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Original Article

Risk factors of disease progression and death in patients with HBV-related primary liver cancer

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Abstract: *Objective:* This study aimed to investigate the relationship between the timing of anti-viral therapy and the progression of hepatitis virus B (HBV) related primary liver cancer (PLC) as well as the risk factors of death in these patients. *Methods:* The clinical information of inpatients who were diagnosed with HBV related PLC and hospitalized between July 2008 and December 2011 was reviewed, the correlation between the timing of anti-viral therapy and progression of PLC was evaluated, and the risk factors related to death of PLC patients were analyzed with Logistic regression analysis. *Results:* In patients receiving antiviral therapy in hepatitis stage, the time from initiation of antiviral therapy to PLC was significantly longer than that in patients receiving antiviral therapy since the diagnosis of hepatic cirrhosis, and the median time was 66 months and 12 months, respectively ($P<0.05$). The risk for death in HBeAg positive PLC patients was 1.438 folds that in HBeAg negative patients. The risk for death in patients with high albumin level was lower than in those with low albumin level. Conclusion: Initiation of antiviral therapy since the hepatitis stage may significantly prolong the time to PLC. Being positive for HBeAg and hypoalbuminemia are risk factors of death in patients with HBV related PLC besides PTA.

Keywords: Primary liver cancer, antiviral therapy, progression, death, risk factors

Introduction

Primary liver cancer (PLC) refers to the malignancy of hepatocytes or intrahepatic bile duct cells and significantly threatens human's health. Currently, the morbidity and mortality of PLC are increasing world wide [1, 2]. It was reported that the annual incidence of PLC was 11.3/100000 in developed countries and 10/100000 in developing countries in 2000 [3]. Males are more likely to develop PLC than females with a ratio of 1.4-3.3:1. The annual mortality of PLC is 9.4/100000 for males and 10.5/100000 for females. Studies have confirmed that hepatitis B virus (HBV) infection is closely related to the pathogenesis of HBV related PLC [4]. For patients with chronic HBV infection, regular antiviral therapy is able to effectively inhibit viral replication and therefore decrease the morbidity and mortality of PLC [5].

In this study, a total of 191 patients who were diagnosed with HBV related PLC and had complete medical record were recruited from the Beijing Ditan Hospital of Capital Medical University between July 2008 and December 2011, and the clinical information was retrospectively reviewed. The timing of antiviral therapy and PLC progression was evaluated, and risk factors affecting the survival time of PLC patients were analyzed with Logistic regression analysis, aiming to provide medical evidence for effective prevention and therapy of liver cancer in clinical practice.

Materials and methods

Patients

Inpatients who were diagnosed with HBV related PLC and had complete medical information were recruited from Beijing Ditan Hospital of Capital Medical University between July 2008 and December 2011. The diagnosis of PLC was based on the diagnostic criteria for PLC developed by the Professional Committee of Liver Cancer of Chinese Anti-Cancer Association in 2000: patients had a history of HBV infection or medical record showed positive for hepatitis B

surface antigen (HBsAg), hepatitis B e-antigen (HBeAg) and/or antibody to hepatitis B e-antigen (anti-HBe); pathological or clinical examinations supported the diagnosis of PLC: 1) intrahepatic or extrahepatic pathological examination confirmed the diagnosis of PLC; 2) two imaging examinations showed PLC like space-occupying lesions, or patients were positive for two markers of liver cancer [fuc α fetoprotein (AFP), abnormal prothrombin, gamma glutamyl transpeptidase isoenzyme II, a-L-fucosidase] and one imaging examination showed PLC like space-occupying lesions; 3) there were clinical manifestations of PLC, extrahepatic metastatic lesions were identified (macroscopic bloody ascites or ascites with cancer cells), and metastatic liver cancer and PLC caused by chronic hepatitis C or other factors were excluded.

Methods

General characteristics, epidemiological information, clinical characteristics, and information about anti-viral therapy were collected from these patients. Patients meeting the diagnostic criteria and with complete medical information were divided into two groups according to the timing of anti-viral therapy: Group A: the anti-viral therapy was initiated in the stage of hepatitis; Group B: the antiviral therapy was initiated in the stage of hepatic cirrhosis; Group C: the anti-viral therapy was initiated after the diagnosis of PLC. The time from anti-viral therapy to the diagnosis of PLC was determined in Group A and Group B and compared between them. The REACH-B was calculated before antiviral therapy in Group A. The correlation of clinical information (quantitative and qualitative data) of PLC patients with death was evaluated in PLC patients, and the incidence of HBeAg seroconversion was calculated in 3 groups after antiviral therapy.

