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ORIGINAL ARTICLE

Efficacy of antiviral therapy in patients with hepatitis B-related primary liver cancer

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Summary

Purpose: *To explore the effect of combined antiviral therapy in patients with hepatitis B-related hepatocellular carcinoma.*

Methods: *82 patients with hepatitis B-related primary liver cancer were selected and divided into two groups. Among them, the control group was treated with routine liver protection, the observation group was treated with antiviral therapy and nucleoside analogues (including lamivudine, entecavir and tibivudine).*

Results: *The alanine transferase (ALT) of the observation group (54.79±13.23) U/L was significantly lower than that in the control group (150.27±18.75) U/L (p<0.05). The unpredictable rate of HBV DNA in the observation group was 48.1% in the 12th month, which was obviously improved compared with the conventional therapy, p<0.05. Among the 18 patients (43.9%) in the observation group, 7 patients with positive HBeAg turned negative and 3 were converted to HBeAb, among which, the HBeAg negative conversion rate was 38.9% and the HBeAg conversion rate was 16.7%. Child-Pugh score of patients with hepatitis B-related primary liver cancer increased with the extension of treatment. In the observation group for 6 and 12 months, Child-Pugh score was significantly lower than that in the control group, p<0.05. The survival rate was 97.6% and 92.7% at the 6th month, 85.4% and 78.0% at the 12th month, 78.0% and 56.1% at the 18th month, the difference was statistically significant (p<0.05).*

Conclusion: *Combined antiviral therapy on the basis of conventional treatment can significantly improve the liver function, reduce the viral load and prolong the survival time of patients with hepatitis B-related hepatocellular carcinoma associated.*

Key words: *antiviral, primary liver cancer, liver disease, liver function, therapeutic effect*

Introduction

Primary liver cancer is a common malignant tumor in China, which refers to cancer in hepatocytes or bile ducts, with high mortality rate [1]. Due to its occult development, many patients are found with primary liver cancer when diagnosed, and some of them have lost the chance of surgery [2]. In order to improve the survival of patients with primary liver cancer and seek new treatment methods, the American College of Surgery issued some common opinion of treatment objectives of primary liver cancer [3]: 1. Cure; 2. Local control of tumor, prepare for transplantation; 3. Local control of tumor, with palliative therapy; 4. Improving the quality of life. However, many patients have been diagnosed as primary liver cancer with no intention or ability to undergo surgical treatment. The recurrence and metastasis rate of liver cancer is still very high with the above treatments, which affect the long-term survival by means of transcatheter arterial chemoembolization (TACE), skin ablation,

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radiotherapy, chemotherapy, biological treatments, etc. [4,5]. The etiology and pathogenesis of primary liver cancer are uncertain and now are considered to be related to conditions such as liver cirrhosis, viral hepatitis and aflatoxin and soil and water factors [6]. The main symptoms are liver pain, fatigue, wasting, abdominal distension, loss of appetite and so on. Therefore, the prevention and treatment of recurrence and metastasis after primary liver cancer, as well as the treatment of primary liver cancer, are still the focus and anxiety of treatment difficulties among researchers [7]. Clinical routine radiotherapy and surgical treatment of hepatitis B-related primary liver cancer cannot effectively remove HBV-DNA, which affects the prognosis of patients recovery. With the development of medical technology, the treatment of hepatitis B and primary liver cancer has become a feasible way, which is related to medical technology [8].

Methods

Case data

Research Subjects

82 patients with primary liver cancer related to chronic hepatitis B visited our hospital from January 2015 to July 2018. They were selected as the research objects, with the mean age of 52.4±3.1 years, including 66 males and 16 females.

Inclusion criteria

Patients who met the diagnostic criteria for hepatitis B in the Guidelines for the Prevention and Treatment of Chronic Hepatitis B (2015 Edition) [9]; Patients who met the diagnosis criteria for primary liver cancer in the Diagnosis and Treatment of Primary Liver Cancer Criteria (2015 Edition) [10]; Patients with positive HBeAg and positive HBsAg tested in the laboratory inspection; Patients who received treatment as directed by doctors.

