4) No complete follow-up information; (5) HCC caused by non-HBV infection.

Therapeutic Regime

After reviewing the case data of the patients included in this study, the patients were divided into HPT group (HAIC + PD-1 inhibitors + TKIs) and PT group (PD-1 inhibitors + TKIs) according to the treatment regimen during admission. PD-1 inhibitors mainly include camrelizumab and sintilimab, as well as TKIs mainly include lenvatinib and sorafenib. FOLFOX (fluorouracil + oxaliplatin) regimen was used in HAIC.

Research Methodology

Clinical Information

Clinical information includes the patient's name, gender, age, height, weight, time of first HCC diagnosis, degree of histologic differentiation, history of radical surgery, the largest lesion size in the liver, number of intrahepatic tumors, presence of extrahepatic metastases and specific organs of metastases, presence of portal or hepatic vein tumor thrombus, whether to use HAIC therapy in combination, different types of PD-1 inhibitors and TKIs, ECOG score, Child-Pugh grade, hematological examination (alanine aminotransferase, aspartate aminotransferase, total bilirubin, serum albumin, peripheral blood monocyte count, lymphocyte count, hemoglobin count, leukocyte count, neutrophil count, platelet

count, α-fetoprotein (AFP) level), imaging examination, the time and reason of first-line progress, evaluation of tumor efficacy, adverse events, survival status up to the last follow-up, time and cause of death, and so on.

Response Evaluation Criteria

The tumor response of the two groups was evaluated by the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST1.1) and the modified RECIST1.1 (mRECIST) criteria, respectively, and was further divided into complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). Objective response rate (ORR) is the proportion of CR and PR patients, as well as disease control rate (DCR) is the proportion of patients other than those with PD. Treatment-related adverse events (TRAEs) were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.

Follow-Up

The follow-up was carried out by re-admission to hospital and telephone contact, with the last follow-up in July 2023. The primary endpoint of this study was OS, defined as the time from the first treatment to death from any cause. Secondary endpoints included PFS, which was defined as the time from the beginning of the HPT or PT treatment to the first tumor progression or death, ORR, DCR and adverse events.

Statistical Methodology

Statistical analyses were performed using SPSS v27.0 software (IBM, Armonk, NY, USA) and the graph were generated using GraphPad Prism 9.0 software. Measurement data with normal distribution were expressed as mean ± standard deviation, and independent sample *t* test was used for comparison between groups. Count data were described as the number of cases (percentage), and the comparison between groups was performed by chi-square test or Fisher's exact test. Survival outcomes were calculated using the Kaplan-Meier method and the survival rate was compared with a Log-rank test. Influential factors were analyzed using the COX hazard regression model, and all variables with a p-value < 0.05 in the univariate analysis were subjected to multivariate analysis. The hazard ratio (HR) and 95% confidence intervals (CI) were calculated. All p-values were two-sided, with p-values < 0.05 considered statistically significant.

Results

Analysis of Clinical Data

From January 2020 to December 2022, a total of 652 patients were treated with HPT or PT regimen, but 194 patients who met the inclusion criteria were enrolled in this retrospective study, and these patients were divided into HPT group (n=99) and PT group (n=95). The exclusion of patients in this study is shown in Figure 1 and the baseline characteristics of the 194 patients included are summarized in Table 1. In both the HPT and PT groups, the range of cycles of PD-1 inhibitors combined with TKIs was 2–14, with a median of 6 cycles in the HPT group, while a median of 5 cycles in the PT group. The EOCG scores of all patients included ranged from 0 to 1, and was predominantly male (159/194, 81.96%).

In all, 116 patients (59.79%) had macrovascular invasion. In the HPT group (59/99, 59.60%), 33 patients had portal vein tumor thrombus (PVTT), 8 patients had hepatic vein tumor thrombus (HVTT), and 18 patients had both PVTT and HVTT. In the PT group (57/95, 60.00%), 49 cases had PVTT, 3 cases had HVTT, and 5 cases had both PVTT and HVTT. The overall intrahepatic metastasis rate was 81.96% (HPT: PT = 82.83%: 81.05%) and the overall extrahepatic metastasis rate was 70.10% (HPT: PT = 65.66%: 74.74%), as well as the most common extrahepatic metastatic organ was the lungs in both groups. The results showed that there was no statistical difference between the two groups in terms of gender, age, BMI, etiology, Child-Pugh classification, ECOG, maximum tumor size, tumor number, intrahepatic metastasis, extrahepatic metastasis, types of PD-1 inhibitors, types of TKIs, histological differentiation, surgery, ALBI, AFP, NLR, PLR, MLR, SII, SIRI (all p value > 0.05). However, there were differences between the two groups in terms of macrovascular invasion (P = 0.005). (Table 1).

