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ORIGINAL ARTICLE

Effect of radical resection combined with antiviral therapy in patients with hepatitis B virus-associated hepatocellular carcinoma and prognostic analysis

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Summary

Purpose: *To observe the clinical effect of radical resection combined with antiviral therapy in patients with hepatitis B virus (HBV)-associated hepatocellular carcinoma (HCC), and to analyze the risk factors affecting its prognosis.*

Methods: *The clinical data of 132 patients with HBV-associated HCC treated in our hospital from January 2015 to December 2016 were retrospectively analyzed, and the patients were randomly divided into Control group (n=66) and Anti-virus group (n=66). The changes in liver function indexes, HBV-deoxyribonucleic acid (DNA) load and alpha fetoprotein (AFP) level were compared between the two groups before and after treatment. The tumor recurrence and patients' survival were recorded during the follow-up period, and the possible influencing factors for the prognosis of patients with HBV-associated HCC were analyzed.*

Results: *After treatment, the levels of alanine aminotransferase (ALT), albumin (ALB), prealbumin (PA) and AFP significantly declined in both groups (p<0.05), while the levels of ALT, PA and AFP were significantly lower in Anti-virus group than those in Control group (p<0.001). After treatment, the HBV-DNA level declined in both groups compared with that before treatment, while it was obviously lower in Anti-virus group than that in Control group (p<0.001). During treatment, the total incidence rate of complications in Anti-virus group was 37.9%, markedly lower than that in Control group 59.1% (p=0.023). The results of log-rank test showed that both OS and PFS rates were far higher in Anti-virus group than those in Control group (p=0.043, p=0.034). The results of Cox multivariate analysis revealed that a low degree of tumor histological differentiation, a large diameter of tumor and no antiviral therapy were independent risk factors affecting the OS rate of patients after treatment (p=0.030, p=0.017).*

Conclusions: *Antiviral therapy after radical resection of HBV-associated HCC can effectively inhibit the replication of HBV, reduce the recurrence rate of tumor, and prolong the OS of patients. Low grade of tumor histological differentiation, large diameter of tumor and no antiviral therapy are independent risk factors affecting the OS rate of patients after treatment.*

Key words: *radical resection of hepatocellular carcinoma, hepatitis B virus, antiviral therapy, efficacy, prognosis*

Introduction

Hepatocellular carcinoma (HCC) is the third major malignant tumor with a higher mortality rate after gastric cancer and esophageal cancer, and the second major one after gastric cancer in some less-developed areas. Its morbidity rate ranks 5th among all cancers in China, seriously threatening the life and its quality [1-5]. Hepatitis B virus (HBV) infection is closely related to the occurrence of HCC. In about 80% of patients HBV infection will progress into cirrhosis and ultimately into HCC [6-10]. Dur-

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ing the carcinogenic process of HBV, the level of virus replication in hepatitis B patients plays an extremely important role. The incidence rate of HCC rises with the increase in HBV-DNA level in a dose-dependent manner [11]. Traditional radical resection is currently a commonly used clinical treatment means for HCC. However, the clinical efficacy will be greatly weakened once there is HCC metastasis or recurrence [12]. It is reported in clinical studies that the HCC metastasis and recurrence are related to the lesions and serum HBV-DNA level after radical resection [13,14]. Therefore, antiviral therapy may have a significant efficacy on the postoperative recurrence of HBV-associated HCC [15].

In the present study, the patients with HBV-associated HCC who underwent traditional radical resection were explored, the efficacy and safety of radical resection combined with antiviral therapy were detected in the treatment of HBV-associated HCC, and the risk factors affecting its prognosis were analyzed.

Methods

General data

A total of 132 patients with HBV-associated HCC treated with radical resection in our hospital from January 2015 to December 2016 were studied, and divided into Control group (n=66) and Anti-virus group (n=66) using a random number table. The patients underwent antiviral therapy and conventional symptomatic treatment after operation, respectively. There were 98 males and 34 females aged 28-78 years, with a median of 53.68 years.