Exclusion criteria

Patients with drug allergy; Patients with indications of surgical treatment; Patients with other organic dysfunction such as heart, lung, kidney; Patients with HBV-DNA detection $<1\times10^3$ copies/ml; Patients with hemorrhage of esophageal and gastric fundus vein rupture; Patients who have received chemotherapy, radiotherapy, antiviral therapy; Patients with distant metastasis suggested by CT; Patients with other combined chronic hepatitis cancer viruses, or chronic cancer diagnosed as a result of drug abuse, alcohol, fatty liver, autoimmune nephritis, liver disease virus.

Treatment programmes

Experiment Group

With the consent of the ethics committee of our hospital and according to the individual wishes of the patients, the patients were divided into two groups: 41 in the observation group, for routine antiviral combined

Table 1. Basic data of patients with hepatitis B-related primary liver cancer (82)

Indicators	*Antiviral treatment group*	*Routine treatment group*	*p*
Number of cases	N=41	N=41	
Gender			>0 05.
Male	31	35	
Female	10	6	
Age, years (median)	503.	56 8.	>0 05.
Liver cancer staging			>0 05.
Stage I	29	32	
Stage II	12	9	
Child-Phgh ranking			>0 05.
A	26	28	
B	15	13	
Liver cancer markers			
AFP (ng/ml)			>0 05.
≤400	39	40	
>400	2	1	
HBeAg +	18	14	>0.05
HBeAg -	23	27	
Alcohol consumption			>0 05.
Yes	16	17	
No	25	24	

treatment, and 41 in the control group, for routine liver protection. There was no significant difference in general data and disease characteristics between the two groups, as shown in Table 1.

Treatment methods

The control group was treated with hepatic artery chemoembolization, and the patients were treated with routine anti-infection therapy for 3-5 days after operation. Then they were treated with potassium magnesium aspartate (National Medicine Standard H33020038, Hangzhou Minsheng Pharmaceutical Co., LTD.), once 20 ml dissolved in 500 ml 10% glucose injection, slowly intravenous infusion, once a day.

On the basis of this treatment, the observation group used entecavir tablets (Shanghai Shigibao Pharmaceutical Co., Ltd., China and the United States) for 10 people at 0.5 mg / day, lamivudine tablets (Anhui Baker Biopharmaceutical Co., Ltd.) for 23 people at 100 mg / day for oral administration, and tibivudine tablets (Beijing Novartis Pharmaceutical Co., Ltd.) for 8 people at 600 mg / day for oral administration. HBV DNA was rechecked once within 3 months after the operation. Imaging examination showed the presence of tumor foci. Surgery, radiation and chemotherapy could be selected for patients with recurrent venereal diseases.

Monitoring indicators

Patients with liver cancer must carefully check their liver functions, HBV DNA, coagulation, hepatitis B, abdominal laser color Doppler ultrasound, etc. before receiving treatment. The cumulative survival rate of patients with liver disease was calculated according to the Child-Pugh score at the 6^{th},12^{th} and 18^{th} month after the treatment.

Criteria for efficacy

Criteria for Liver Function: the changes in ALT levels. Criteria for Determining HBV DNA Level: HBV DNA undetectable rate, HBeAg serum negative conversion rate and HBeAg serum conversion rate. Criteria for Liver Reserve Capacity: Child-Pugh score.Criteria for Determination of Mid-term and Long-term Outcomes: cumulative survival after 18 months of treatment

Experimental instruments

Beeman DXC 8001 biochemical analyzer, Beeman ACL 9000 coagulation routine analyzer, KPS-KM automatic washing plate RT3000, HBV DNA kit were from Sun Yat-sen University, Da'an. Ultra-clean table was from Suzhou Antai Air Technology Co., Ltd.. Ordinary high-speed centrifuge was from Shanghai Medical Centrifuge