Efficacy Analysis

By the end of the last follow-up (July 31, 2023), a total of 92.27% of patients (179/194) had disease progression and 79.90% of the patients (155/194) had reached the mortality endpoint. The OS and PFS of the HPT group were

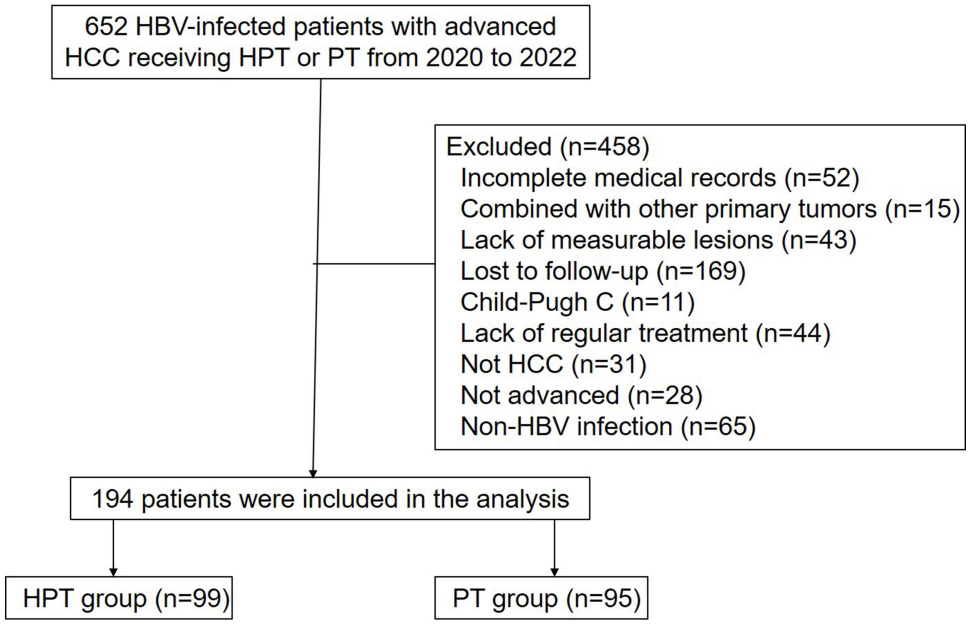

Figure 1 Patient screening flowchart.
Abbreviations: HCC, hepatocellular carcinoma; HPT, hepatic artery infusion chemotherapy combined with programmed cell death protein-1 inhibitors plus tyrosine kinase inhibitors; PT, programmed cell death protein-1 inhibitors plus tyrosine kinase inhibitors.

significantly longer than those of the PT group. The 3-, 6-, 12- and 15-month OS of the HPT group were 100%, 94.9%, 64.6% and 52.5%, respectively, and in the PT group, the OS at 3, 6, 12, and 15 months were 95.8%, 73.7%, 43.2% and 23.2%, respectively. The median OS of patients treated with combined with HAIC was significantly longer than that of patients treated with targeted combined immunotherapy alone by 5.53 months, which was 18.10 months (95% CI: 15.069–21.131) and 12.57 months (95% CI: 9.775–15.365) in the two groups, respectively (HR = 0.519, 95% CI: 0.374–

Table 1 Baseline Clinical Characteristics

Variables	HPT (n=99)	PT (n=95)	*p*-value
Combined with HAIC	Yes	No	< 0.001
Age, years	56.40 ± 8.70	57.11 ± 8.60	0.573
Sex			0.959
Male	81	78	
Female	18	17	
BMI, kg/m^2	22.42 ± 3.37	21.66 ± 2.75	0.860
Child-Pugh			0.424
A	70	72	
B	29	23	
ECOG			0.161
0	26	17	
1	73	78	
ALBI			0.514
< −2.59	41	35	
≥ −2.59	58	60	

(*Continued*)

Table 1 (Continued).

Variables	HPT (n=99)	PT (n=95)	*p*-value
Maximum tumor size, cm			0.101
≤ 10	51	60	
> 10	48	35	
Tumor number			0.375
Solitary	17	12	
Multiple	82	83	
Macrovascular invasion			0.005
Absent	40	38	
PVTT	33	49	
HVTT	8	3	
Both PVTT and HVTT	18	5	
Intrahepatic metastasis			0.748
Absent	17	18	
Present	82	77	
Extrahepatic metastasis			0.408
Absent	34	24	
Lung	30	33	
Bone	4	9	
Celiac lymph nodes	26	23	
Others	5	6	
Differentiation degree			0.080
Well	13	5	
Moderately	17	22	
Poorly	27	36	
Unknown	42	32	
Types of PD-1 inhibitors			0.945
Camrelizumab	80	75	
Sintilimab	14	15	
Others	5	5	
Types of TKIs			0.975
Lenvatinib	83	80	
Sorafenib	7	6	
Others	9	9	
Surgery			0.168
Yes	21	13	
No	78	82	
AFP, ng/mL			0.252
≤ 400	45	51	
> 400	54	44	

(*Continued*)

Table 1 (Continued).

Variables	HPT (n=99)	PT (n=95)	*p*-value
NLR			0.322
< 3	56	47	
≥ 3	43	48	
PLR			0.244
< 108.47	37	28	
≥ 108.47	62	67	
MLR			0.185
< 0.31	37	27	
≥ 0.31	62	68	
SII			0.862
< 532.22	54	53	
≥ 532.22	45	42	
SIRI			0.181
< 1.33	48	37	
≥ 1.33	51	58	

Notes: HPT, hepatic artery infusion chemotherapy combined with programmed cell death protein-1 inhibitors plus tyrosine kinase inhibitors; PT, programmed cell death protein-1 inhibitors plus tyrosine kinase inhibitors; SII, multiplying the platelet count by the neutrophil count divided by the lymphocyte count; SIRI, multiplying the monocyte count by the neutrophil count divided by the lymphocyte count.

