Original Article

Incidence and Characteristic of Hepatocellular Carcinoma in Hepatitis B Related Cirrhosis

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Background: Hepatocellular carcinoma (HCC) and liver decompensation are the serious complications of chronic hepatitis B (CHB) especially after development of cirrhosis. Current treatment of CHB is nucleos(t)ide analogues (NA).

Objective: To evaluate the incidence and characteristic of HCC in patients with HBV cirrhosis as well as the rate of hepatic decompensation in NA treated CHB.

Materials and Methods: A retrospective chart review of the patients with HBV associated cirrhosis who had attended Hepatitis Clinic, Siriraj Hospital between December 1, 2010 to December 31, 2011 was conducted. The hospital charts were reviewed to capture HBV related treatment, cirrhotic complication, occurrence, and characteristic of HCC.

Results: There were 241 HBV related compensated cirrhosis enrolled in the study. Among these, 234 patients received NA treatment. There were 29 (12%) patients developed HCC during a median follow-up of 4.6 years and the incidence rates of HCC per 100 person-year was 2.6. There was no risk factor that predicted the occurrence of HCC, however, from multivariate analysis, older age, male gender, diabetes mellitus, HBeAg positive, alpha-fetoprotein (AFP) >10 IU/mL and HBV DNA >2,000 IU/ml at baseline trended to have a higher risk of HCC but did not reach statistical significance. Most HCCs found in the present study were asymptomatic and were found during surveillance and were single lesion located in the right lobe without portal involvement. Most of the HCC patients received potentially curative treatment (37.9%). Moreover, we found that the incidence of liver decompensation was 0.53 per 100 person-year. Two HCC patients died because of progressive liver disease.

Conclusion: HCC is among the most serious complication of HBV related cirrhosis and occurred 2.6 per 100 person-year in the present study. It is unclear whether treatment would reduce HCC since most of the patients received treatment. Liver decompensation was found at 0.53 per 100 person-year which is lower than previous report.

Keywords: Chronic hepatitis B, Hepatocellular carcinoma, Incidence, Liver decompensation, Hepatitis B treatment, Treatment

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Chronic hepatitis B (CHB) is one of the major public health issues worldwide. It is estimated that as many as 350 million people suffer from CHB and about 600,000 die each year from hepatitis B related complication such as cirrhosis and its complication, hepatocellular carcinoma (HCC)[1]. The annual incidence of HCC in hepatitis B cirrhosis was about 2.5% and increased with age.[2] A cohort study of 349 compensated cirrhosis from Western European showed that the incidence of HCC and liver decompensation for a mean follow-up period of 73 months was 9% and 28%, respectively. In the present study, the probability of remaining compensated was 77% and 63% at 5 and 10 years after diagnosis[3]. Another study also from Western Europe, a retrospective cohort study of 297 untreated patients with compensated viral cirrhosis (Child class A; 161 patients with hepatitis type B and 136 with type C) who were followed for a median period of 6.6 year. The incidence of HCC and hepatic decompensation in HBV cirrhosis was 2.2 and 3.3 per 100 person-year, respectively[4]. A cohort study from Taiwan, during 102 months of follow-up, 93 untreated HBV compensated cirrhosis developed hepatic decompensation, HCC, and liver related mortality in 1.5%, 2.7% and 1.4% per year, respectively[5]. Although the incidence of new infection of HBV decreased because of HBV vaccination in newborns and screening of blood donors, there are many people who have been infected and are at risk for developing chronic complication. Host and viral risk factors for developing HCC in HBV infection include older age, male gender, family history of HCC, cigarette smoking, alcoholic drinking, presence of cirrhosis, HBV genotype C, core promoter mutation, and co-infection with HCV[2,8].

Many studies showed that there were clinical differences between HBV related HCC and HCC from other causes. Study from Japan showed that among 205 patients with HCC, HCV-related HCC occupied over 80% of total

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HCC in Japan, which were characterized by older age and more severe cirrhosis, as compared with HBV-related HCC[6]. The male-to-female ratio was higher in HBV-related HCC than in HCV-related HCC. In most patients with HBV-related HCC, the tumors were commonly infiltrative and multinodular whereas in HCV-related HCC, the tumors were more likely to be solitary, smaller in size and encapsulated. Extensive hepatic involvement and portal vein invasion by the tumor were found in HBV-related HCC more than HCV-related HCC[7].

