Research Paper

Effect and Influencing Factors of Programmed Cell Death Protein-1 Inhibitor on Hepatitis B Virus-Related Hepatocellular Carcinoma Undergoing Hepatic Arterial Chemotherapy

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In this study, we analyzed the efficacy and influencing factors of programmed cell death protein 1 inhibitors for hepatitis B virus-associated liver cancer undergoing hepatic arterial chemotherapy. Study the therapeutic effect and influencing factors of programmed cell death protein 1 inhibitor on hepatitis B virus-related liver cancer undergoing hepatic arterial chemotherapy. This study was a retrospective study. Hepatitis B virus -infected patients with liver cancer who received hepatic arterial chemotherapy in hospital from January 2018 to January 2022 were selected. Among 158 patients, there was no statistically significant difference in hepatitis B virus reactivation and ALT elevation between hepatic arterial chemotherapy combined with programmed cell death protein 1 inhibitor and hepatic arterial chemotherapy alone. The overall tumor progression (odds ratio, 2.400 (95 % confidence interval, 1.183-4.871), p=0.015), tumor growth (odds ratio, 2.296 (95 % confidence interval, 1.098-4.803), p=0.027), lesion size increased (odds ratio, 2.401 (95 % confidence interval, 1.017-5.670), p=0.046), lesion number increased (odds ratio, 3.614 (95 % confidence interval, 1.443-9.053), p=0.006), new tumor metastasis (odds ratio, 2.742 (95 % confidence interval, 1.127-6.672), p=0.026) and new distant metastasis (odds ratio, 3.281 (95 % confidence interval, 1.226-8.779), p=0.018) were statistically significant. The number of tumor progression was lower in patients treated with antiviral therapy at baseline compared with those treated without antiviral therapy (odds ratio, 0.459 (95 % confidence interval, 0.214-0.984), p=0.045), with a statistically significant difference between the two groups. Programmed cell death protein 1 receptor inhibitors (odds ratio, 2.400 (95 % confidence interval, 1.183-4.871), p=0.015) and lymph node metastasis (odds ratio, 0.300 (95 % confidence interval, 0.119-0.754) were not used in the analysis of factors associated with overall tumor progression. p=0.010) was a risk factor for overall tumor progression. Overall tumor progression was independent of baseline hepatitis B virus deoxyribonucleic acid level, age, sex, eastern cooperative oncology group, hepatitis B e-antigen, type of programmed cell death protein 1 inhibitor, and type of hepatic arterial chemotherapy (p>0.05).

Key words: Primary liver cancer, radical surgery, chronic hepatitis B, chemotherapy, tumor

Primary liver cancer is one of the most common malignant tumor diseases. It ranks 5th in the global cancer incidence rate and 3rd in the mortality rate. It is a serious hidden danger to human health[1]. In clinical practice, due to atypical early symptoms, most patients have already entered the mid to late stage of diagnosis, and only about 1/3rd can still undergo radical surgery. Therefore, for patients with advanced liver cancer who have lost the opportunity for surgery, hepatic arterial chemotherapy, immunotherapy, and molecular targeted therapy have become their preferred treatment methods.

In clinical practice, Transarterial Chemoembolization (TACE) and Hepatic Arterial Infusion Chemotherapy (HAIC) can create surgical resection opportunities for patients with advanced unrespectable liver cancer and prolong their survival. For patients with a risk of recurrence after surgery, research has confirmed that TACE treatment has the effect of reducing the probability of recurrence and prolonging survival for postoperative patients[2,3]. The median survival

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period after TACE is (16-45) mo in the early stage (Barcelona Clinic Liver Cancer (BCLC) 0-A), (15.6-26.3) mo in the middle stage (BCLC B), and (6.8-13.6) mo in the late stage (BCLC C)[4]. Programmed Cell Death Protein-1 (PD-1) inhibitors are currently a hot topic in cancer research. The survival benefits of PD-1 inhibitors for unrespectable liver cancer patients are borderless, with an average Overall Survival (OS) of 13.9-15.6 mo, and their treatment-related toxic effects are relatively low[5].