Abbreviations: HAIC, hepatic artery infusion chemotherapy; BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; ALBI, albumin-bilirubin; PVTT, portal vein tumor thrombus; HVTT, hepatic vein tumor thrombus; PD-1, programmed cell death protein-1; TKIs, tyrosine kinase inhibitors; AFP, α-fetoprotein; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; SII, systemic immune inflammation index; SIRI, systemic inflammatory response index.

0.722, P < 0.001). The median PFS in the HPT group was 9.20 months (95% CI: 7.717–10.683) compared to 6.33 months (95% CI: 4.566–8.094) from the PT group (HR = 0.632, 95% CI: 0.470–0.851, P = 0.002). The OS and PFS survival curves in both groups are presented as in Figure 2.

A total of 64 cases (64/194, 32.99%) reached PR, 109 cases (109/194, 56.19%) reached SD, and 21 cases (21/194, 10.82%) reached PD according to RECIST version 1.1 criteria, whereas a total of 83 cases (83/194, 42.78%) reached PR, 90 cases (90/194, 46.39%) reached SD, and 21 cases (21/194, 10.82%) reached PD according to mRECIST criteria. Based on the RECIST version 1.1 criteria, the ORR and DCR in HPT group were significantly higher than those in PT group, 43.4% versus 22.1% (P = 0.002) and 94.9% versus 83.2% (P = 0.008), respectively. Based on the mRECIST criteria, compared with the PT group, the HPT group also had higher ORR and DCR, which were 53.5% versus 31.6% (P = 0.002) and 94.9% versus 83.2% (P = 0.008), respectively. Table 2 summarizes the overall response of the tumor and the remission of the two groups of intrahepatic target lesions as shown in Figure 3.

Analyzing Influencers

To sum up, both PFS and OS were significantly improved in the HPT group compared with the PT group. The OS of the HPT group was 5.53 months longer than that of the PT group (18.10 months versus 12.57 months, P < 0.001), and the PFS was extended by 2.87 months (9.20 months versus 6.33 months, P = 0.002). Univariate COX regression analysis in the combined HAIC treatment group showed that Child-Pugh A, smaller liver tumor size, high histologic differentiation, ALBI<-2.59, NLR<3, and SIRI<1.33 were associated with better survival (all p value < 0.05). The above factors were included in COX multivariate regression analysis. Multivariate COX regression analysis indicated that Child-Pugh

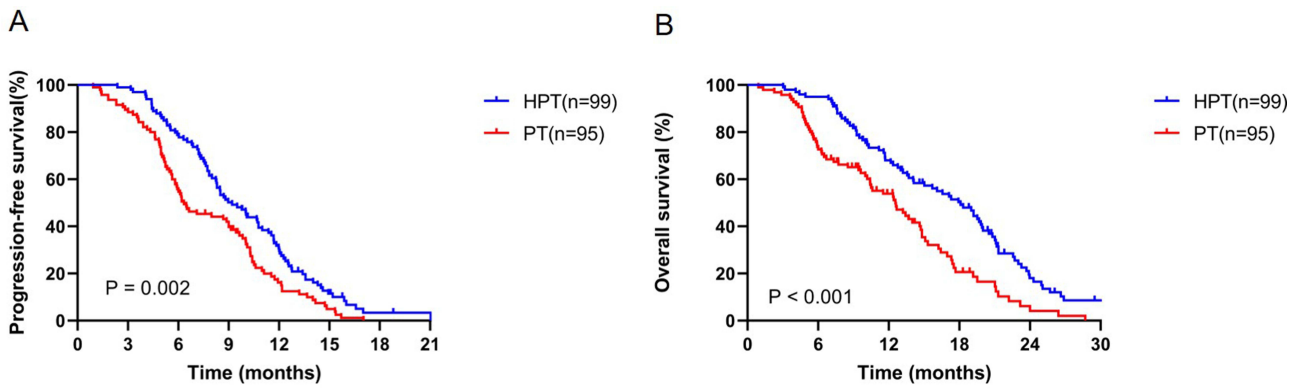

Figure 2 Kaplan–Meier curves for progression-free survival (**A**) and overall survival (**B**).
Abbreviations: HPT, hepatic artery infusion chemotherapy combined with programmed cell death protein-1 inhibitors plus tyrosine kinase inhibitors; PT, programmed cell death protein-1 inhibitors plus tyrosine kinase inhibitors.

