Use of serum hepatitis B viral DNA in prognostication of patients undergoing non-surgical therapy for liver cancer

SL Chan *, FKF Mo, PKS Chan, W Yeo

KEY MESSAGES

1. Hepatitis B virus (HBV) load is not a prognostic factor for patients with advanced HBV-related hepatocellular carcinoma (HCC) undergoing non-surgical therapy.
2. Antiviral therapy for HBV-related HCC is associated with improved survival outcome.

Hong Kong Med J 2014;20(Suppl 6):S32-4
RFCID project number: 09080422

[1] SL Chan *, [1] FKF Mo, [2] PKS Chan, [1] W Yeo

[1] *Department of Clinical Oncology, The Chinese University of Hong Kong*
[2] *Department of Microbiology, The Chinese University of Hong Kong*

* Principal applicant and corresponding author: L_chan@clo.cuhk.edu.hk

Introduction

Chronic hepatitis B virus (HBV) infection is the most common cause of hepatocellular carcinoma (HCC) in Hong Kong. The HBV mediates hepatocarcinogenesis via its direct oncogenic effects and/or indirect mechanism of cirrhotic damage to the liver. Viral load is monitored by serum HBV DNA during treatment of chronic HBV infection; the HBV DNA level in serum is associated with risk of HCC development.[1] The clinical impact of viral load on the outcome of patients with malignancy remains unclear.

In this study, we aimed to validate the prognostic impact of baseline serum HBV DNA in patients with inoperable HCC undergoing non-surgical therapy. In addition, the impact of antiviral therapy on HBV viral load during treatment of HCC was evaluated.

Methods

This study was conducted from October 2009 to September 2010. Serum HBV DNA levels from prospectively collected serum samples of patients with inoperable HCC were analysed. Consecutive patients with inoperable HBV-related HCC who attended the Joint Hepatoma Clinic, Prince of Wales Hospital, Hong Kong, from 2004 to 2006 were included. The HBV status was confirmed by positive hepatitis B surface antigen for ≥6 months. The diagnosis was either confirmed histologically or by the presence of characteristic imaging findings in contrast scan together with α-fetoprotein of >500 ng/mL. Patients were treated according to the standard practice of the department. Patients were followed up regularly every 4 to 8 weeks, or more frequently if indicated clinically.

The blood sample on the day of diagnosis of HCC was used for quantitation of serum HBV DNA. If not available, another sample taken within 2 months and nearest to the date of HCC diagnosis was used. The HBV DNA was quantified by TaqMan real-time polymerase chain reaction assay as described previously.[2] The range of HBV DNA detection was from 102 to 109 copies/mL, with correlation coefficient of the standard curve routinely >0.990.

Antiviral therapy was defined as the use of any approved nucleoside/nucleotide analogues for HBV infection for >6 months.

Clinical factors, laboratory results and tumour factors at baseline were determined. These parameters correlated with survival using Cox's proportional hazard model to detect independent prognostic factors for overall survival. Multivariate analysis was carried out using a stepwise model building procedure based on a significance value of 0.05 for both inclusion and exclusion of prognostic factors.

Results

A total of 135 men and 15 women aged 18 to 86 (median, 60) years were analysed (Table 1). The median follow-up time was 15.0 (11.8-18.2) months. Most (71.3%) patients had multifocal intrahepatic tumours. In terms of tumour staging, 68.7% had tumour, node, metastasis (TNM) stage IV disease, 47.3% had Okuda stage B disease, and 46.8% had Chinese University Prognostic Index intermediate stage disease. About 52.7% of patients received palliative treatment (including transarterial or systemic therapy) and 42.0% received supportive care.

The median overall survival was 7.8 (95% confidence interval [CI], 5.3-9.4) months. The median serum HBV DNA level at the time of diagnosis of HCC was 6.12 (range, 2.0-9.2) $\log_{10}$ copies/mL. In

univariate analysis, serum HBV DNA at diagnosis of HCC was not prognostic of overall survival (hazard ratio [HR]=1.0; 95% CI, 0.9-1.0; P=0.13).

A total of 35 (23.3%) patients received antiviral therapy (nucleoside/nucleotide analogues) for >6 months and had better overall survival than patients who did not receive antiviral therapy (20.9 vs. 4.4 months; HR=0.22; 95% CI, 0.12-0.40; P<0.0001). Antiviral therapy remained an independent prognostic factor (HR=0.17; 95% CI, 0.09-0.32; P<0.0001) after adjusting for all factors. Patients with antiviral therapy had better liver reserves at the time of diagnosis of HCC (lower alkaline phosphatase, international normalised ratio, and bilirubin levels) and higher rates of receiving antineoplastic treatment for HCC (Table 1). The two groups did not differ significantly in terms of the HBV DNA level at the time of HCC diagnosis, TNM staging, or largest tumour diameter.