Chronic hepatitis B is a chronic progressive disease that, if not treated in a timely manner, can lead to cirrhosis, liver cancer, and even liver failure and death[6]. Existing studies have shown that the higher the viral load level of Hepatitis B Virus (HBV) infected individuals, the greater the risk of poor prognosis in disease progression. Therefore, using antiviral drugs to control HBV-Deoxyribonucleic Acid (DNA) levels can reduce the risk of disease progression and improve the long-term prognosis of patients. Related studies have found that common treatment measures for liver cancer, such as surgery, hepatic artery chemoembolization, radiofrequency ablation, and chemotherapy, can cause varying degrees of HBV reactivation. Although HBV reactivation may automatically improve in some patients, in many cases, it inevitably leads to delayed chemotherapy plans and interruption of cytotoxic treatment plans. In more severe cases, anticancer treatment is often terminated early; this can affect the long-term prognosis of individual cancer treatment. In addition, in the most severe cases, HBV reactivation can directly lead to fatal liver failure. Therefore, preventive use of antiviral drugs can significantly reduce the incidence of HBV reactivation events, improve liver function, and increase patient survival rate.

Research has shown that hepatic arterial chemotherapy, as a commonly used treatment method for liver cancer patients, can easily lead to reactivation of HBV-DNA in HBV related liver cancer patients, and should be highly valued in clinical practice. Effective antiviral therapy should be used to treat HBV related liver cancer patients receiving hepatic arterial chemotherapy, which can inhibit and prevent HBV reactivation, improve liver function, and reduce the incidence of adverse events such as liver failure and even death.

At the same time, studies have found that in patients with hepatitis B, HBV specific Cluster of Differentiation (CD)-8^+ T lymphocytes express PD-1 molecules highly and are inversely proportional to their replication ability. Antiviral therapy can inhibit HBV replication and also reduce PD-1 expression[7-10]. Blocking the PD-1 signaling pathway can inhibit the replication of HBV virus, which has been confirmed in clinical studies[11].

Animal experiments have shown that, compared with the HBV negative control group, the positive group animals have high expression of PD-1 molecules on HBV specific $CD8^+$ T lymphocytes. Blocking the PD-1 signaling pathway can promote anti HBV specific $CD8^+$ T lymphocyte response, thereby promoting virus clearance. More importantly, research on patients with chronic HBV infection has also confirmed its correlation with humans. The HBV-specific T cells present in the peripheral blood of patients with chronic HBV infection express high levels of PD-1, which impairs their function. However, after the infection is resolved, the T cells found in the patient's body function is intact, and the expression of PD-1 is significantly reduced[8].

Although there are some case reports indicating that some patients who have resolved HBV infection have experienced HBV reactivation during PD-1 inhibitor treatment. However, studies have shown that PD-1 inhibitors are effective and safe treatment methods for advanced liver cancer patients, and HBV reactivation or HBV related hepatitis associated with PD-1 inhibitors is mild and controllable[12-14].

Related studies have shown that the combination of PD-1 inhibitors and HAIC can improve patient prognosis and prolong patient survival. And studies have shown that TACE can increase the expression level of PD-1, which is closely related to the therapeutic effect of TACE and patient prognosis. These provide a theoretical basis for the use of PD-1 inhibitors in liver cancer patients undergoing hepatic arterial chemotherapy. TACE is commonly used in the clinical practice of hepatic arterial chemotherapy, but there are currently few published clinical studies on the combination of PD-1 inhibitors and hepatic arterial chemotherapy. Among them, hepatic arterial chemotherapy is limited to HAIC and does not involve the discussion of HBV reactivation. Therefore, we will conduct an analysis of PD-1 inhibitors on HBV reactivation and efficacy in HBV related liver cancer patients who have undergone hepatic arterial chemotherapy.