classification (A versus B, HR = 3.121, 95% CI: 1.811–5.378, P < 0.001), different tissue differentiation types (well versus poorly, HR = 3.981, 95% CI: 1.699–9.330, P = 0.001), ALBI (<-2.59 versus ≥-2.59, HR = 2.220, 95% CI: 1.306–3.776, P = 0.003), SIRI (<1.33 versus ≥1.33, HR = 1.925, 95% CI: 1.132–3.275, P = 0.016) were independent risk factors for OS in the combined HAIC treatment group (Table 3). The time-dependent receiver operating characteristic (ROC) curves for 1-year OS in patients treated with combined HAIC are shown in Figure 4. The results showed that the area under the ROC curve (AUC) of SIRI was 0.632, the sensitivity was 67.7%, and the specificity was 55.9% (P = 0.036, 95% CI: 0.510–0.754). The AUC for ALBI was 0.675, with a sensitivity of 83.9% and a specificity of 54.4% (P = 0.005, 95% CI: 0.566–0.784). In addition, the Kaplan–Meier curves for overall survival of SIRI and ALBI showed that low SIRI and low ALBI were associated with better survival (all p value < 0.05), as shown in Figure 5. Therefore, we propose that SIRI and ALBI can be used as predictors of the survival of HAIC treatment in patients with HCC-related advanced HCC.

Safety Analysis

Almost all patients had different types and degrees of TRAEs, and the total incidence was 97.9% (190/194), which were 98.0% (97/99) and 97.9% (93/95) in the HPT and PT group, respectively. All TRAEs were mainly grade 1–2 level, with an incidence of 97.9% (190/194), mainly including 67.5% (131/194) of aspartate aminotransferase elevation, 66.0% (128/194) of bilirubin elevation, 62.4% (121/194) of hypoalbuminemia, 55.7% (108/194) of alanine aminotransferase elevation, 53.6% (104/194) of fatigue, 36.1% (70/194) of thrombocytopenia, etc. The total incidence of grade 3–4 level

Table 2 Summary of Best Response

	RECIST version 1.1			mRECIST		
	HPT (%)	PT (%)	*p*-value	HPT (%)	PT (%)	*p*-value
CR	0(0)	0(0)	-	0(0)	0(0)	-
PR	43 (43.4)	21 (22.1)	0.002	53 (53.5)	30 (31.6)	0.002
SD	51 (51.5)	58 (61.1)	0.181	41 (41.4)	49 (51.6)	0.156
PD	5(5.1)	16 (16.8)	0.008	5(5.1)	16 (16.8)	0.008
ORR	43 (43.4)	21 (22.1)	0.002	53 (53.5)	30 (31.6)	0.002
DCR	94 (94.9)	79 (83.2)	0.008	94 (94.9)	79 (83.2)	0.008

Abbreviations: HPT, hepatic artery infusion chemotherapy combined with programmed cell death protein-1 inhibitors plus tyrosine kinase inhibitors; PT, programmed cell death protein-1 inhibitors plus tyrosine kinase inhibitors; RECIST version 1.1, Response Evaluation Criteria in Solid Tumors version 1.1; mRECIST, modified Response Evaluation Criteria in Solid Tumors; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate.

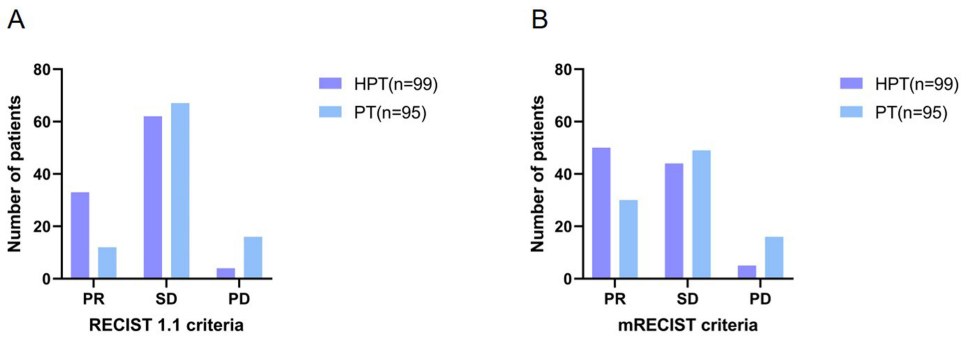

Figure 3 Best assessment of intrahepatic target lesions in both groups.
Notes: (**A**) Evaluated according to RECIST 1.1 criteria. (**B**) Evaluated according to mRECIST criteria.
Abbreviations: HPT, hepatic artery infusion chemotherapy combined with programmed cell death protein-1 inhibitors plus tyrosine kinase inhibitors; PT, programmed cell death protein-1 inhibitors plus tyrosine kinase inhibitors; RECIST1.1, Response Evaluation Criteria in Solid Tumors version 1.1; mRECIST, modified Response Evaluation Criteria in Solid Tumors; PR, partial response; SD, stable disease; PD, progressive disease.

TRAEs was 34.5% (67/194), mainly including 8.3% (16/194) of thrombocytopenia, 6.7% (13/194) of elevated aspartate aminotransferase and hypoalbuminemia, 5.15% (10/194) of leukopenia/neutropenia, 4.64% (9/194) of elevated alanine aminotransferase and nausea/vomiting, 4.12% (8/194) of elevated bilirubin, and so on.