Since most studies were from Western countries or Japan where HCV-related HCC was more prevalence as compare with HCC in Thailand[8], the present study aimed to assess the incidence of HCC in HBV-related cirrhosis. Moreover, we would like to identify risk factors and tumor characteristic of HCC as well as incidence of hepatic decompensation in this group of patients.

Materials and Methods

Study design

This is a cross-sectional retrospective study conducted at hepatitis clinic, Siriraj Hospital from December 1, 2010 to December 31, 2011. The patients were included if they were older than 18 years with evidence of compensated HBV-related cirrhosis as defined by presence of HBsAg in the serum plus evidence of cirrhosis by histology, clinical evidence such as splenomegaly, esophageal varices, liver imaging or Fibroscan measurement in the range of cirrhosis. Exclusion criteria included co-infection with hepatitis C or HIV, coexisting significant liver disease such as hemochromatosis, decompensated cirrhosis (Child-Pugh B or C), evidence of HCC within 6 months of follow-up. The study was approved by Siriraj Institutional Review Board (Si 426/2010, renewal).

Data collection

Chart review was performed to find out the onset of cirrhosis, complication of cirrhosis such as liver decompensation and hepatocellular carcinoma. HBV treatment included interferon or nucleos(t)ide analogue (NA), including lamivudine, adefovir, tenofovir, telbivudine, entecavir). Clinical variables were obtained such as age, gender, history of smoking and alcohol use, family history of HCC, comorbidity, biochemical data, HBeAg status, baseline HBV viral load, alpha-fetoprotein level (AFP), details of the treatment. All patients had more than 6 months of follow-up between January 1, 1995 and December 31, 2011. The time of observation was calculated from the date of entry until death or the end of the study period (December 31, 2011). HCC surveillance program consisted of ultrasound with or without AFP every 6 to 12 months. Model for end-stage liver disease (MELD) score, Child-Pugh score and alfa-fetoprotein (AFP) were obtained when the patients were diagnosed HCC or liver decompensation if data available.

Clinical events

The primary outcome of this study was the incidence of HCC which was diagnosed according to European Association for the Study of the Liver (EASL) guideline[9] and HCC were staged based on the Barcelona Clinic-Liver-Cancer (BCLC)[10]. The secondary outcome was the development of liver failure defined as ascites confirmed by ultrasonography or computed tomography, variceal bleeding, hepatic encephalopathy, new onset of jaundice, and hepatic decompensation as determined by worsening of Child-Pugh score.

Statistical analysis

Statistical analyses were performed using SPSS version 13 for Windows. Categorical variables were analyzed using the Chi-square test or Fisher's exact test when appropriate. Continuous variables with normal distribution were expressed as mean, standard deviation and analyzed using the Student's t-test. Cox proportional hazards models were used to determine which baseline factors were associated with development of HCC.

Results

There were 241 compensated HBV related liver cirrhosis in the study, 234 patients received treatment (3 were considered NR), only 7 patients did not receive any treatment due to persistently HBV low viral load. No patients with high HBV DNA were untreated and all of those who received treatment, HBV DNA was below detection limit. Among 241 patients, 29 (12%) patients developed HCC. Table 1 shows patient baseline characteristic comparing between non-HCC (212 patients) and HCC group (29 patients) at the time of enrollment. When patients with and without HCC were compared, there was not statistically significant in term of age, sex, duration of follow-up, family history of HCC, baseline HBV viral load, HBeAg status and treatment. However, history of smoking and level of AFP at baseline was higher in HCC group. There were higher adjusted odd ratios in developing HCC with older age, male gender, DM, HBeAg positive, alpha-fetoprotein >10 IU/mL and HBV DNA more than 2,000 IU/ml at baseline but all of these factors did not reach statistically significant as shown in Table 2.