MATERIALS AND METHODS

Research object:

In this experiment, patients with HBV related liver cancer who received hepatic artery chemotherapy in Lianyi Hospital from January 2018 to mid-January 2022 were selected.

Inclusion criteria: Hepatitis B surface Antigen (HbsAg) positive and/or HBV DNA >20 IU/ml and/or previous diagnosis of hepatitis B was clear; phase II and III liver cancer confirmed by histology/imaging; Eastern Cooperative Oncology Group (ECOG)-PS ≤2; having good organ and bone marrow function; follow up time exceeding 12 w; receive at least one course of hepatic arterial chemotherapy.

Exclusion criteria: Presence of other malignant tumors; having a history of autoimmune diseases; lack of HBV DNA and liver function testing before initial treatment and during follow-up.

Grouping: Patients who use hepatic artery chemotherapy alone; patients who use a combination of hepatic arterial chemotherapy and PD-1 inhibitors[15-20].

Observation indicators:

Hepatitis episodes related to HBV reactivation refer to Alanine Transaminase (ALT) elevation ≥3 times the baseline level and absolute value >100 U/l. HBV reactivation refers to patients with persistent stability of HBV DNA, where HBV DNA elevation is ≥2 log10 IU/ml, or baseline HBV DNA negative individuals transition from negative to positive and ≥100 IU/ml, and those without baseline HBV DNA have HBV DNA ≥20 000 IU/ml.

Statistical processing:

Establish a database and use Statistical Package for the Social Sciences (SPSS) 25.0 statistical software for analysis. $p<0.05$ indicates statistically significant differences.

RESULTS AND DISCUSSION

From January 2018 to January 2022, 158 HBV related liver cancer patients who received hepatic arterial chemotherapy met the inclusion criteria. 82 patients who received hepatic arterial chemotherapy alone, and 76 patients who received combination therapy with PD-1 inhibitors were shown in fig. 1.