The incidence of grade 1–2 level AEs was 98.0% (97/99) and 97.9% (93/95) in the HPT group and the PT group, respectively, while the incidence of grade 3–4 level AEs was 36.4% (36/99) and 32.6% (31/95), respectively. The

Table 3 Univariate and Multivariate Analysis of Risk Factors for Overall Survival in Combined HAIC Group

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Age (years)	0.997	0.971–1.024	0.834			
Sex, (female/male)	0.922	0.506–1.682	0.792			
AFP (ng/mL), (≤/>400)	1.545	0.965–2.476	0.070			
Extrahepatic metastasis, (no/yes)	1.122	0.687–1.832	0.645			
Child-Pugh, (A/B)	3.153	1.922–5.174	<0.001*	3.121	1.811–5.378	<0.001*
Largest liver tumor size (cm)	1.057	1.008–1.109	0.023*	1.017	0.960–1.078	0.567
Tumor number, (1/>1)	1.373	0.717–2.627	0.339			
Macrovascular invasion, (no/yes)	1.489	0.943–2.354	0.088			
Differentiation degree						
Well						
Moderately	1.470	0.609–3.550	0.391			
Poorly	3.465	1.530–7.846	0.003*	3.981	1.699–9.330	0.001*
Types of PD-1 inhibitors(camrelizumab/sintilimab)	0.982	0.674–1.430	0.923			
Types of TKIs (lenvatinib/sorafenib)	0.852	0.583–1.244	0.406			
Surgery, (no/yes)	0.591	0.329–1.063	0.079			
ALBI, (<-2.59/≥-2.59)	1.827	1.160–2.878	0.009*	2.220	1.306–3.776	0.003*
MLR, (<0.31/≥0.31)	1.232	0.786–1.931	0.363			
NLR, (<3/≥3)	1.812	1.158–2.834	0.009*	1.016	0.578–1.785	0.956
PLR, (<108.47/≥108.47)	1.564	0.981–2.495	0.060			
SIRI, (<1.33/≥1.33)	2.061	1.306–3.253	0.002*	1.925	1.132–3.275	0.016*
SII, (<532.22/≥532.22)	1.292	0.828–2.015	0.259			

Note: *Referred to p<0.05 in univariate and multivariate analysis.
Abbreviations: HAIC, hepatic artery infusion chemotherapy; AFP, α-fetoprotein; PD-1, programmed cell death protein-1; TKIs, tyrosine kinase inhibitors; ALBI, albumin-bilirubin; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; SII, systemic immune inflammation index (multiplying the platelet count by the neutrophil count divided by the lymphocyte count); SIRI, systemic inflammatory response index (multiplying the monocyte count by the neutrophil count divided by the lymphocyte count).

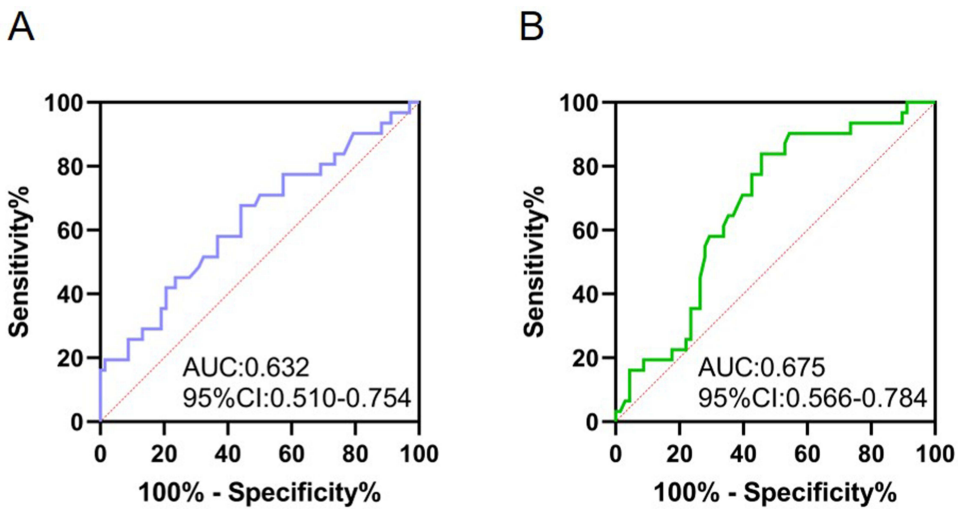

Figure 4 Time-dependent ROC curve of overall survival at 1 year for SIRI (**A**) and ALBI (**B**).
Abbreviations: AUC, area under the curve; ROC, receiver operating characteristic; SIRI, systemic inflammatory response index; ALBI, albumin-bilirubin.