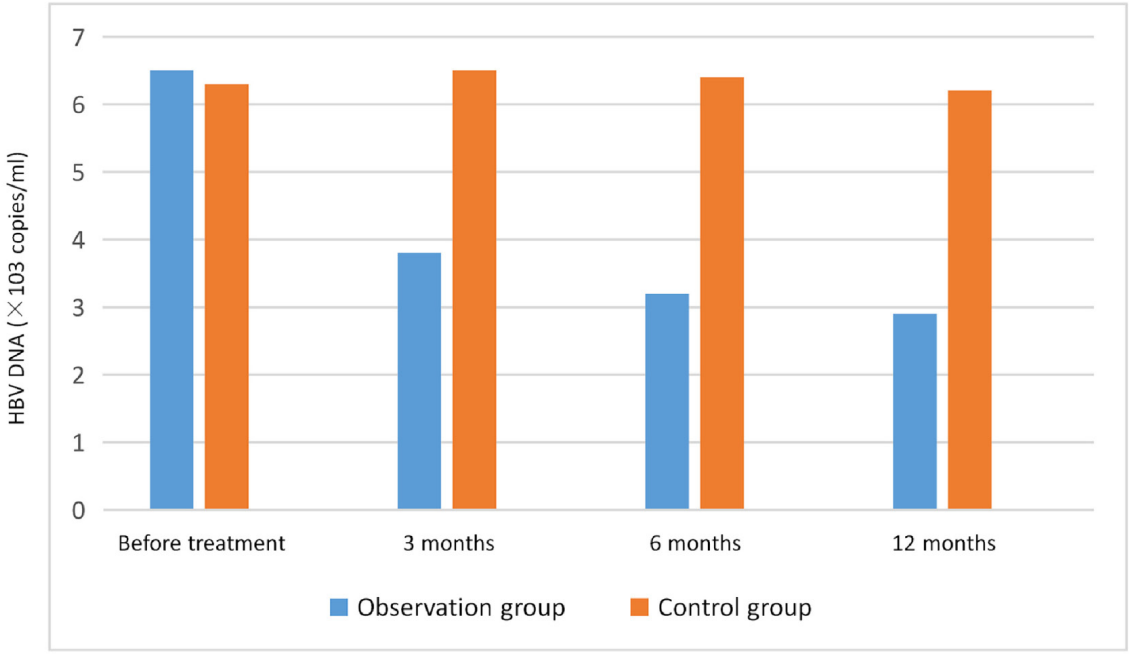

Figure 1. Effect of antiviral therapy on HBV DNA levels in patients with hepatitis B-related primary liver cancer (p=0.004).

Table 2. Effects of antiviral therapy on ALT levels in patients with hepatitis B-related primary liver cancer

Observational indicators/ ALT (U/L)	*Basic values*	*Treatment for 3 months*	*Treatment for 6 months*	*Treatment for 12 months*
Antiviral treatment group	209. 43±14. 51	106. 04±11. 57	67. 48±13. 34	54. 79±13. 23
Routine treatment group	206. 92±12. 86	192. 63±10. 74	173.98±21.81	150. 27±18. 75

Factory. Cryogenic ultracentrifugation was from German HERAEUS company. Adjustable fluid shifter, PCR analysis system Lop, DMW 600 Bath Box were from Jiangxi Daomei Intelligent Technology Co., Ltd.

Statistics

SPSS23.0 statistical software was used to carry out the statistical analyses. The measurement data were expressed by mean ± standard deviation. The categorical data was expressed by (%). P<0.05 showed that the difference was statistically significant.

Results

Effects of antiviral therapy on ALT levels in patients with hepatitis B-related primary liver cancer

The overall ALT effect of long-term antiviral therapy on patients with hepatitis B-related primary liver cancer was further assessed and the results showed that after antiviral therapy, the ALT level of patients in the long-term observation control group was significantly lower than that in the control group in the same period, being statistically significant (p<0.05), as shown in Table 2.