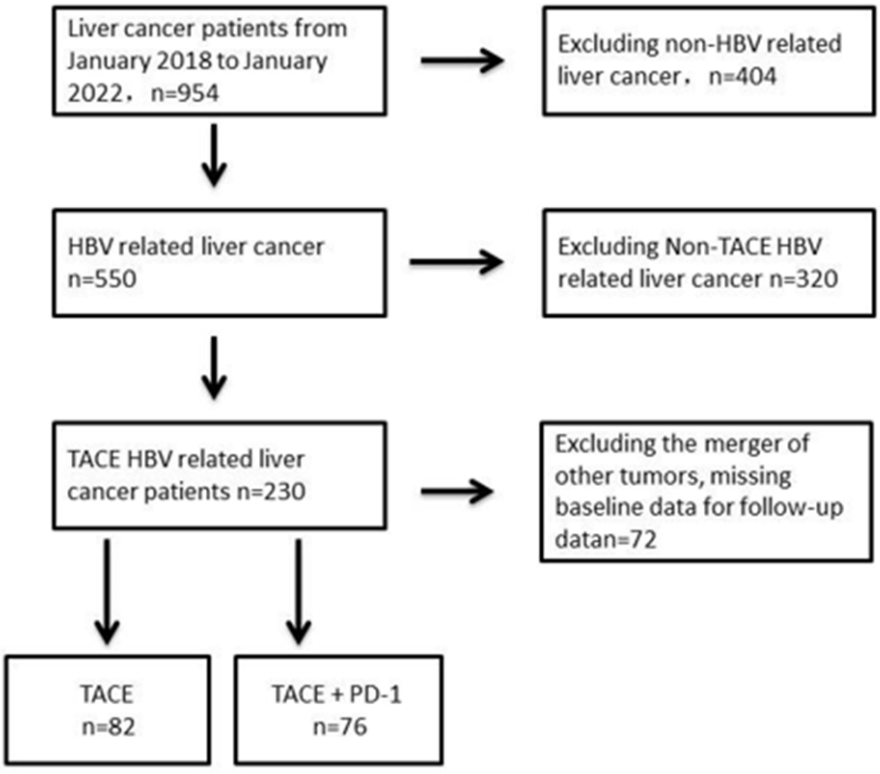

Fig. 1: Grouping process

A total of 158 patients were enrolled, of which 82 were treated solely with hepatic arterial chemotherapy and 76 were treated with a combination of hepatic arterial chemotherapy and PD-1 inhibitor. There was no statistically significant difference in general status such as gender (χ^2=1.114, p=0.291) and age (χ^2=0.171, p=0.679) between the two groups of patients. The proportion of patients who received a combination of hepatic arterial chemotherapy and PD-1 inhibitors had portal vein cancer thrombi and distant metastasis was higher (17.07 % and 44.74 %, p<0.001; 2.44 % and 13.16 %, p<0.05), and there was a statistical difference between the two groups as shown in Table 1.

Among 158 patients, 10 (6.33 %) experienced HBV reactivation, including 8 patients treated with a combination of hepatic arterial chemotherapy and PD-1 inhibitors, and 2 patients treated solely with hepatic arterial chemotherapy (Odds Ratio (OR), 0.213 (95 % Confidence Interval (CI), 0.044-1.035), p=0.055).

Among these 10 patients, the HBV DNA of 4 patients increased by more than 2 logs (100 times) compared to baseline, and the baseline HBV DNA levels of 6 patients were lower than the detectable value, with HBV DNA ≥3 logs (1000) IU/ml. The highest level of HBV DNA at diagnosis of HBV reactivation is 1.47×10^ 7 IU/ml, with the highest ALT level of 894.99 U/l.

Among 10 patients with HBV reactivation, 8 were males and 2 were females; four patients were diagnosed with HBV related hepatitis, with a sudden increase in HBV DNA levels followed by an ALT outbreak; all patients recovered from HBV related hepatitis after treatment, and there were no deaths related to HBV reactivation or HBV related hepatitis.

Among 158 patients, 14 (8.86 %) showed a 3-fold increase in ALT with an absolute value greater than 100 U/l. Among patients treated with combination of hepatic artery chemotherapy and PD-1 inhibitors, 20 (OR, 0.576 (95 % CI, 0.267-1.244), p=0.160) showed no statistically significant difference between the two groups as shown in Table 2.

TABLE 1: BASIC CLINICAL CHARACTERISTICS OF PATIENTS

		TACE (n=82)	TACE+PD-l inhibitor (n=76)	p
Age (year)	<50	24 (29.3)	20 (26.3)	0.679
	≥50	58 (70.7)	56 (73.7)	
Gender	Male	70 (85.37)	60 (78.95)	0.291
	Female	12 (14.63)	16 (21.05)	
AFP (ng/ml)	<5	22 (26.8)	10 (13.2)	0.088
	5400	32 (39.0)	32 (42.1)	
	≥400	28 (34.1)	34 (44.7)	
HBeAg	+	22 (26.8)	14 (18.4)	0.208
	-	60 (73.2)	62 (81.6)	
HcvAb	+	2 (2.44)	2 (2.63)	0.939
	-	80 (97.56)	74 (97.37)	
Baseline HBV-DNA (IU/ml)	<500	28 (34.15)	30 (39.47)	0.488
	≥500	54 (65.85)	46 (60.53)	
Anti-virus	Yes	40 (48.78)	26 (34.21)	0.064
	No	42 (51.22)	50 (65.79)	
Cirrhosis	Yes	52 (63.41)	54 (71.05)	0.307
	No	30 (36.59)	22 (28.95)	
Portal vein tumor thrombus	No	68 (82.93)	42 (55.26)	<0.001
	Yes	14 (17.07)	34 (44.74)	
Lymph node metastasis	No	72 (87.80)	64 (84.21)	0.514
	Yes	10 (12.20)	12 (15.79)	