Inclusion criteria: 1) patients diagnosed with HBV-associated HCC; 2) those undergoing radical resection of HCC; 3) those with a surgical margin ≥1.0 cm and a negative pathological margin; 4) those without tumor recurrence according to imaging and tumor marker reexamination at 2 months after operation; and 5) those with an estimated survival time >6 months.

Exclusion criteria: 1) hepatitis B surface antigen-negative patients; 2) those complicated with severe dysfunction of heart, lung or kidney; 3) those undergoing other antiviral therapies before enrollment; 4) those com-

Table 1. Demographic and general clinical data of all studied patients

Parameters	*Antiviral group (n=66)*	*Control group (n=66)*	*p value*
Gender (Male/Female)	51/15	47/19	0.551
Age (years)	54.34±9.71	53.08±9.22	0.446
Number of tumors			0.499
1	14	10	
≥2	52	56	
Tumor diameter (cm)	2.5±0.6	2.3±0.7	0.080
Grade of differentiation			0.664
High	13	15	
Moderate	42	37	
Low	11	14	
Clinical stage			0.389
I	38	34	
II	17	24	
III	11	8	
HBeAg, n (%)			0.483
+	31 (30.4)	27 (37.7)	
-	35 (69.6)	39 (62.3)	
HBV DNA level (copies/ml), n (%)			0.215
$<10^4$	12 (46.4)	7 (52.2)	
$\geq 10^4$	54 (53.6)	59 (47.8)	
Child-Pugh class, n (%)			0.347
A	48 (84.1)	43 (91.3)	
B	18 (15.9)	23 (8.7)	
PVTT, n (%)			0.315
+	14 (18.8)	19 (30.4)	
-	52 (81.2)	47 (69.6)	
AFP (μg/L)	449.61±28.43	456.92±30.77	0.159

HBeAg: hepatitis Be antigen; HBV: hepatitis B virus; AFP: alpha fetoprotein; PVTT: portal vein tumor thrombus

plicated with other viral hepatitis, alcoholic cirrhosis, autoimmune hepatitis or other primary malignant tumors; 5) those complicated with uncontrolled high blood pressure or high blood glucose; or 6) those who were unable to communicate due to disturbed consciousness.

The gender, age, number of tumors, tumor size, grade of histological differentiation, clinical stage, hepatitis B e antigen (HBeAg), HBV-DNA load, liver function Child-Pugh class, portal vein tumor thrombus, and alpha fetoprotein (AFP) level had no statistically significant differences between the two groups before operation, and they were comparable (p>0.05) (Table 1). All patients enrolled abided by the *Declaration of Helsinki*, and signed the informed consent form. This study was approved by the Ethics Committee of Changle People's Hospital.

Preoperative evaluation

The patients in both groups underwent radical resection, as follows: After admission, relevant examinations were performed, the lesions were positioned by ultrasound or CT, and regular hepatectomy or irregular hepatectomy were conducted in line with the principles of radical resection. The success criteria for operation were the clear fibrous envelope between liver tissues and tumor or clear boundary between liver tissues and small HCC, and no obvious bile duct or vascular invasion on the resection specimens. The abdominal cavity was rinsed after operation, the liver cross-section was excised after complete hemostasis, and the peritoneal drainage tube was indwelled, followed by routine postoperative treatment [16].

The patients in the Control group were treated with conventional symptomatic treatment after radical resection of HCC, such as liver protection, anti-infection and nutritional support. In the Antiviral group, antiviral therapy was performed additionally using Entecavir (Bristol-Myers Squibb, New York, NY, USA, NMPN H20080798, batch No.: AAP7671) (per os, once a day, 0.5 mg/time) for 3 consecutive months.

Observation indexes

The levels of liver function indexes [alanine aminotransferase (ALT), albumin (ALB) and prealbumin (PA)], AFP and HBV-DNA were compared between the two groups before and after treatment. Before treatment and at 4 weeks after treatment, 5 mL of fasting venous blood was drawn in the morning. The serum was separated via centrifugation and stored in a refrigerator at -45°C for later detection. Then the levels of ALT, ALB and PA were determined using a full-automatic biochemical analyzer, and the HBV-DNA level was detected using fluorescence quantitative polymerase chain reaction instrument. The length of hospitalization, medical expenses and complications were recorded.