Effects of antiviral therapy on HBV DNA levels in patients with hepatitis B-related primary liver cancer

The effect of antiviral therapy on the HBV DNA level of patients with hepatitis B-related primary liver cancer was assessed and the results showed that the HBV DNA level of patients in the observation group decreased gradually with the extension of treatment. The HBV DNA unpredictable rate reached 34.4% after 3 months, 47.5% after 6 months and 48.1% after 12 months. There was a significant increase compared with the control group, but there was no significant change in the HBV DNA level of the control group (ΔP=0.004), as shown in Figure 1.

Effect of antiviral therapy on HBeAg negative conversion rate and HBeAg conversion rate in patients with hepatitis B-related primary liver cancer

The effect of antiviral therapy on the rate of HBeAg negative conversion rate and HBeAg conversion rate was further observed in patients with hepatitis B-related primary liver cancer at 12 months. The results showed that 7 of the 18 (43.9%) HBeAG-positive patients in the observation group turned negative at the 12th month after treatment. Three of them had HBeAg conversion to HBeAb, with a negative conversion rate of 38.9% and a conversion rate of 16.7%. There was no patient with HBeAg negative conversion or HBeAg conversion observed in the conventional treatment group, and the rate and change speed of HBeAg negative conversion were significantly faster than those in the control group at 12 months.

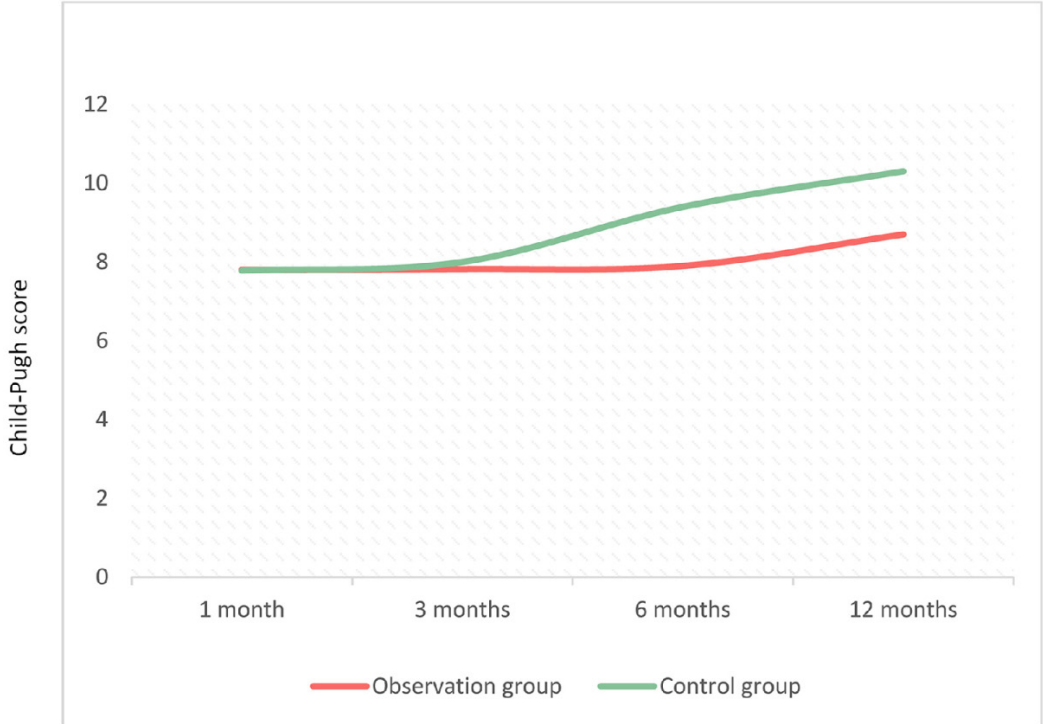

Figure 2. Effect of antiviral therapy on the Child-Pugh score of patients with hepatitis B patients with primary liver cancer (p=0.037).