Patient with HCC

There were 29 patients who had HCC, only one patient did not receive treatment due to persistently low HBV DNA, 2 patients were NR to pegylated interferon and 2 relapsed after pegylated interferon treatment but all re-treated with NA as shown in Table 3. The incidence of HCC in HBV compensated cirrhosis was 2.6 per 100 person-year with mean age at diagnosis of 59.7 years old, mean duration from onset of cirrhosis to development of HCC was 3 years. Most of HCCs in the present study were single lesion, involved right lobe, no portal vein involvement, no extra-hepatic metastasis which were in the early BCLC stage 69%. Eleven patients (37.9%) received potentially curative treatment e.g. radiofrequency ablation (RFA), surgery, liver transplantation and 16 (55.2%) patients received

Table 1. Baseline clinical characteristics among 241 hepatitis B related cirrhotic patients

	Non-HCC (n = 212)	HCC (n = 29)	*p*-value
Age (years), mean (SD)	52.9 (10.7)	56.6 (10.7)	0.08
Male	131 (61.8)	21 (72.4)	0.27
Duration of cirrhosis (year) mean (SD)	4.8 (3.1)	4.7 (2.3)	0.81
BMI (kg/m^2), mean (SD)	24.9 (4.5)	25.4 (4.3)	0.63
Use of alcohol	46 (27.7)	10 (41.7)	0.16
Smoking	16 (13)	3 (33.3)	0.03
Family history of HCC	25 (12)	3 (10.3)	1.00
Diabetes	45 (21.2)	9 (31)	0.24
Hypertension	71 (33.5)	12 (41.4)	0.40
Dyslipidemia	39 (18.4)	6 (20.7)	0.77
CKD	4 (1.9)	1 (3.4)	0.48
Ischemic heart disease	10 (4.7)	1 (3.4)	1.00
HBeAg positive	71 (34.1)	10 (35.7)	0.87
HBV DNA (IU/mL)			
<2,000	25 (13.3)	4 (15.4)	0.76
≥2,000	163 (86.7)	22 (84.6)	
AFP (IU/mL)			
≤10	147 (77)	14 (56)	0.02
>10	44 (23)	11 (44)	
Treatment	206 (97.2)	28 (97.2)	0.59

Data are expressed as number (%) unless specified.
BMI = body mass index; CKD = chronic kidney disease; HCC = hepatocellular carcinoma

Table 2. Multivariate analysis of risk factors for the development of hepatocellular carcinoma among 241 hepatitis B related cirrhotic patients

	Adjust odd ratio	95% confidence interval	*p*-value
Age	1.03	0.98 to 1.08	0.21
Male	2.23	0.75 to 6.67	0.15
Diabetes	2.19	0.79 to 6.10	0.13
HBeAg positive	1.36	0.47 to 3.90	0.57
AFP >10 IU/mL	1.61	0.58 to 4.46	0.36
HBV DNA >2,000 IU/mL	1.03	0.25 to 4.27	0.26

loco-regional treatment e.g. transarterial chemo-embolization (TACE), TACE plus RFA due to limited liver reserve. Mean survival until end of the study was 17.2 months as shown in Table 4. Two HCC patients presented with liver decompensation which was considered for palliative treatment and death because of liver decompensation.

Liver decompensation

There were 6 patients developed liver decompensation (bleeding varices, ascites, jaundice, and hepatic encephalopathy) all of them subsequently developed hepatocellular carcinoma and two died due to progressive disease as mentioned earlier. The incidence of liver decompensation was 0.53 per 100 person-year.

Discussion

CHB increases the risk of developing cirrhosis, hepatic decompensation, and HCC[1] with annual incidence of HCC in HBV-related cirrhosis of about 2.5% and increases with age[2]. From previous studies, risk factors of HCC in

Table 3. Characteristic of hepatocellular carcinoma at the time of diagnosis

Characteristic	Results	Minimum, maximum
Age (year), mean (SD)	59.7 (10.6)	35.4, 79.2
Duration after diagnosis (year), mean (SD)	3.0 (1.9)	0.5, 8.3
Log HBV DNA (IU/mL), mean (SD)	1.8 (1.9)	0.7, 8.0
Child-Pugh score, mean	5.4	5.0, 7.0
A, n (%)	28 (96.6)	
B, n (%)	1 (3.4)	
MELD score, mean	6.5	0.8, 11.5
Location of HCC, n (%)		
Right lobe	17 (58.6)	
Left lobe	9 (31)	
Both lobes	3 (10.4)	
Number of HCC, n (%)		
1	21 (72.4)	
2	3 (10.4)	
3	3 (10.4)	
≥4	2 (6.8)	
Size of HCC (cm), mean (SD)	2.5 (1.4)	1.0, 10.0
Portal vein involvement, n (%)	3 (10.4)	
BCLC stage, n (%)		
Very early	12 (41.4)	
Early	8 (27.6)	
Intermediate	8 (27.6)	
Advanced	0	
Terminal	1 (3.4)	