The patients were reexamined once every 3 months within 2 years after operation, and then once every 6 months after 2 years. CT or MRI were performed once every 6 months or when tumor recurrence or metastasis was suspected. Intrahepatic recurrence or metastasis were confirmed if typical manifestations of HCC were found in the two imaging examinations. PET/CT was performed to confirm the diagnosis if necessary. The patients were followed up until December 2019. The overall survival (OS) and progression-free survival (PFS) were recorded during the follow-up period. OS refers to the duration from operation to death or last follow-up, and PFS refers to the duration from operation to tumor recurrence.

Statistics

SPSS 22.0 software (IBM, Armonk, NY, USA) was used for statistical analyses. Normally distributed measurement data were expressed as mean±SD, and *t*-test or Mann-Whitney U test were used for continuous variables. Abnormally distributed measurement data were expressed as median and range. Categorical variables were expressed as count (percentage), and x^2 test or corrected x^2 test was performed for intergroup comparison. The survival curves were plotted using the Kaplan-Meier method, and significant survival differences were assessed with log-rank test. The influencing factors for the long-term survival were analyzed using univariate and multivariate Cox regression analyses. P<0.05 was considered to be statistically significant.

Results

Comparison of liver function indexes between the two groups before and after treatment

Before treatment, the levels of ALT, ALB, total bilirubin (TBil), PA and AFP had no statistically significant differences between the two groups (p>0.05). After treatment, the levels of ALT, ALB, PA and AFP were significantly lower in both groups than those before treatment (p<0.05), and the level of TBil declined in both groups compared with that before treatment, but without statistically significant difference (p=0.226, p=0.086). After treatment, the levels of ALT, PA and AFP were significantly lower in the Antiviral group than those in the Control group, and the differences were statistically significant (p<0.001), while the levels of ALB and TBil were higher in the Antiviral group than those in the Control group, but there were no statistically significant differences (p>0.05) (Table 2).

Comparison of HBV-DNA level between the two groups before and after treatment

Before treatment, no statistically significant difference was found in the HBV-DNA level between the two groups (p>0.05). After treatment, the HBV-DNA level was obviously lower in the Antiviral group than that before treatment, with a statistically significant difference (p<0.05), while it was also lower in the Control group than that before treatment, but without statistically significant difference (p>0.05). After treatment, the HBV-DNA level was obviously lower in the Antiviral group than in the Control group, and there was a statistically significant difference (p<0.001) (Table 2).

Comparison of hospitalization-related indexes between the two groups

In the Antiviral group the length of hospitalization was evidently shorter than in the Control group, with a statistically significant difference (16.88±3.75 days *vs.* 19.03±4.64 days, t=4.951, p=0.018). The medical expenses were evidently lower than those in the Control group, with a statistically significant difference (3.11±0.84 10.000 thousand yuan *vs.* 4.04±0.92 10.000 yuan; t=5.290, p=0.003).

Comparison of complications between the two groups

After operation, there were 2 cases of hepatic encephalopathy, 2 cases of hepatorenal syndrome, 3 cases of liver failure, and 12 cases of fever and fatigue in varying degrees in the Antiviral group. In the Control group there were 4 cases of hepatic encephalopathy, 3 cases of hepatorenal syndrome, 5 cases of liver failure, and 15 cases of fever and fatigue in varying degrees. During treatment, varying degrees of complications such as incision infection, gastrointestinal bleeding, ascites and biliary fistula occurred in the two groups. The total incidence rate of complications in the Antiviral group was 37.9% (25/66), lower than that in the Control group (59.1%; 39/66; p=0.023, Table 3).