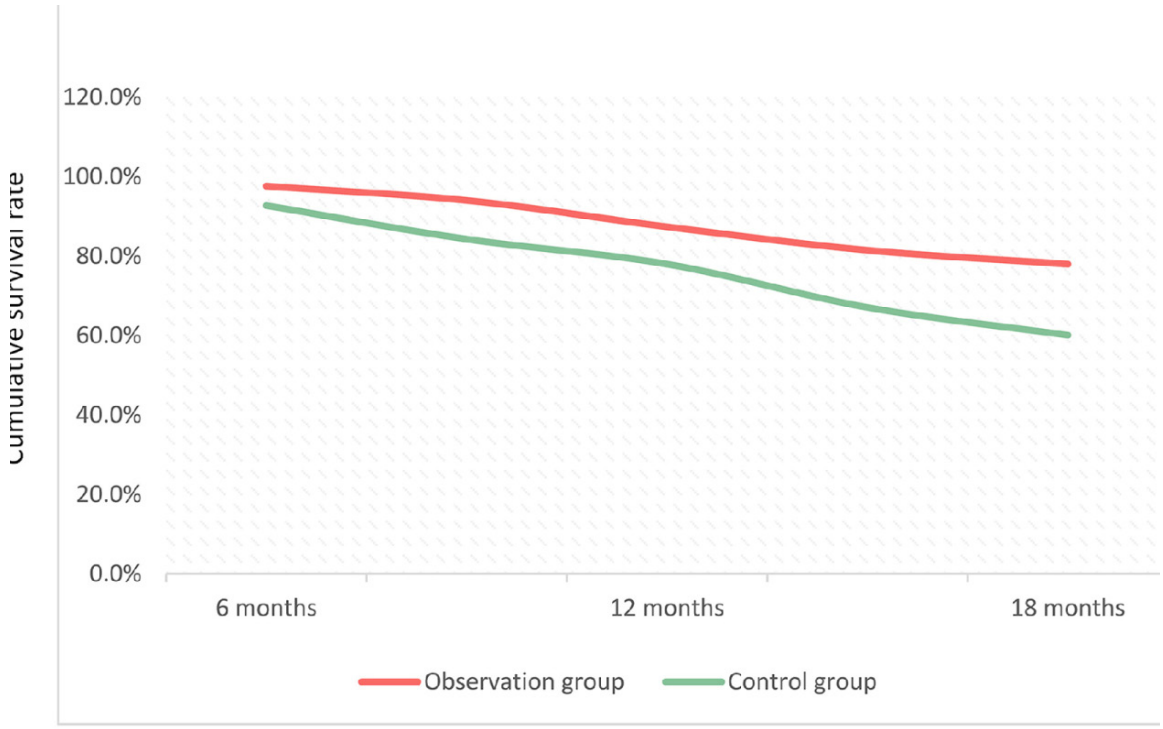

Figure 3. Cumulative survival rate of 18 months in patients with hepatitis B primary liver cancer treated with antiviral therapy (p=0.043).

Effect of antiviral therapy on the Child-Pugh score of patients with hepatitis B-related primary liver cancer

The effect of antiviral therapy on the Child-Pugh score of patients with hepatitis B-related primary liver cancer was further observed. The results showed that the Child-Pugh score of patients with hepatitis B-related primary liver cancer in the two groups increased gradually with the extension of treatment. The score in the observation group was significantly lower than that in the control group from 6 months to 12 months ($p<0.05$), as shown in Figure 2.

Effect of antiviral therapy on 18-month cumulative survival in patients with hepatitis B-related primary liver cancer

The effect of antiviral therapy on the cumulative 18-month survival rate of patients with hepatitis B-related primary liver cancer was further observed. The results showed that the survival rate of patients with two treatment options was 97.6% and 92.7% in 6 months, 85.4% and 78.0% in 12 months, 78.0% and 56.1% in 18 months, and the 18-month survival rate of the patients in the observation group was significantly higher than that in the control group ($\Delta P=0.043$), as shown in Figure 3.