BCLC = Barcelona clinic liver cancer; HCC = hepatocellular carcinoma; MELD = Model for end-stage liver disease

Table 4. Modality of hepatocellular carcinoma treatment

Treatment modalities	Number (%)	Mean follow-up (months)
Potential curative		
Surgery	2 (6.9)	4.9
Liver transplantation	1 (3.4)	27.8
TACE then surgery	1 (3.4)	9.3
RFA	7 (24.1)	7.3
Locoregional		
TACE	10 (34.5)	23.0
TACE + RFA	6 (20.7)	27.5
Palliative	2 (6.9)	-

HCC = hepatocellular carcinoma; RFA = radiofrequency ablation; TACE = transarterial chemoembolization

this group include male gender, family history of HCC, older age, cigarette smoking, alcoholic drinking, presence of cirrhosis, HBV genotype C, HBV core promoter mutation, and co-infection with HCV[2,9-12].

In the present study, we found that the incidence of HCC in HBV-related cirrhosis was 2.6 per 100 person-year which was similar to previous studies[2,12]. The mean age of patients who had HCC was about 60 years old. Our study represents the incidence of HCC in CHB cirrhosis who had been treated because 97% of our patients received treatment. However, the study did not find any factors that may predispose to the development of HCC. There were many factors that had high odd ratios such as older age, male gender, DM, HBeAg positive, alpha-fetoprotein >10 IU/mL, HBV DNA more than 2,000 IU/ml but all these factors did not reach statistically significant. This result is limited by small sample size in our study since there were only 29 HCC. Our patients have undergone regular surveillance for HCC including serum AFP and liver ultrasound every 6 to 12 months and a recall policy was practiced once the ultrasound showed new lesion which include contrast imaging either computerized scan or magnetic resonance imaging. As the result, most HCC detected were single lesion with size less than 3.0 centimeters without vascular involvement which was good candidate for curative treatment. However, not every patient with this early stage can be treated with curative treatment because of low liver reserve, not suitable for hepatic resection. Mean follow-up of HCC patients may mislead since this was cross-sectional retrospective study and unfortunately those who received surgery or RFA were recently diagnosed HCC.

The incidence of hepatic decompensation was 0.53 per 100 person-year in our study which occurred at the median time of 3.8 years after diagnosed cirrhosis and, all of whom subsequently developed HCC. Our incidence of liver decompensation was lower than previous report of about 1.5% per year or 3.3 per 100 person-year. This may be the result that majority of our patients received treatment[4,13]. However, more data with more patients needed to confirm such finding.

The present study was limited by retrospective data collection, not all information was collected. As mentioned earlier, our study represents CHB patients who were treated, however, there were a few untreated since during the present study conducted treatment was not recommended for HBV-related cirrhosis with low but detectable HBV viral load.

Conclusion

HCC is among the most serious complication of HBV related cirrhosis occurs 2.6 per 100 person-year in the present study. Most HCC in our study were in the early stage with potential curative treatment. Liver decompensation was found at 0.53 per 100 person-year which is lower than previous reports because our most of our CHB patients received treatment.

What is already known on this topic?

HBV related cirrhosis increases the risk of HCC and liver decompensation and treatment can reduce liver decompensation and development of HCC. There are many factors that predispose to the progressive disease and development of HCC.

What this study adds?

In the population of mostly treated HBV related cirrhosis, development of HCC and liver decompensation was 2.6 and 0.53 per 100 person-year, respectively. In these treated HBV cirrhosis, no additional risk factors were identified in the patients who developed HCC.

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Conflicts of interest

The authors declare no conflict of interest.