Statistical analysis

Statistical analysis was performed with SPSS version 16.0. Qualitative data are expressed as percentage and quantitative data as mean ± standard deviation (SD). The time from antiviral therapy to the diagnosis of PLC was compared with rank sum test. Factors with significant difference were subjected to Logistic regression analysis. The correlation of characteristics of PLC patients at baseline with PLC progression and death was evaluated. A value of $P<0.05$ was considered statistically significant.

Results

Clinical characteristics of patients with HBV related PLC

A total of 882 patients who were diagnosed with HBV related PLC in the Beijing Ditan Hospital of Capital Medical University between July 2008 and December 2011. There were 679 males and 203 females with the male to female ratio of 3.34:1. The mean age was 56.43±10.16 years (range: 24-88 years). There were 372 patients receiving anti-viral therapy, of which 86 received antiviral therapy after the diagnosis of PLC. Thus, 596 patients did not receive anti-viral therapy before the diagnosis of PLC and accounted for 67.57% of patients recruited. Before the diagnosis of PLC, 286 had received antiviral therapy and accounted for 32.43%.

Of the 286 patients receiving antiviral therapy before the diagnosis of PLC, clinical information could not confirm the stage at which antiviral therapy was initiated and thus further analysis was impossible. The remaining 191 patients with complete medical information were recruited for further analysis, including 28 patients who received antiviral therapy at the stage of chronic hepatitis B (Group A), 77 received antiviral therapy at the stage of hepatic cirrhosis (55 at the stage of decompensated cirrhosis) (Group B) and 86 received antiviral therapy after the diagnosis of PLC (Group C).

In Group A and Group B, the median time from antiviral therapy to the diagnosis of PLC was 66 months and 12 months, respectively, showing significant difference ($P<0.05$). It is suggested that the time interval from the initiation of antiviral therapy to the presence of PLC is significantly longer in Group A than in Group B. In Group A, the baseline REACH-B score was 6-17 (mean: 11.75±3.68).

Risk factors of death in patients with HBV related PLC

1) Following qualitative parameters were collected from the medical record: gender, age, family history, history of drinking, history of

Table 1. Potential risk factors of death in PLC patients

Factors	Name of variables	Assignment
Gender	X_1	Male=1, female=2
Age	X_2	
Family history	X_3	Yes=1, No=2
History of drinking	X_4	Yes=1, No=2
History of blood transfusion	X_5	Yes=1, No=2
HBeAg	X_6	Positive=1, negative=2
Anti-viral therapy	X_7	Yes=1, No=2
Concomitant use of drugs	X_8	Yes=1, No=2
Concomitant therapy	X_9	Yes=1, No=2
Death	Y	Control/survival=0, death=1

Table 2. Incidence of HBeAg seroconversion in different groups

	Cases and Incidence of HBeAg seroconversion	
	Cases (n)	Incidence (%)
Group A	16	57.14
Group B*	10	12.99
Group C	11	12.79

Notes: *11.54% for patients at the stage of decompensated cirrhosis; 33.33% for patients at the stage of compensated cirrhosis. Group A: the anti-viral therapy was initiated in the stage of hepatitis; Group B: the anti-viral therapy was initiated in the stage of hepatic cirrhosis; Group C: the anti-viral therapy was initiated after the diagnosis of PLC.

blood transfusion, HBeAg status on the diagnosis of PLC, anti-viral therapy, concomitant use of drugs, surgical intervention. Their relationship with death in patients with HBV related PLC was evaluated by Logistic regression analysis (**Table 1**). Results showed the regression equation was as follow: $\log_{it}P=-1.266+1.438X_6$ (OR=1.438, 95% *CI* 1.000-2.066), $\chi^2=3.874$, P<0.05. This indicates that the risk for death in patients positive for HBeAg is 1.438 folds that in those negative for HBeAg when the other factors remain comparable. That is, HBeAg positive is a risk factor of death in patients with HBV related PLC.

The incidence of HBeAg seroconversion was calculated in three groups (**Table 2**). It was 57.14% in Group A, 12.99% in Group B (33.33% in compensated cirrhosis; 11.54% in decompensated cirrhosis) and 12.79% in Group C. The incidence of HBeAg seroconversion in patients who received antiviral therapy at the stage of decompensated cirrhosis or after the diagnosis of PLC is significantly lower than that in those receiving antiviral therapy at the stage of hepatitis or compensated cirrhosis.

2) Following quantitative parameters were collected from patients with HBV related PLC: alanine aminotransferase (ALT), total bilirubin (TBIL), albumin (ALB), HBV DNA, HBeAg and AFP. Their relationship with death in patients with HBV related PLC was evaluated by Logistic regression analysis. Results showed the regression equation was as follows: $\log_{it}P=1.151-0.056\times ALB$ (OR=0.946, 95% *CI*=0.904-0.989), *P*<0.05. This indicates that high albumin level reduces the risk for death in patients with HBV related PLC.