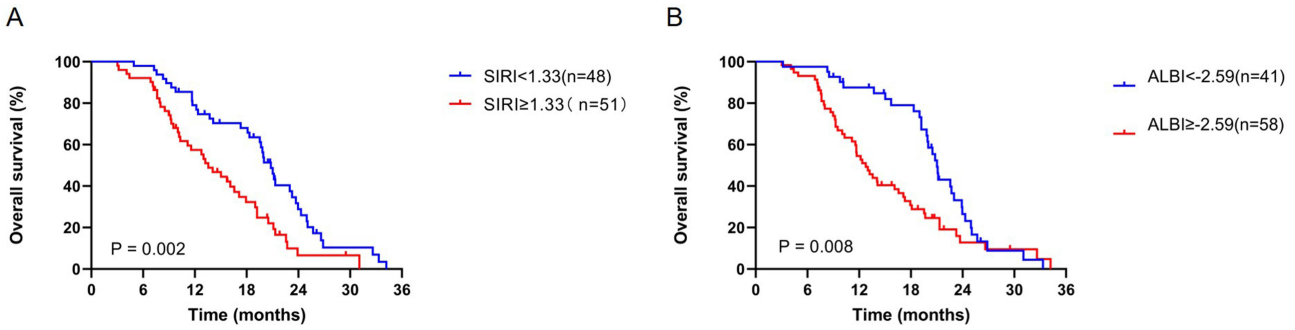

Figure 5 The OS of patients with HBV-related advanced HCC treated with HAIC combined with PD-1 inhibitors plus TKIs. Notes: (**A**) OS according to the SIRI. (**B**) OS according to the ALBI value.
Abbreviations: OS, overall survival; PD-1, programmed cell death protein-1; TKIs, tyrosine kinase inhibitors; HAIC, hepatic artery infusion chemotherapy; HCC, hepatocellular carcinoma; SIRI, systemic inflammatory response index; ALBI, albumin-bilirubin.

difference was not statistically significant (P = 1.000 and P = 0.585, respectively). In the HPT group, elevated aspartate aminotransferase (70/99, 70.7%), elevated bilirubin (66/99, 66.7%), hypoalbuminemia (63/99, 63.6%), and elevated alanine aminotransferase (56/99, 56.6%) were the common grade 1–2 level AEs, whereas thrombocytopenia (10/99, 10.1%), leukopenia/neutropenia (7/ 99, 7.1%), elevated alanine aminotransferase (7/99, 7.1%), elevated aspartate aminotransferase (7/99, 7.1%), hypoalbuminemia (7/99, 7.1%) and nausea/vomiting (7/99, 7.1%) were common grade 3–4 level AEs. In the PT group, elevated bilirubin (62/95, 65.3%), elevated aspartate aminotransferase (61/95, 64.2%), hypoalbuminemia (58/95, 61.1%), and elevated alanine aminotransferase (52/95, 54.7%) were common grade 1–2 AEs, while thrombocytopenia (6/95, 6.32%), elevated aspartate aminotransferase (6/95, 6.32%), hypoalbuminemia (6/95, 6.32%), and hyperbilirubinemia (5/95, 5.26%) were common grade 3–4 level AEs.

There was no significant difference between the two groups in any grade hepatic and renal dysfunction, such as elevated alanine aminotransferase, elevated aspartate aminotransferase, hyperbilirubinemia, hypoalbuminemia, elevated creatinine, and any grade bone marrow suppression, such as leukopenia or neutropenia, hemoglobin reduction, and thrombocytopenia (all p value > 0.05). Whether in HPT group or PT group, elevated aspartate aminotransferase was the most common adverse event, with the incidence of 77.8% (77/99) and 70.5% (67/95), respectively, and thrombocytopenia was the most common grade 3–4 level adverse event, with the incidence of 10.1% (10/99) and 6.3% (6/95), respectively. Patients in the HPT group had more obvious peripheral neurotoxicity (14.1% versus 1.1%, P < 0.001), and

Table 4 Treatment-Related Adverse Events

Adverse events	HPT (n=99)		PT (n=95)		*p*-value	
	Any grade (%)	Grade 3–4(%)	Any grade (%)	Grade 3-4(%)	Any grade (%)	Grade 3-4(%)
Laboratory-related AEs, n (%)						
Leukopenia/neutropenia	40 (40.4)	7(7.1)	29 (30.5)	3(3.2)	0.151	0.364
Thrombocytopenia	45 (45.5)	10 (10.1)	41 (43.2)	6(6.3)	0.748	0.338
Hemoglobin decreased	15 (15.2)	4(4.0)	8(8.4)	2(2.1)	0.147	0.716
Elevated ALT	63 (63.6)	7(7.1)	54 (56.8)	2(2.1)	0.334	0.193
Elevated AST	77 (77.8)	7(7.1)	67 (70.5)	6(6.3)	0.248	0.833
Hyperbilirubinemia	69 (69.7)	3(3.0)	67 (70.5)	5(5.3)	0.900	0.674
Hypoalbuminemia	70 (70.7)	7(7.1)	64 (67.4)	6(6.3)	0.615	0.833
Hematuria/proteinuria	7(7.1)	1(1.0)	2(2.1)	0(0)	0.193	1.000
Creatinine increased	3(3.0)	0(0)	1(1.1)	0(0)	0.643	1.000
Other-related AEs, n (%)						
Fatigue	58 (58.6)	1(1.0)	49 (51.6)	3(3.2)	0.327	0.584
Pain	31 (31.3)	4(4.0)	29 (30.5)	2(2.1)	0.906	0.716
Hypertension	24 (24.2)	2(2.0)	23 (24.2)	0(0)	0.996	0.498
Rash	6(6.1)	1(1.0)	3(3.2)	1(1.1)	0.536	1.000
Pruritus	3(3.0)	0(0)	5(5.3)	2(2.1)	0.674	0.239
Fever	14 (14.1)	0(0)	15 (15.8)	0(0)	0.748	1.000
Nausea/vomiting	38 (38.4)	7(7.1)	30 (31.6)	2(2.1)	0.321	0.193
Diarrhea	15 (15.2)	0(0)	11 (11.6)	1(1.1)	0.456	0.490
Decreased appetite	31 (31.3)	0(0)	36 (37.9)	1(1.1)	0.335	0.490
Dental ulcer	21 (21.2)	1(1.0)	18 (18.9)	1(1.1)	0.694	1.000
Hypothyroidism	11 (11.1)	0(0)	16 (16.8)	0(0)	0.249	1.000
Peripheral neurotoxicity	14 (14.1)	0(0)	1(1.1)	0(0)	<0.001	1.000