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อุบัติการณ์และลักษณะของมะเร็งตับปฐมภูมิในผู้ป่วยตับแข็งจากไวรัสตับอักเสบบี

สุพจน์ นิ่มอนงค์, ลักขณา ปรีชาสุข, ทวีศักดิ์ แทนวันดี

ภูมิหลัง: มะเร็งตับปฐมภูมิและภาวะตับวายเป็นภาวะแทรกซ้อนที่สำคัญ ในผู้ป่วยไวรัสตับอักเสบบีเรื้อรัง โดยเฉพาะในผู้ป่วยที่มีภาวะตับแข็งในปัจจุบันการรักษาที่สำคัญคือ ยารับประทาน nucleos(t)ide analogues (NA)

วัตถุประสงค์: เพื่อประเมินอุบัติการณ์และลักษณะของมะเร็งตับปฐมภูมิและภาวะตับวายในผู้ป่วยตับแข็งจากไวรัสตับอักเสบบี ซึ่งส่วนใหญ่ได้รับการรักษาด้วย NA

วัสดุและวิธีการ: เป็นการศึกษาแบบย้อนหลังในสถาบันเดียว โดยการรวบรวมผู้ป่วยตับแข็งจากไวรัสตับอักเสบบีเรื้อรังในผู้ใหญ่ที่ยังไม่มีภาวะตับวายที่มารับการรักษาคลินิกโรคตับโรงพยาบาลศิริราชตั้งแต่วันที่ 1 ธันวาคม พ.ศ. 2553 ถึง วันที่ 31 ธันวาคม พ.ศ. 2554 โดยการเก็บข้อมูลจากแฟ้มประวัติผู้ป่วย

ผลการศึกษา: มีผู้ป่วยทั้งหมด 241 ราย โดย 234 ราย ได้รับการรักษาด้วย NA มีผู้ป่วย 29 ราย (ร้อยละ 12) เกิดมะเร็งตับปฐมภูมิหลังจากติดตามเฉลี่ย 4.6 ปี โดยมีอุบัติการณ์ที่ 2.6 ต่อร้อยคนต่อปี ในการศึกษานี้ไม่พบปัจจัยที่เพิ่มความเสี่ยงต่อการเกิดมะเร็งตับปฐมภูมิ แม้ว่ามีแนวโน้มว่าผู้ป่วยอายุมาก, เพศชาย, เบาหวาน, HBeAg บวก, ระดับแอลฟาฟีโตโปรตีนสูง และระดับไวรัสตับอักเสบบีมากกว่า 2,000 ยูนิต/มล. มีแนวโน้มเพิ่มความเสี่ยงแต่ยังไม่มีนัยสำคัญทางสถิติ มะเร็งตับปฐมภูมิที่พบในการศึกษาไม่มีอาการ พบขณะติดตามและมักเป็นก้อนเดียวที่ตับกลีบขวาโดยไม่มีการกระจายไปที่หลอดเลือดดำพอร์ทัล ผู้ป่วยร้อยละ 37.9 ได้รับการรักษาที่หวังผลหายขาด นอกจากนั้นจากการศึกษานี้พบว่าอัตราการเกิดภาวะตับวายอยู่ที่ร้อยละ 0.53 ต่อร้อยคนต่อปี มีผู้ป่วยมะเร็งตับปฐมภูมิเสียชีวิตเมื่อแรกวินิจฉัยจากภาวะตับวาย

สรุป: มะเร็งตับปฐมภูมิซึ่งเป็นภาวะแทรกซ้อนที่สำคัญในผู้ป่วยตับแข็งจากไวรัสตับอักเสบบี พบที่ 2.6 ต่อร้อยคนต่อปี ในการศึกษานี้ เนื่องจากผู้ป่วยเกือบทั้งหมดได้รับการรักษา ดังนั้นไม่สามารถบอกได้ว่าการรักษาช่วยลดอุบัติการณ์มะเร็งตับปฐมภูมิหรือไม่ นอกจากนั้นพบอัตราการเกิดภาวะตับวายที่ร้อยละ 0.53 ต่อร้อยคนต่อปี ซึ่งน้อยกว่าการศึกษาก่อน ๆ