Discussion

PLC is a common malignancy in clinical practice. It has insidious onset, but may progress rapidly, causing a short survival time. Thus, most patients are often diagnosed with PLC at late stage, predicting a poor prognosis. China has a high incidence of PLC. It was reported that the incidence of PLC was 29.9/100000 and its mortality was 27.7/100000 in China in 2008 [3].

In China, HBV related PLC accounts for more than 70% of PLC [6, 7]. Epidemiological studies [8-10] indicate that hepatic cirrhosis patients with high HBV DNA load are more susceptible to PLC, and the active replication of HBV is a factor promoting the occurrence and development of cirrhosis as well as the malignant transformation of hepatocytes. Carcinogenic genes may be integrated into hepatocytes via HBV DNA replication and also cause allelic loss and point mutations of tumor suppressor genes [11]. Anti-viral therapy belongs to pathogen targeting treatment and is also a basic treatment, which has been an international consensus and widely accepted. Under this condition, the hospitalized patients with PLC still increase, but whether they receive antiviral therapy and whether antiviral therapy affects the occurrence and development of PLC are still unclear and investigated in this study.

In Beijing Ditan Hospital of Capital Medical University, a total of 882 patients were diagnosed with HBV related PLC between July 2008 and December 2011. Before the diagnosis of HBV related PLC, the majority of patients (67.57%) did not receive antiviral therapy. In the remaining patients receiving antiviral therapy before the diagnosis, it was initiated since the hepatic cirrhosis was present, suggesting that the initiation of antiviral therapy is relatively late in these patients, and the delayed anti-viral therapy may be one of risk factors of PLC. According to the baseline characteristics of hepatitis B patients (gender, age, ALT, HBeAg status and HBV DNA load), the score is calculated with the highest score of 17, and the lower the score is, the lower the risk for liver cancer is. The REACH-B scoring system is simple and easy to use and can be used to predict the risk for liver cancer in patients with chronic hepatitis B [12-16]. In recent years, some investigators attempt to use this system to evaluate the necessity of antiviral therapy. According to the findings reported by Chen et al [12], REACH-B score of ≥7 in HBeAg positive patients and REACH-B score of ≥7 for HBeAg negative patients are indications to antiviral therapy. In this study, the REACH-B score was relatively high before the antiviral therapy in 28 patients who received antiviral therapy since the stage of hepatitis, suggesting that these patients have a high risk for liver cancer. Although these patients received antiviral therapy since the stage of hepatitis, they developed PLC a median of 66 months later. In addition, for patients who received antiviral therapy since the stage of hepatic cirrhosis, the time to the diagnosis of PLC was shorter (median: 12 months), and significantly different from that in above patients. These findings indicate that early antiviral therapy may prolong the time to PLC: the time to PLC is shorter when the antiviral therapy is initiated at stage of hepatitis than that when it starts at the stage of cirrhosis. On one hand, antiviral therapy prolongs the survival time, and on the other hand, the time from hepatic cirrhosis to liver cancer is shorter than that from hepatitis to liver cancer. Overall, early antiviral therapy is recommended once indications to antiviral therapy are present. Especially, chronic hepatitis B patients with high baseline REACH-B score and those with hepatic cirrhosis need active antiviral therapy and close monitoring and management because they have a high risk for PLC.

In this study, the risk for death was also investigated in these patients. Prothrombin activity-prothrombin time activity (PTA) is a risk factor affecting the survival of liver disease patients [17-19]. Logistic regression analysis showed the risk for death in HBeAg positive patients was 1.438 folds that in HBeAg negative patients, suggesting that positive for HBeAg is an important factor affecting the survival of PLC, which is consistent with previously reported [20, 21]. The incidence of HBeAg seroconversion was also compared among groups. Results showed more patients achieved HBeAg seroconversion when the antiviral therapy was initiated at the stage of hepatitis as compared to patients receiving antiviral therapy after the diagnosis of cirrhosis and PLC. This suggests that early antiviral therapy may achieve a rapid HBeAg seroconversion and thereafter reduce the morbidity and mortality of liver cancer. However, the sample size was small in this study, and more cohort studies with large sample size are required to confirm our findings. In addition, ALB level is a major indicator reflecting the liver's synthetic function. High ALB level indicates a better compensated capability of the liver and thus the risk for PLC related death is also low under this condition.

Our results indicate that anti-viral therapy may not completely inhibit the occurrence of HBV related PLC, but regular antiviral therapy in patients with chronic hepatitis B may significantly delay the occurrence of liver cancer [22]. For patients with HBV related PLC, early diagnosis and early treatment are helpful for the prolongation of survival time and improvement of prognosis.

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Disclosure of conflict of interest

None.

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