Distant metastasis	No	80 (97.56)	66 (86.84)	0.025
	Yes	2 (2.44)	10 (13.16)	
Number of tumors	diffuse	24 (29.27)	12 (15.79)	
	1 indivual	26 (31.71)	28 (36.84)	0.249
	2 indivual	4 (4.88)	4 (5.26)	
	>3 indivual	28 (34.15)	32 (42.11)	
Hepatic arterial chemotherapy cycle	1	32 (65.00)	44 (57.89)	0.284
	2	16 (20.00)	22 (28.95)	
	3	6 (7.50)	2 (2.63)	
	≥4	6 (7.50)	8 (10.53)	
Operation	Non	68 (82.93)	44 (57.89)	<0.001
	Other	8 (9.76)	6 (7.89)	
	Liver radiofrequency ablation	6 (7.32)	26 (34.21)	
ECOG	0	14 (17.07)	22 (28.95)	0.06
	1	28 (34.15)	30 (39.47)	
	2	40 (48.78)	24 (31.58)	
Child-Pugh	Grade A	56 (68.29)	44 (57.89)	0.175
	Grade B	26 (31.71)	32 (42.11)	

TABLE 2: THE EFFECT AND COMPARISON OF TREATMENT METHODS ON THE INCIDENCE OF HBV REACTIVATION AND ALT ELEVATION

	TACE (n=82)	TACE+PD-1 inhibitor (n=76)	OR (95 % CI)	p	22 (28.95)
HBV reactivation	Yes	2 (1.27)	8 (5.06)	0.213	0.055
	No	80 (43.04)	68 (41.77)	(0.044-1.035)	
ALT elevation	Yes	14 (8.86)	20 (12.66)	0.576	0.16
	No	68 (43.04)	56 (35.44)	(0.267-1.244)	

Among 158 patients, 10 (6.33 %) experienced HBV reactivation, with 8 patients receiving baseline antiviral treatment and 2 patients not receiving antiviral treatment (OR, 0.328 (95 % CI, 0.067-1.598), p=0.168). There was no statistically significant difference between the two groups.

Among 158 patients, 18 patients received baseline antiviral treatment, and 16 patients without antiviral treatment showed a 3-fold increase in ALT with an absolute value greater than 100 U/l (OR, 1.316 (95 % CI, 0.613-2.822), p=0.481), with no statistically significant difference between the two groups as shown in Table 3.

Patients who only use hepatic artery chemotherapy have a higher number of tumor progression compared to those who use a combination of hepatic artery chemotherapy and PD-1 inhibitors. Overall tumor progression (OR, 2.400 (95 % CI, 1.183-4.871), p=0.015), tumor growth (OR, 2.296 (95 % CI, 1.098-4.803), p=0.027), and increased lesion volume (OR, 2.401 (95 % CI, 1.017-5.670), p=0.046). The differences in the number of lesions increased (OR, 3.614 (95 % CI, 1.443-9.053), p=0.006), new tumor metastasis (OR, 2.742 (95 % CI, 1.127-6.672), p=0.026), and new distant metastasis (OR, 3.281 (95 % CI, 1.226-8.779), p=0.018) were all statistically significant as shown in Table 4.

The number of tumor progression in patients receiving baseline antiviral therapy was lower compared to those without antiviral therapy (OR, 0.459 (95 % CI, 0.214-0.984), p=0.045), and there was a statistically significant difference between the two groups as shown in Table 5.

Failure to use PD-1 receptor inhibitors (OR, 2.400 (95 % CI, 1.183-4.871), p=0.015) and lymph node metastasis (OR, 0.300 (95 % CI, 0.119-0.754), p=0.010) are risk factors for overall tumor

progression. The overall progression of the tumor was not related to baseline HBV DNA levels, age, gender, ECOG, HBeAg, PD-1 inhibitor type, and hepatic arterial chemotherapy type (p>0.05) as shown in Table 6[21-25].