Follow-up results of patients' survival

All patients were followed up for 6-36 months, and 2 cases in the Antiviral group (at 31 and 35 months after treatment) and 3 cases in the Control

Table 2. Comparison of liver function indexes, AFP and HBV-DNA levels of patients in the two studied groups

Liver function	*Antiviral group (n=66)*	*Control group (n=66)*	*p value*
ALT (U/L)			
Pretreatment	141.42±21.71	142.10±20.08	0.852
Posttreatment	87.63±11.23	105.60±13.84	0.001
ALB (g/L)			
Pretreatment	45.38±5.92	45.99±6.11	0.561
Posttreatment	42.80±5.21	41.79±4.97	0.257
TBil (μmol/L)			
Pretreatment	26.90±13.73	27.62±14.22	0.768
Posttreatment	24.13±12.37	23.29±13.48	0.598
PA (mg/L)			
Pretreatment	174.39±23.85	176.03±22.49	0.685
Posttreatment	166.78±20.75	151.28±19.67	0.001
AFP (μg/L)			
Pretreatment	449.61±28.43	456.92±30.77	0.159
Posttreatment	380.21±10.57	427.39±15.64	0.001
HBV-DNA level			
Pretreatment	6.45±1.01	6.78±1.14	0.081
Posttreatment	4.51±0.80	6.37±0.79	0.001

ALT: alanine transaminase; ALB: albumin; TBil: total bilirubin; PA: prealbumin; AFP: alpha fetoprotein; HBV: hepatitis B virus

Table 3. Comparison of adverse reactions of patients in the two studied groups

Parameters	*Antiviral group (n=66)* *n (%)*	*Control group (n=66)* *n (%)*
Incision infection	2 (3.0)	2 (3.0)
Gastrointestinal bleeding	2 (3.0)	3 (4.5)
Ascites	1 (1.5)	4 (6.1)
Biliary fistula	1 (1.5)	3 (4.5)
Hepatic encephalopathy	2 (3.0)	4 (6.1)
Hepatorenal syndrome	2 (3.0)	3 (4.5)
Liver failure	3 (4.5)	5 (7.6)
Fever, Fatigue	12 (18.2)	15 (22.7)

group (at 28, 30 and 33 months after treatment) were lost to follow-up. In the Antiviral group and the Control group the median survival time was 22.4 months *vs.* 19.1 months, the 1-, 2- and 3-year OS rates were 90.9% (60/66) *vs.* 83.3% (55/66), 74.2% (49/66) *vs.* 66.7% (44/66), and 51.5% (34/66) *vs.* 39.4% (26/66), and the 1-, 2- and 3-year PFS rates were 78.8% (52/66) *vs.* 63.6% (43/66), 59.1% (39/66) *vs.* 45.5% (30/66), and 40.9% (27/66) *vs.* 25.8% (17/66). The Kaplan-Meier survival curves in the two groups after treatment are shown in Figure 1. The results of log-rank test showed that both OS and PFS rates were far higher in the Antiviral group than those in the Control group (p=0.043, p=0.034).

Analysis of prognostic factors of patients with HBV-associated HCC

The gender, age, grade of tumor histological differentiation, number of tumors, tumor diameter, HBeAg, HBV-DNA level, portal vein tumor thrombus complicated or not, AFP level before treatment and antiviral therapy combined or not were included into the univariate analysis. The results manifested that low grade of tumor histological differentiation, large diameter of tumor, HBV-DNA load ≥10^4 copies/mL and no antiviral therapy were risk factors affecting the OS rate of patients after treatment [hazard ratio (HR)=2.892, 95% confidence