Abbreviations: AEs, adverse events; HPT, hepatic artery infusion chemotherapy combined with programmed cell death protein-1 inhibitors plus tyrosine kinase inhibitors; PT, programmed cell death protein-1 inhibitors plus tyrosine kinase inhibitors; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

all were grade 1–2, which may be related to the cumulative effect of oxaliplatin toxicity. No fatal TRAEs occurred in this study, and all adverse events were alleviated by drug reduction, drug withdrawal or drug treatment.

The total incidence of immune-related adverse events (irAEs) was 29.9% (28.3% versus 31.6%, respectively, in HPT group and PT group), and the total 3–4 level irAEs were 1.5% (2.0% versus 1.0%, respectively, in HPT group and PT group). The most common potentially irAEs was grade 1–2 level hypothyroidism (22.7%, 44/194). Among these 1–2 level irAEs, there were 32 cases (16.5%) of immune capillary hyperplasia (HPT: PT = 14.1%: 18.9%, P = 0.367), 35 cases (18.0%) of immune fever (HPT: PT = 18.2%: 17.9%, P = 0.959), and 44 cases (22.7%) of immune hypothyroidism (HPT: PT = 19.2%: 26.3%, P = 0.236). Grade 3–4 level irAEs included 1 case of immune pneumonia (PT group), 1 case of immune colitis (HPT group), and 1 case of immune hepatitis (HPT group). Patients with immune hepatitis, immune colitis and immune pneumonia improved after glucocorticoid treatment and discontinuation of one cycle of immunotherapy, and then continued to use PD-1 inhibitors. Treatment-related adverse events in the HPT and PT groups are summarized in Table 4.

Discussion

Although relevant studies have reported the efficacy and safety of HAIC combined with PD-1 inhibitors plus TKIs in unresectable HCC, which was certainly confirmed in our study, we differed from them in that our study targeted patients with HBV-related advanced HCC. Compared with previous single-arm or small-sample studies, our retrospective study included more patients and set up a standard PD-1 inhibitors combined with TKIs as a control group.[14–16] A Phase II, single-center, single-arm study included 36 patients with high-risk HCC who were treated with lenvatinib, toripalimab (a PD-1 inhibitor) plus FOLFOX-HAIC. The PFS rate at six months was 80.6% (primary end-point), with a median PFS of

10.4 months (95% CI, 5.8–15.0) and a median OS that was not reached. Thrombocytopenia and elevated aspartate aminotransferase were the main treatment-related adverse events. This study showed good safety and anti-tumor activity in patients with advanced HCC, supporting our findings.[17] The TRIPLET trial (NCT04191889) showed that the regimen combining camrelizumab (a PD-1 inhibitor), apatinib, and HAIC demonstrated efficacy and safety in treating BCLC stage C HCC patients, with a median PFS of 10.38 months (95% CI: 7.79 to 12.45) and an unattained OS. ORR and DCR were 77.1% and 97.1%, according to RECIST 1.1 criteria, but the findings were affected by the small sample size (n=35) and the inherent limitations of a single-arm trial.[18] Yizhen Fu et al also found that HAIC can improve the efficacy of lenvatinib and PD-1 inhibitors in the treatment of HCC with portal vein tumor thrombosis.[19] Our study demonstrated that the OS and PFS of the triple therapy of HPT were longer than those of PT, and there was a statistical difference, which was not related to the types of PD-1 inhibitors and TKIs, and the safety was tolerable. The median OS and median PFS in the HPT group were prolonged by 5.53 months and 2.87 months compared with the PT group, and the ORR and DCR improved by 21.9% and 11.7% (according to the mRECIST criteria) and 21.3% and 11.7% (according to the RECIST1.1 criteria), respectively. In addition, we further found that the new systemic inflammatory response index and liver function evaluation index-ALBI score can be used to predict the long-term survival of this combination therapy.

Systemic inflammatory response index (SIRI) was first proposed by Qi et al, which is a more comprehensive chronic low-grade inflammatory marker based on monocyte, neutrophil and lymphocyte counts, as well as is considered to play an important role in the prognosis evaluation of cancer and infectious diseases.[20,21] SIRI is used to describe the balance between inflammation and immune response. Studies have found that SIRI can more accurately predict the poor prognosis of patients with colorectal cancer, esophageal cancer and pancreatic cancer than NLR and PLR, and is associated with the survival of gastric, breast, nasopharyngeal, head and neck, cervical, and liver cancers.[20,22–29] A retrospective study of 160 patients showed that high SIRI was associated with decreased survival in HCC patients treated with immune checkpoint inhibitors and TKIs.[30] Our study found for the first time that SIRI can be used to predict the prognosis of HAIC combined with PD-1 inhibitors plus TKIs in the treatment of patients with HBV-related advanced HCC, and low SIRI is associated with longer survival.