The etiology of liver cancer is complex, highly malignant, and difficult to treat. Although significant progress has been made in recent years, the current use of various treatment methods and drugs has limited effectiveness in prolonging the survival period of patients with advanced liver cancer. Currently, the overall 5 y survival rate of liver cancer patients in China is <15 %[25-30]. Although early diagnosis is crucial for the effective treatment and prolongation of life expectancy of liver cancer, due to the clinical asymptomatic nature of early liver cancer and the lack of liver cancer monitoring programs in many regions of the world, most patients have entered the mid to late stage once diagnosed, losing the opportunity for curative treatment such as radical resection and liver transplantation. Therefore, systemic therapies such as hepatic arterial chemotherapy, radiation therapy, molecular targeted therapy, and immune checkpoint inhibitor therapy have become the standard treatment methods for patients with advanced liver cancer who have lost surgical opportunities[31-34].

TABLE 3: THE IMPACT AND COMPARISON OF BASELINE ANTIVIRAL STATUS ON THE INCIDENCE OF HBV REACTIVATION AND ALT ELEVATION

		Baseline anti-virus			
		Yes (n=66)	No (n=92)	OR (95 % CI)	p
HBV reactivation	Yes	2 (1.27)	8 (5.06)	0.328 (0.067-1.598)	0.168
	No	64 (40.51)	84 (53.16)		
ALT elevation	Yes	16 (10.13)	18 (11.39)	1.316 (0.613-2.822)	0.481
	No	50 (31.65)	74 (46.84)		

TABLE 4: THE IMPACT AND COMPARISON OF TREATMENT METHODS ON TUMOR PROGRESSION

		TACE (n=82)	TACE+PD-1 inhibitor (n=76)	OR (95 % CI)	p value
Survival rate (6 mo)	Survival	75 (91.4)	74 (97.4)	3.453 (0.694-17.172)	0.13
	Death	7 (8.6)	2 (2.6)		
Survival rate (12 mo)	Survival	50 (61.1)	61 (80.3)	1.888 (0.908-3.925)	0.089
	Death	32 (38.9)	15 (19.7)		
Overall progression of tumors	Yes	32 (20.25)	16 (10.13)	2.400 (1.183-4.871)	0.015
	No	50 (31.65)	60 (37.97)		
Tumor growth	Yes	28 (17.72)	14 (8.86)	2.296 (1.098-4.803)	0.027
	No	54 (34.18)	62 (39.24)		
Increase in volume	Yes	20 (12.66)	9 (5.70)	2.401 (1.017-5.670)	0.046
	No	62 (39.24)	67 (42.40)		
Increased number of lesions	Yes	22 (13.92)	7 (4.43)	3.614 (1.443-9.053)	0.006
	No	60 (37.97)	69 (43.67)		
New tumor metastasis	Yes	20 (12.66)	8 (5.06)	2.742 (1.127-6.672)	0.026
	No	62 (39.24)	68 (43.04)		
Newly added portal vein cancer thrombus	Yes	2 (1.27)	2 (1.27)	0.925 (0.127-6.735)	0.939
	No	80 (50.63)	74 (44.30)		
Remote metastasis	Yes	18 (11.39)	6 (3.80)	3.281 (1.226-8.779)	0.018
	No	64 (40.51)	70 (44.30)		
New lymph node metastasis	Yes	10 (6.33)	4 (2.53)	2.5 (0.749-8.339)	0.136
	No	72 (45.57)	72 (45.57)		