Discussion

Clinical research reports show that there are many causes of primary liver cancer. Hepatitis B is an important factor leading to primary liver cancer in China. There is no complete treatment for this disease, and in the course of its treatment, TACE of chemotherapy and targeted anti-cancer drugs are usually used to control the patient's situation, inhibit the spread of cancer cells and prolong life exptectancy [11-13].

Clinically HBV chronic infection exacerbates the immune response, leading to hepatocyte injury and inflammation, while long-term inflammation can cause malignant transformation of newborn hepatocytes [14]. HBV DNA replication of the immune system can lead to infected liver cells, liver cell damage, inflammatory response, and accelerate the process of liver cirrhosis and liver fibrosis. Therefore, attention should be paid to the application of antiviral therapy in patients with hepatitis B-related primary liver cancer [15,16]. Through this study, the ALT level of patients in the observation group was more significantly improved after 6 months. There was no significant difference in the HBV-DNA level before and after the treatment in the control group, and the HBV-DNA level decreased significantly after the treatment in the observation

group. The results indicated that antiviral therapy can effectively improve the liver function of patients and reduce the load of HBV-DNA in patients [17]. Lamivudine can inhibit the activity of HBV reverse transcriptase, rapidly remove HBV-DNA, and promote HBeAg transformation. Entecavir can be converted into active triphosphate, which can inhibit HBV DNA transcription and replication and reduce the viral load by competing with DEoxyguanine nucleoside (dGTP) triphosphate. Tibiff is a thymosin analogue, which can be phosphorylated into active triphosphate by cell kinases. HBV DNA polymerase substrate thymosin 5 ring phosphate competition inhibit its activity, and embed HBV DNA chain synthesis, termination of DNA chain synthesis, inhibit HBV replication, and achieve antiviral effect [18-20]. At the same time, antiviral therapy can effectively inhibit the replication of viral cells, promote the gradual recovery of the immune system, improve the damage of liver cells, regulate the level of liver function indicators, and thus improve the overall liver function of patients. The antiviral therapy in the control group after 6 months can also significantly improve liver function, reduce the Child-Pugh score, conserve positive HBV DNA to negative basically, and prevent liver cancer patients from dying of liver failure [21,22].

The results showed that the survival rate of the observation group after 18 months of antiviral treatment was significantly higher than in the control group with conventional treatment, indicating that antiviral treatment could prolong the survival time of the patients. Studies [23-25] have shown that after antiviral treatment, the HBV DNA level decreased significantly, which can effectively improve the damage of liver cells, promote the improvement of liver function, and thus prolong the patient's survival. To sum up, antiviral therapy can improve liver function, reduce HBV DNA level and prolong patient survival in hepatitis B-related primary liver cancer [24].

Therefore, it can be said that the combination of anti-HBV therapy on the basis of conventional drug therapy can obviously improve the ALT level of patients with hepatitis B-related primary liver cancer, reduce the HBV-DNA level significantly, increase the rate of undetectable HBV-DNA, increase the rate of HBeAg negative conversion, and reduce the Child-Pugh score. It can improve the cumulative survival rate of patients with hepatitis B-related primary liver cancer for 18 months, thus greatly improve the efficiency of treatment, shorten the recovery time of patients, improve the quality of life, and ease the economic burden of patients and their families. In the process of gradually emproving the patient's condition, patients and family members show increased confidence in cure or improvement and their trust in doctors, thus improving the compliance of hepatitis B-related primary liver cancer treatment.

Conclusion

To sum up, anti-HBV therapy combined with conventional drug therapy significantly improved the ALT level of hepatitis B-related primary liver cancer, reduced the HBV-DNA level of the patients with hepatitis B-related primary liver cancer, and reduced the positive rate of HBV-DNA. It also improved HBeAg negative conversion rate and HBeAg conversion rate. Antiviral therapy combined with conventional drug therapy can significantly reduce the Child-Pugh score of patients with hepatitis B-related primary liver cancer, and improve the cumulative survival rate of patients with hepatitis B-related primary liver cancer.

Conflict of interests

The authors declare no conflict of interests.

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