Liver function influences clinical decisions and the overall survival of patients with HCC. Albumin-bilirubin (ALBI) has become an alternative, repeatable and objective measure of liver function reserve in HCC patients and has shown better discriminant ability than Child-Pugh in predicting the prognosis of HCC patients.[31,32] A number of studies have verified that ALBI can predict the survival rate, toxicity and postoperative liver failure of patients receiving radio-frequency ablation, transcatheter arterial chemoembolization, liver resection, external beam radiotherapy as well as multi-kinase inhibitors and immune checkpoint inhibitors therapy.[31,33–38] There is a lack of reports on ALBI predicting the prognosis of HAIC treatment. Our study obtained a cut-off value of −2.59 for ALBI based on the ROC curve, which is similar to the ALB level 1 (≤ −2.60) given by Johnson PJ et al.[39] This retrospective study found that patients with low ALBI (<-2.59) had longer OS than those with high ALBI (≥-2.59), and ALBI was an independent prognostic factor for combined HAIC treatment (P = 0.003), as well as could be used to predict the survival of PD-1 inhibitors combined with TKIs plus HAIC treatment.

HAIC, PD-1 inhibitors and TKIs exert synergistic anti-tumor effects through different mechanisms. Firstly, HAIC directly kills tumor cells through local continuous high-concentration chemotherapy drugs and promotes the secretion of cytokines to enhance T cell response, increasing antigenicity through immunogenic cell death of tumor cells to increase immunotherapy.[40,41] Secondly, multi-kinase inhibitors and PD-1 inhibitors that inhibit VEGF receptor can reverse VEGF-mediated dendritic cell maturation inhibition, lead to effective initiation and activation of T cells, normalize tumor vascular system and promote effective infiltration of T cells, and inhibit the activity of MDSC, Treg and TAM to reprogram the immunosuppressive microenvironment into an immunostimulatory microenvironment, and ultimately the PD-1 antibody can enhance the ability of T cells to attack tumor cells.[42,43] Finally, the combination of the three treatments can inhibit the hypoxic microenvironment of tumors, transforming cold tumors into hot ones and enhancing the efficacy of PD-1.[44]

This retrospective study is authentic and practical, and can provide some evidence for the first-line clinical treatment of HBV-related advanced HCC. There are still some limitations in our research. First of all, this is a single-center, retrospective study that inevitably introduces inherent information and case selection bias. Second, this study was

conducted on patients with hepatitis B virus infection in a specific Chinese setting, and the generalization of the findings to Western countries where hepatitis C and alcoholic liver disease are the main causes of the disease is uncertain. Third, treatment regimens are influenced by physicians' medication habits as well as patients' economic status, and selection bias is inevitable. Fourth, there is a lack of consistency in the treatment regimens of PD-1 inhibitors and TKI types in this study, and the small sample size of this study prevented subgroup analysis, and the optimal combination needs to be further explored. Fifth, OS may be affected by confounding variables such as subsequent treatment. Sixth, due to the sample size limitation, the interpretation and promotion of optimal thresholds for inflammatory indices such as NLR, SIRI, etc. should be done with extra caution. Although our study found that the inflammatory index SIRI and the liver function index ALBI were associated with patients' prognosis, due to the limitations of retrospective studies, the effects of other potential factors on inflammation and liver function indices cannot be excluded. So, further validation through prospective, multicenter, randomized controlled trials is needed to obtain a higher level of medical evidence.

Conclusion

In conclusion, compared with PD-1 inhibitors combined with TKIs, PD-1 inhibitors combined with TKIs plus HAIC have better efficacy and survival benefits in patients with HBV-related advanced HCC, and the safety is tolerable. Moreover, SIRI inflammatory markers and ALBI liver function indicators can be used as biomarkers to predict and evaluate the survival of PD-1 inhibitors combined with TKI inhibitors plus HAIC therapy.

Data Sharing Statement

The datasets generated during the current study are available from the corresponding author on reasonable request.

Ethics Approval

The study followed the World Medical Association Declaration of Helsinki and was approved by the Ethics Committee of Harbin Medical University Cancer Hospital before implementation (approval number: KY2022-14). The study participants provided written informed consent, agreeing to release any potentially recognizable images or data contained in this article. All patients included in this study signed the Second Use Informed Consent for Historical Data/ Biospecimens at Harbin Medical University-affiliated Oncology Hospital.

Author Contributions

Dazhen Wang and Zhengfeng Zhang contributed equally to this work and should be considered co-first authors. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting or writing, substantially revising or critically reviewing the article; gave final approval of the version to be published; reviewed and agreed on all versions of the article before submission, during revision, the final version accepted for publication, and any significant changes introduced at the proofing stage; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no competing financial interest.

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