Apart from antiviral therapy, other independent prognostic factors included advanced Okuda stage, high α-fetoprotein value, presence of portal vein thrombosis, and low albumin level based on multivariate analyses (Table 2).

Discussion

In this study, the HBV viral load at baseline was not a prognostic factor for overall survival. This finding is contrary to our previous findings from another patient cohort with advanced HCC undergoing cytotoxic chemotherapy.[3] We postulated that the differences are due to different patient populations and changing practices for prescription of antiviral therapy over time. Our previous report focused on a phase III clinical trial comparing two different regimens of systemic chemotherapy.[3] Prophylactic use of antiviral therapy had not been established at the time of the previous study. Patients with higher baseline serum HBV DNA had higher risk for and/or a more severe form of HBV reactivation. Accordingly, the poorer prognosis in patients with higher baseline HBV DNA was due to poor outcome among HCC patients with HBV reactivation. In the

TABLE 1. Patient characteristics

Variable	Antiviral therapy (n=35)	Others (n=115)	Total (n=150)	P value
.	33			
M	ʒ			n
E n n)				0.
0	12			
1	22			
2	0			
3	1			
M 10			12	n
M		.		n
M 9/				n
M 9/				n
M		)		n
M	34)			n
M	434)			n
M				n
M	0.			n
M	4)			n
M α-			ʒ	n
	2			
				h
		4		
				0.
	12			ng
M	23			
M		)		n

TABLE 2. Multivariate analysis

Variable	Hazard ratio (95% CI)	P value
[illegible]		
n		
L [illegible] α-		
≤3[illegible]		

present study, a large number of patients underwent loco-ablative therapy. It was routine practice for patients undergoing systemic chemotherapy to be given prophylactic antiviral therapy. It is therefore likely that patients with higher serum HBV DNA levels at baseline could be salvaged from HBV reactivation and hence had a better prognosis than the previous cohort.

Antiviral therapy was an independent prognostic factor for patients with HCC, even after adjusting for other prognostic factors. Antiviral therapy for patients with dual pathologies (malignancy and cirrhosis) of HCC can theoretically improve liver function and prognosis. This concept has been suggested by a case-control study[4] and a small-scale observation series.[5]

There were three limitations to the present study. First, during recruitment of the cohort, antiviral therapy was not reimbursable for most patients, and there was no consensus guideline on prescribing antiviral therapy after the diagnosis of HCC. The prescription pattern could have been subject to potential bias or unknown confounding factors. Second, serial measurements of serum viral loads were lacking, and therefore it is unclear whether and by how much the antiviral therapy exerted its viral suppressive effects during the course of HCC. The potential benefits of antiviral therapy are hypothesis generating only. Further studies are required to validate the findings. Finally, the retrospective nature of the study may have led to bias in the interpretation of data.

Conclusion

Serum HBV DNA level at baseline was not a prognostic factor for patients with inoperable HCC. Prescription of antiviral therapy at the time or after diagnosis of HCC was associated with better overall survival of patients with HCC.

Acknowledgement

This study was supported by the Research Fund for the Control of Infectious Diseases, Food and Health Bureau, Hong Kong SAR Government (#09080422).

References

1. Chan HL, Tse CH, Mo F, et al. High viral load and hepatitis B virus subgenotype ce are associated with increased risk of hepatocellular carcinoma. J Clin Oncol 2008;26:177-82.
2. Chan HL, Chui AK, Lau WY, et al. Factors associated with viral breakthrough in lamivudine monoprophylaxis of hepatitis B virus recurrence after liver transplantation. J Med Virol 2002;68:182-7.
3. Yeo W, Mok TS, Zee B, et al. A randomized phase III study of doxorubicin versus cisplatin/interferon alpha-2b/doxorubicin/fluorouracil (PIAF) combination chemotherapy for unresectable hepatocellular carcinoma. J Natl Cancer Inst 2005;97:1532-8.
4. Kuzuya T, Katano Y, Kumada T, et al. Efficacy of antiviral therapy with lamivudine after initial treatment for hepatitis B virus-related hepatocellular carcinoma. J Gastroenterol Hepatol 2007;22:1929-35.
5. Koda M, Nagahara T, Matono T, et al. Nucleotide analogs for patients with HBV-related hepatocellular carcinoma increase the survival rate through improved liver function. Intern Med 2009;48:11-7.