TABLE 5: THE IMPACT AND COMPARISON OF BASELINE ANTIVIRAL STATUS ON TUMOR PROGRESSION

		Baseline anti-virus			
		Yes (n=66)	No (n=92)	OR (95 % CI)	p value
Survival rate (6 mo)	Survive	63 (95.45)	86 (93.48)	0.683 (0.164-2.834)	0.599
	Die	3 (4.55)	6 (6.52)		
Survival rate (12 mo)	Survive	44 (66.67)	73 (79.35)	1.921 (0.936-3.942)	0.075
	Die	22 (33.33)	19 (20.65)		
Overall progression of tumors	Have	18 (11.39)	30 (18.99)	0.775 (0.387-1.533)	0.472
	None	48 (30.38)	62 (39.24)		
Tumor growth	Have	12 (7.60)	30 (18.99)	0.459 (0.214-0.984)	0.045
	None	54 (34.17)	62 (39.24)		
Increase in volume	Have	5 (3.16)	24 (15.19)	0.232 (0.083-0.646)	0.005
	None	61 (38.61)	68 (43.04)		
Increased number of lesions	Have	9 (5.70)	20 (12.66)	0.568 (0.241-1.343)	0.198
	None	57 (36.08)	72 (45.57)		
New tumor metastasis	Have	12 (7.59)	12 (7.59)	1.481 (0.620-3.541)	0.377
	None	54 (34.18)	80 (50.63)		
Newly added portal vein cancer thrombus	Have	4 (2.53)	0 (0)	/	/
	None	62 (39.24)	92 (58.23)		
Remote metastasis	Have	12 (7.59)	12 (7.59)	1.481 (0.620-3.541)	0.377
	None	54 (34.18)	80 (50.63)		
New lymph node metastasis	Have	3 (1.90)	11 (6.96)	0.351 (0.094-1.310)	0.119
	None	63 (39.87)	81 (51.27)		

TABLE 6: ANALYSIS OF RELEVANT FACTORS FOR OVERALL TUMOR PROGRESSION

		Overall tumor progression			
		No.	No. of progress	No.	No. of progress
Age (year)	<50	44	10	0.588 (0.263-1.316)	0.197
	≥50	114	38	1	
Gender	Male	130	40	1.111 (0.451-2.734)	0.819
	Female	28	8	1	
AFP (ng/ml)	<5	32	6	0.684 (0.427-1.095)	0.113
	5-400	64	20	/	
	≥400	72	22	/	
HbeAg	-	122	36	1.194 (0.540-2.644)	0.661
	+	36	12	1	
Baseline HBV-DNA	<500 IU/ml	58	18	1.050 (0.521-2.118)	0.892
	≥500 IU/ml	100	30	1	
Baseline anti-virus	Yes	66	18	0.775 (0.387-1.553)	0.472
	No	92	30	1	
Portal vein tumor thrombus	Yes	48	14	0.920 (0.438-1.933)	0.827
	No	110	34	1	
lymph node metastasis	Yes	22	12	0.300 (0.119-0.754)	0.01
	No	136	36	1	

metastasis	Yes	12	2	2.300 (0.484-10.921)	0.295
	No	146	46	1	
Number of tumors	Diffuse	36	16	1.283 (0.963-1.710)	0.089
	1	54	16	/	
	2	8	0	/	
	≥3	60	16	/	
PD-1 inhibitor used	No	82	32	2.400 (1.183-4.871)	0.015
	Yes	76	16	1	
PD-1 inhibitor type	Karelizumab	48	14	2.225 (0.894-5.534)	0.085
	Xindilizumab	12	0	/	
	Trepril monoclonal antibody	16	2	/	
HBV reactivation	Yes	10	4	1.576 (0.424-5.860)	0.497
	No	148	44	1	
Operation	None	112	36	1.191 (0.771-1.842)	0.431
	Other	14	4	/	
	Liver radiofrequency ablation	32	8	/	
ECOG	0	36	12	1.194 (0.540-2.644)	0.661
	≥1	122	36	1	

In clinical practice, TACE and HAIC are often used as treatment methods for advanced liver cancer, which can reduce tumor recurrence and prolong patient survival. TACE has become the standard for treating patients with large or multiple tumors, or small tumors that cannot be removed or percutaneous ablation[35-40]. The median survival period of patients after TACE treatment is 16-45 mo in the early stage (BCLC 0-A), 15.6-26.3 mo in the middle stage (BCLC B), and 6.8-13.6 mo in the late stage (BCLC C)[41-46]. The median survival period after HAIC is (2.8-15.9) mo [47-50].

