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The Study of Intervention of Antiviral Therapy to Chronic Hepatitis B-Related Carcinogens

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ABSTRACT Objective: To investigate the intervention of antiviral therapy on the risk factors of chronic hepatitis B-related hepatocellular carcinoma. **Methods:** 249 hospitalized cases of hepatocellular carcinoma in Qingdao Infectious Diseases Hospital from February 2010 to June 2012 were retrospectively analyzed. The relevant data recorded on the questionnaire prepared by the unified was used to compare the distribution of various factors between antiviral treatment group and no-antiviral treatment group. **Results:** The differences of time of HBV infection and that of cirrhosis before diagnosed with HCC, and HBV DNA level between antiviral treatment group and no-antiviral treatment group were statistically significant, P<0.05; HBV infection patterns, AFP, CEA had no significant differences between the two groups. Differences of related indicators of liver function were statistically significant. **Conclusions:** Antiviral therapy could significantly reduce the percentage of the carcinogenic factors associated with chronic hepatitis B in patients, and it can effectively inhibit the replication of HBV DNA, which maybe reduce the incidence of HBV-related HCC.

Key words: Hepatocellular carcinoma; Chronic hepatitis B; Risk factors; Antiviral therapy

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Introduction

Chronic hepatitis B virus (HBV) infection is the main reason of hepatocellular carcinoma(HCC)in China. The majority of HCC is evolved from cirrhosis after HBV infection [1,2], and the relevant information shows that high HBV DNA level is the absolute risk factor for HCC[3] . Nucleoside analogues were used in antiviral therapy of patients with decompensated cirrhosis in early mid-nineties of the last century, and it can obviously improve Child-Pugh score in patients with cirrhosis, as well as the survival rate [4,5]. However, the clinical study on intervention of antiviral therapy to chronic hepatitis B-related carcinogens is rare. This research aims at studying the effect of nucleoside antiviral therapy for chronic hepatitis B-related carcinogenic factors by retrospective clinical analysis.

1 Subjects and Methods

1.1 Subjects and grouping

All cases were hospitalized cases of HCC in Qingdao Infectious Diseases Hospital from February 2010 to June 2012, and there were 249 cases; They were diagnosed by the diagnostic criteria for HCC which was revised by Professional Committee of liver cancer in Chinese Anti-Cancer Association [6]; The diagnosis of cirrhosis was based on the diagnostic criteria for chronic hepatitis B cirrhosis in the " prevention and treatment guidelines of chronic hepatitis B "[7], EASL and AASLD criteria[8]. Each of cases was required to exclude hepatitis C virus infection, drug-induced, autoimmune, metabolic and other reasons cirrhosis, the cancer of other parts and metastatic liver cancer also were removed. The subjects are divided into antiviral treatment group and no-antiviral treatment group based that if they took the oral nucleoside antiviral drugs.

1.2 Contents of the observation

All objects were retrospectively surveyed with the questionnaire prepared by the unified, which included gender, age, history of antiretroviral therapy, history of HBV, history of cirrhosis, hepatitis B infection model, HBV DNA level, alpha fetoprotein (AFP), carcinoembryonic antigen(CEA), alanine aminotransferase (ALT), aspartate aminotransferase (AST), GGT and so on. History of antiretroviral therapy is defined as the application of nucleoside antiviral drugs for six months or more; HBV infection model is divided into " HbeAg positivity" (HBsAg, HBeAg and anti-HBc are positive), " anti-Hbe positivity " (HBsAg, anti-HBe and anti-HBc are positive) and others.

1.3 Statistical analysis

Statistical software package SPSS 17.0 was employed for all analyses. The variables of measurement data between the two groups were compared by independent sample t-test; The diversity of count data were compared by using the x^2 test; Statistically significant P value was defined as a value < 0.05. The quantification of related variables was shown in the table 1.