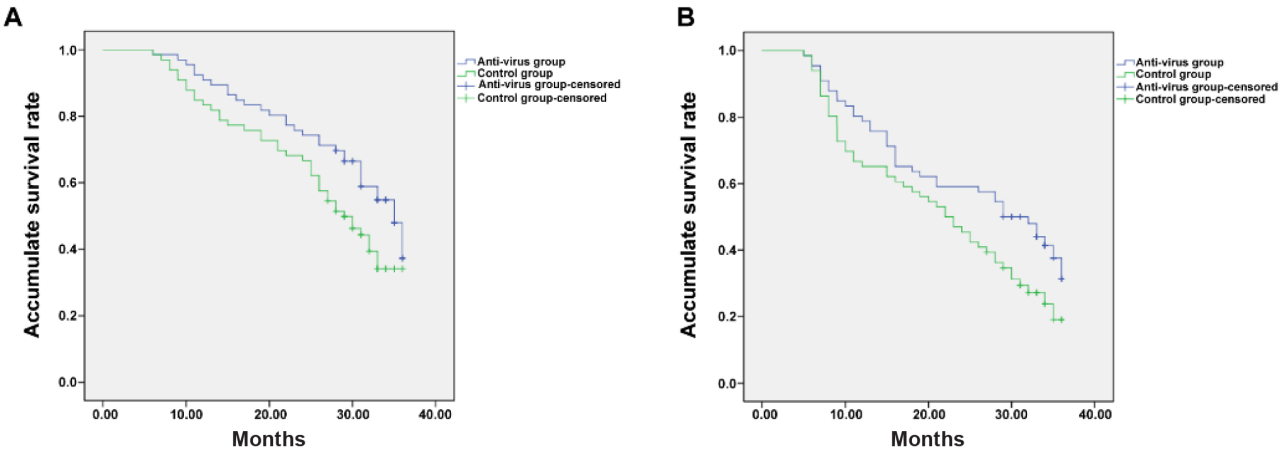

Figure 1. Kaplan-Meier survival curves of patients in the Antiviral group and the Control group. The overall survival rate **(A)** and tumor-free survival rate **(B)** of patients in the Antiviral group was significantly higher than that of the Control group (p=0.043, p=0.034).

Table 4. Univariate and multivariable Cox regression analysis of predictors for overall survival of hepatitis B virus-related hepatocellular carcinoma patients

Parameters	*HR value*	*95% CI*	*p value*
Univariate analysis			
Gender	1.515	0.928-2.122	0.117
Age	1.406	0.916-2.034	0.135
Grade of differentiation	2.892	1.128-8.741	0.039
Tumor number	1.608	0.963-1.970	0.088
Tumor diameter	2.418	1.383-5.621	0.021
HBV DNA ≥10^4 copies/ml	3.547	1.579-9.950	0.006
HBeAg	1.792	0.855-2.276	0.091
Portal vein tumor thrombus	1.195	0.919-1.414	0.104
AFP	1.436	0.876-1.742	0.336
Antiviral therapy	2.493	1.569-4.076	0.013
Multivariate analysis			
Grade of differentiation	1.474	1.028-1.852	0.030
HBV DNA ≥10^4 copies/ml	3.032	0.981-8.843	0.099
Tumor diameter (cm)	1.488	1.965-3.671	0.079
Antiviral therapy	2.217	1.119-4.489	0.017

HR: Hazard ratio; CI: Confidence interval; HBV: Hepatitis B virus; HBeAg: Hepatitis Be antigen; AFP: alpha fetoprotein

interval (CI)=1.128-8.741, p=0.039; HR=2.418, 95% CI=1.383-5.621, p=0.021; HR=3.547, 95% CI=1.579-9.950, p=0.006; HR=2.493, 95% CI=1.569-4.076, p=0.013] (Table 4). Then, the factors with statistical differences in the univariate analysis were included into the Cox multivariate analysis and the results showed that low grade of tumor histological differentiation, large diameter of tumor and no antiviral therapy were independent risk factors affecting the OS rate of patients after treatment (HR=1.474, 95% CI=1.028-1.852, p=0.030; HR=2.088, 95% CI=1.465-3.671, p=0.019; HR=2.217, 95% CI =1.119-4.489, p=0.017) (Table 4).