A study targeting patients with unrespectable advanced liver cancer suggests that as the number of TACE treatments increases[51-54], the proportion of patients with complete and partial remission gradually decreases, and the proportion of patients with disease progression gradually increases. Therefore, it is urgent to seek new combined treatment options.

Related studies have shown that the combination of PD-1 inhibitors and HAIC can improve patient prognosis and prolong survival. The most commonly used hepatic arterial chemotherapy in clinical practice is TACE[55-57]. However, this study did not include patients treated with TACE. This is the first study to compare the efficacy of simple hepatic arterial chemotherapy (including TACE and HAIC) and hepatic arterial chemotherapy (including TACE and HAIC) combined with PD-1 inhibitors in the treatment of HBV reactivation and efficacy analysis in HBV related liver cancer.

As a local method, hepatic arterial chemotherapy can control intrahepatic lesions. Unfortunately, it is not as effective in controlling extrahepatic metastasis. Anti PD-1 therapy can stimulate the systemic immune response, which may compensate for the limitations of single therapy for hepatic arterial chemotherapy. The results of this experiment demonstrate that the combination of PD-1 inhibitors can reduce the risk of distant metastasis in patients (OR, 3.281 (95 % CI, 1.226-8.779), p=0.018), and the combination of the two has positive significance in delaying intrahepatic growth of tumors (OR, 2.296 (95 % CI, 1.098-4.803), p=0.027). Lymph node metastasis (OR, 0.300 (95 % CI, 0.119-0.754), p=0.010) is also a risk factor for tumor progression, which may be related to patients with lymph node metastasis often reaching advanced stages of cancer, making disease progression more difficult to control.

The risk of HBV reactivation is high in patients with HBV associated liver cancer, which has been identified as an adverse prognostic factor for overall

survival[58]. According to reports, the mortality rate associated with HBV is 20 %-30 %[59]. In addition to the direct cause of death, the deterioration of liver function caused by HBV reactivation may lead to treatment interruption in liver cancer patients, which has a negative impact on their prognosis. Therefore, during the treatment of HBV related liver cancer patients, preventive antiviral therapy is recommended regardless of HBV DNA levels[60]. This experiment also demonstrated that baseline antiviral therapy is effective in delaying tumor progression (OR, 0.459 (95 % CI, 0.214-0.984), p=0.045).

Virological factors, anti-tumor cytotoxic drugs, anti-rejection therapy after tissue and organ transplantation, immunosuppressive therapy for non-tumor diseases, surgery, and other factors may all cause HBV reactivation. TACE, as a common treatment method for advanced liver cancer patients who have lost surgery opportunities, can severely inhibit the immune function of primary liver cancer patients, thereby breaking the original balance of immune function within the body. The rapid replication of HBV cells leads to reactivation of HBV. Although studies have confirmed that blocking the PD-1 signaling pathway can inhibit the replication of HBV virus, there are still reports of HBV reactivation in patients using PD-1 inhibitors. The results of this study indicate that the incidence of HBV reactivation and ALT elevation is low in both groups of patients, and no significant differences were observed. This indicates that on the basis of using hepatic arterial chemotherapy for liver cancer, the combination of PD-1 inhibitors does not increase the risk of HBV reactivation in patients.

This study has some limitations. Firstly, this is a retrospective study. Prospective cohort studies are needed to increase data. Secondly, the total number of patients in this experimental study is relatively small, and it is necessary to expand the sample size to increase the credibility of the experimental results.

Authors' contribution:

Wenqian Qi and Yiting Liu have contributed equally to this study.

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