2 Results

2.1 General situation

A total of 249 cases of HCC was collected, excluded 17 cases which lack of hepatitis B infection model, HBV DNA level and other quantitative data, 232 cases(93.17%) were effective. Among them, the number of males was 193 and the number of females

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Table1 The transformation of related variables

Variable	Evaluation
Gender	Female=0，male=1
History of HBV	<10year=0，10~20 year =1，20~30 year =2，30~40 year =3，>40 year =4
History of cirrhosis	<10 year =0，10~20 year =1，20~30 year =2，30~40 year =3，>40 year =4
HBV infection model	"HbeAg positivity"=0，"anti-Hbe positivity"=1，other=2
HBV DNA level	$<10^3$copies/ml=0，10^3~10^4copies/ml=1，10^4~10^5copies/ml=2，10^5~10^6copies/ml=3，10^6~10^7copies/ml=4，>107copies/ml=5

was 39 (male: female = 4.95:1), with the mean age of (56.13 ± 9.36)y; The number of antiviral treatment group was 68, including 53 males and 15 females (male: female = 3.53:1), with the mean age of (58.29 ± 9.51)y; There were 164 cases in the other group, 140 males and 24 females(male: female = 5.83:1), with the mean age of (55.62 ± 9.02)y. Upon statistical analysis, the differences of gender and age between the two groups had no signification(P>0.05).

2.2 The distribution of HCC related factors between the two groups

2.2.1 The distribution of the history of HBV The number of patients infected with HBV for 20 to 30 years before they were diagnosed HCC was the most (36.76%) in the antiviral treatment group; and in no-antiviral treatment group, the majority, accounting for 31.09%, was diagnosed with HCC after they were infected with HBV for 10 to 20 years. Upon statistical analysis, P<0.05, the difference was statistically significant.

Table 2 Distribution of the history of HBV before diagnosed HCC

Group	The history of HBV(Y)					Total
	<10	10~20	20~30	30~40	>40	
Antiviral treatment group	6(8.82%)	18(26.47%)	25(36.76%)	15(22.06%)	4(5.89%)	68
No-antiviral treatment group	50(30.49%)	51(31.09%)	43(26.22%)	17(10.37%)	3(1.83%)	164
Total	56	69	68	32	7	232

Note: X^2=19.177, P=0.001.

2.2.2 The distribution of the history of liver cirrhosis In the antiviral treatment group, patients with liver cirrhosis for 10 to 20 years before diagnosed with HCC accounted for the most, about 50.59%; and in no-antiviral treatment group, the majority was those with liver cirrhosis for less than 10 years before they were diagnosed with HCC, accounting for 60.02%. Upon statistical analysis<0.05, the difference was statistically significant.

Table 3 Distribution of the history of liver cirrhosis before diagnosed HCC

Group	The history of HBV(Y)					Total
	<10	10~20	20~30	30~40	>40	
Antiviral treatment group	23(33.82%)	34(50.59%)	9(13.24%)	1(1.22%)	1(1.22%)	68
No-antiviral treatment group	105(64.02%)	42(25.61%)	10(6.10%)	5(3.05%)	2(1.22%)	164
Total	128	76	19	6	3	232

Note: X^2=9.842, P=0.043.

Table 4 Distribution of HBV infection mode

Group	HBV infection mode			Total
	HbeAg positivity	Anti-Hbe positivity	Others	
Antiviral treatment group	12(17.65%)	39(57.35%)	17(25.00%)	68
No-antiviral treatment group	39(23.78%)	85(51.83%)	40(24.39%)	164
Total	51	124	57	232

Note:X^2=1.10, P=0.576.

2.2.3 The distribution of HBV infection mode The number of "anti-Hbe positivity" was major in the both group, However, the difference was not statistically significant (P>0.05).

2.2.4 The distribution of HBV DNA level In the antiviral treatment group, the HBV DNA level of most patients (57.35%) was less than 10^3copies/mL, while in no-antiviral treatment group, patients with HBV DNA level between 10^4 to 10^5copies/mL were the most, accounting for 26.83%; the difference was statistically significant (P <0.05).

Table 5 The distribution of HBV DNA leve

Group	HBV DNA level(copies/mL)						Total
	$<10^3$	10^3~10^4	10^4~10^5	10^4~10^5	10^6~10^7	$>10^7$	
Antiviral treatment group	39(57.35%)	14(20.59%)	6(8.82%)	33(20.12%)	2(2.95%)	2(1.22%)	68
No-antiviral treatment group	41(25.00%)	31(18.90%)	44(26.83%)	33(20.12%)	13(7.93%)	2(1.22%)	164
Totle	80	45	50	39	15	3	232

Note: X^2=20.589, P=0.000.

2.2.5 The distribution of serum tumor markers and liver function The difference of ALT, AST and GGT between the antiviral treatment group and the no-antiviral treatment group was statistically significant; the difference of AFP, CEA was not statistically significant.