Discussion

HBV infection occurs in 80-90% of patients with primary HCC, which has been recognized as a major independent factor for the pathogenesis of primary HCC [17]. According to related research, HBV replication and the resulting immune response lead to repeated necrosis and hyperplasia of liver cells, and cell division and aneuploidy promote gene mutation in liver cells, thereby making liver cells prone to malignant transformation [18]. Currently, the main clinical treatment of HCC is surgical resection, but there is a high recurrence rate and a low survival rate of patients after surgical resection, and the therapeutic effect is less satisfactory. The possible reason is that only local treatments of HCC (surgery, transarterial chemoembolization, etc.) are emphasized, but antiviral therapy able to relieve liver inflammation is ignored [19]. Radical resection of HBV-associated HCC can activate and cause massive replication of HBV in the liver, thus rapidly weakening the liver function and affecting the patient's postoperative recovery. In the treatment of HBV-DNA-positive patients, regular antiviral therapy can effectively lower the serum HBV-DNA level, and prolong the postoperative OS and PFS [20,21]. In addition, it is reported that a high HBV-DNA load is an important risk factor for cirrhosis and HCC in patients with chronic hepatitis B, and standardized antiviral therapy after operation can effectively reduce the recurrence of HCC and improve the quality of life of patients [22-24].

Entecavir is a kind of novel antiviral nucleoside, which can effectively and quickly inhibit the replication of HBV-DNA and improve the liver injury [25,26]. In this study, the effect of antiviral therapy on the clinical outcome after radical resection of HBV-associated HCC was explored and it was found that the recovery of liver function was greatly superior in the Antiviral group to that in Control group, but without statistically significant difference (p>0.05). After treatment, the HBV-DNA level in the Antiviral group was greatly lower than that in the Control group (p<0.001). The Antiviral group had a markedly lower level of tumor marker AFP than the Control group after treatment (p<0.001). It can be seen that radical resection of HCC combined with antiviral therapy can effectively ameliorate the liver function and improve the condition of disease in HCC patients with hepatitis B. The possible reason is that entecavir can effectively inhibit the HBV-DNA replication via competing with the natural substrate deoxyadenosine triphosphate, suppress the development of disease and promote the postoperative viral clearance and liver function recovery.

Studies have revealed that entecavir exerts an antiviral effect via inhibiting HBV-DNA positive-chain synthesis, and it has satisfactory efficacy in hepatitis B patients with active viral replication and active liver histological lesions [27]. After radical resection of HCC, entecavir can effectively remove HBV, reduce the incidence rate of complications and the recurrence rate of disease, shorten the length of hospitalization, and raise the quality of life of patients [28]. In this study, the total incidence rate of complication in the Antiviral group (37.9%) was far lower than that in the Control group (59.1%) (p=0.023). The Antiviral group had a distinctly shorter length of hospitalization and distinctly lower medical expenses than the Control group. According to follow-up results, the 3-year OS rate was 51.5% (34/66) and 39.4% (26/66), and the PFS rate was 40.9% (27/66) and 25.8% (17/66), respectively, in the two groups. The results of log-rank test showed that both OS and PFS rates were far higher in the Antiviral group than those in the Control group (p=0.043, p=0.034).

The survival time of patients after radical resection of HCC is affected by complicated factors. In this study, the results of Cox multivariate analysis manifested that low grade of tumor differentiation, large tumor diameter and no antiviral therapy were independent risk factors affecting the OS rate of patients after treatment. It can be inferred that when antiviral therapy is performed to prolong the survival of HCC patients after intrahepatic recurrence it is an important factor positively affecting their survival.

We acknowledge that this study has some limitations. For example, this was a single-center retrospective study, the sample size was limited, and the effects of different methods of radical resection on the prognosis were not analyzed. In the future, the conclusion of this study needs to be confirmed by prospective multicenter large-sample randomized studies.

Conclusions

Antiviral therapy after radical resection of HBV-associated HCC can effectively inhibit the replication of HBV, reduce the recurrence rate of tumor, and prolong the survival time of patients. Low grade of tumor histological differentiation, large diameter of tumor and no antiviral therapy are independent risk factors affecting the OS rate of patients after treatment.

Conflict of interests

The authors declare no conflict of interests.

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