Table 6 The distribution of serum tumor markers and liver function

Items	$\bar{x} \pm s$		t	P
	Antiviral treatment group	No-antiviral treatment group		
AFP	315.72± 445.64	418.62± 523.41	1.519	0.131
CEA	4.36± 12.22	10.53± 78.61	0.643	0.521
ALT	52.46± 19.50	109.26± 129.71	5.462	0.000
AST	61.63± 30.67	146.62± 133.62	7.673	0.000
GGT	105.24± 84.55	218.45± 199.28	6.075	0.000

3 Discussion

HCC is the 5th most common cancer globally, and has the fastest growing cancer mortality[9]. In China there are about 350,000 annual incidences, and about 320,000 people die of the disease[10] with an increasing trend year by year. The incidence of HCC between the gender is significantly different. 232 patients shown the male-female ratio of 3.53:1, which was in accordance with the report by Qin Lun-xiu claimed the high incidence male [11]. It may be long-term alcoholism, higher social pressure [12], personality and other factors that caused this status. In this study, the average age when they were diagnosed with HCC was (56.13 ± 9.36) years old, suggesting that HCC patients in this region mainly concentrated in the senile stage.

The related survey showed that incidence of HCC in people with HBV infection was over about 200 times higher than people of matched group [13,14]. Nowadays, there are a lot of basic, clinical and epidemiological date confirmed the high correlation between HBV infection and the occurrence of HCC [15]. Chronic hepatitis B-related HCC generally experienced the process of "chronic hepatitis B infection-cirrhosis-HCC" [16] which was customarily called "Trilogy". Antiviral therapy is currently the key therapeutic measures to delay the occurrence of cirrhosis and improve the long-term prognosis of patients[17].

The results of this study showed the differences of the history of HBV infection and cirrhosis before diagnosed HCC between the two groups were statistically significant, Either the history of HBV infection or the history of cirrhosis of the antiviral treatment group was significantly longer than that of the other group, which suggested that antiviral therapy could delay the progress of "trilogy". The reason maybe that antiviral therapy could depress the replication of viral in the hepatocyte and lower the conversion rate of normal hepatocytes into cancerous cells[18]. However, the patients in both groups were diagnosed with HCC, and it is still unsure whether antiviral therapy can reduce the incidence of HCC.

The study on carcinogenesis of HBV concluded that the mechanism of HCC may be related with the integration of HBV DNA and host cell gene, the expression of HBV gene, changes in sequence of gene [19], and the HCC correlated to higher HBV DNA level [20]. This study showed that the difference of HBV DNA level in two groups was statistically significant which indicated that antiviral treatment can effectively reduce the replication of HBV

DNA; AFP and CEA showed no significant differences, which suggested antivi ral treatment does not correspondingly reduce levels of tumor markers; Although the differences of ALT, AST and GGT that reflected the liver function were statistically significant, it was not enough to explain antiviral therapy could significantly improve liver function in patients of hepatitis B-related carcinogens. Because that in a retrospective study the medications for subjects were not specifically known, not to exclude some relevant confounding factors.

In summary, the antiviral treatment of HBV infection can delay the development to HCC from HBV, to reduce the dangerousness of HBV-related carcinogenic factors; It can also effectively inhibit the replication of HBV DNA, protect liver function to a certain extent. To chronic HBV patients early application of antiviral drugs is expected to improve the quality of patient's life, or to further reduce the incidence of HBV-related HCC.

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抗病毒治疗对慢乙肝相关致癌因素的干预研究

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摘要 目的: 研究抗病毒治疗对原发性肝癌的慢性乙型肝炎相关危险因素的干预作用。**方法:** 回顾性分析青岛市传染病医院 2010 年 2 月至 2012 年 6 月住院的原发性肝癌患者病例 249 例,经统一编制的调查表记录相关数据,分析比较抗病毒治疗组与无抗病毒治疗组两组间各因素的分布差异。**结果:** 抗病毒治疗组与无抗病毒治疗组患者被诊断为 HCC 前的 HBV 感染时间、肝硬化史以及 HBV DNA 载量,P<0.05,差异均有统计学意义;两组间的 HBV 感染模式、AFP、CEA 差异无统计学意义;相关肝功能指标经统计学处理差异均有意义。**结论:** 抗病毒治疗可以明显降低慢乙肝相关致癌因素在患者中的分布,有效抑制 HBV DNA 复制,进而或可降低乙肝相关性肝癌的发病率。

关键词: 原发性肝癌;慢性乙型肝炎;危险因素;抗病毒治疗

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