RESEARCH ARTICLE

Hepatitis B Virus Infection Is Associated with Poor Prognosis in Patients with Advanced Non Small Cell Lung Cancer

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Abstract

Background: Hepatitis B virus (HBV) infection has been reported to be associated with inferior prognosis in hepatocellular and pancreatic carcinoma cases, but has not been studied with respect to non small cell lung cancer (NSCLC). The purpose of this study was to investigate the prognostic significance of HBV infection in advanced NSCLC patients. Materials and Methods: A retrospective cohort of 445 advanced NSCLC patients was recruited at our hospital from January 1, 2003 until August 30, 2014. Serum HBV markers were tested by enzyme-linked immunosorbent assay. COX proportional hazards analysis was used to evaluate associations of HBV infection with overall survival (OS). Results: Of 445 patients who were qualified for the study, 68 patients were positive for HBsAg, also considered as HBV infection. Patients in HBsAg negative group were found to have better OS (12.6 months [12.2-12.9]) than those in HBsAg positive group (11.30 months [10.8-11.9]; *p*=0.001). Furthermore, COX multivariate analysis identified HBV infection as an independent prognostic factor for OS (HR 0.740 [0.560, 0.978], *p*=0.034). Conclusions: Our study found that HBsAg-positive status was an independent prognostic factor for OS in patients with advanced NSCLC. Future prospective studies are required to confirm our findings.

Keywords: Hepatitis B virus - hepatitis B surface antigen - non small cell lung cancer - survival - prognosis

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Introduction

Due to high prevalence of hepatitis B virus (HBV) infection and cancer in some developing countries, especially China, concurrent infection with HBV is not uncommon in cancer patients (Sun et al., 2002; Lu et al.,2010; Xie et al., 2012; She et al., 2013; Deng et al., 2014; Liu et al., 2014). Recently, the association of HBV infection and cancer has been extensively investigated. It has been shown that that HBV reactivation is a well-described complication in hepatitis B surface antigen (HBsAg) positive cancer patients after chemotherapy, including advanced non small cell lung cancer (NSCLC), resulting in considerable morbidity and mortality (Yeo et al., 2006; Hoofnagle et al., 2009; Chen et al., 2012; Tang et al., 2013; Lin et al., 2014). In addition, HBV infection, as an independent prognostic factor, was demonstrated to confer poor survival in patients with pancreatic cancer and hepatocellular carcinoma (Hatanaka et al., 2007; Wei et al., 2013). However, the influence of HBV infection on prognosis in lung cancer patients is not well elucidated. The purpose of this study was to investigate the prognostic significance of HBV infection in patients with advanced NSCLC.

Materials and Methods

Ethic statement

This study was approved by the ethics committee of Zhongshan Hospital of Sun Yat-sen University. And written informed consent was obtained from all patients prior to treatment.

Patients

From January 1, 2003 until August 30, 2014, all patients with advanced NSCLC at Zhongshan Hospital of Sun Yat-sen University were retrospectively collected. Eligible patients were those who were pathologically confirmed NSCLC, had stage IIIB (with malignant pleural or pericardial effusion) or stage IV disease based on imaging examination, and were tested for HBV at the first visit.

Serologic assay for HBV infection

Blood samples for the test of HBV infection were collected at the first visit of all patients. Enzyme-linked immunosorbent assay was used to the tests of hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), hepatitis B e antigen (HBeAg), hepatitis B e

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antibody (anti-HBe) and hepatitis B core antibody (anti-HBc).

Statistical analysis

Differences of baseline parameters between HBsAg positive and negative group were compared by chi-square test. Overall survival (OS) was defined as the time from the date of diagnosis to death, irrespective of cause. Survival curves were made with the Kaplan-Meier method, and differences were compared with log-rank test. A Cox regression was used for univariate and multivariate analysis. Hazard ratio (HR) and 95% confidence interval (95% CI) were computed with the Cox proportional-hazards model, the forward stepwise method was selected to test the multivariable analysis. The statistical analyses were performed with SPSS 16.0 software (SPSS, Chicago, IL, USA). A two tailed p value <0.05 was considered statistically significant.

Table 1. Comparison of Baseline Clinical Characteristics Stratified By HBsAg Status

Characteristics	HBsAg positive group		HBsAg negative group		p
	No. of patients (n = 68)	%	No. of patients (n = 377)	%	
Gender					0.733
Male	42	61.8	241	63.9	
Female	26	38.2	136	36.1	
Age(years)					0.099
<65	39	57.4	255	67.6	
≥65	29	42.6	122	32.4	
ECOG performance status					0.407
<2	44	64.7	263	69.8	
≥2	24	35.3	114	30.2	
Histology					0.28
SCC	36	52.9	226	59.9	
Non-SCC	32	47.1	151	40.1	
Liver metastasis					0.257
No	38	55.9	238	63.1	
Yes	30	44.1	139	36.9	
Chemotherapy					0.309
No	28	41.2	131	34.7	
Yes	40	58.8	246	65.3	

*ECOG, Eastern Cooperative Oncology Group; SCC, squamous cell carcinoma; HBsAg, hepatitis B surface antigen

Results

Baseline characteristics

A total of 445 patients were eligible for the study. The median age at diagnosis was 58.6 years (range, 33-73 years). The ratio of male to female was about 1.75:1 (283:162). 307 (68.9%) patients had Eastern Cooperative Oncology Group (ECOG) performance status of less than 2. Pathologically, squamous cell carcinoma (SCC) was found in 262 (58.9%) patients. Liver metastasis was seen in 169 (37.9%) patients. Additionally, 286 (64.3%) patients received chemotherapy. All patients were followed up until December 31, 2014. The median follow-up duration was 13.6 months (range, 4.1-27.9 months). Based on HBsAg status, 445 patients were divided into two groups, HBsAg positive and negative groups. 68 patients were assigned to the HBsAg-positive group. The comparisons of baseline characteristics between the HBsAg positive and negative groups are listed in Table 1. No significant difference was noted in terms of gender, age, ECOG performance status, histology, liver metastasis and treatment with chemotherapy.

Survival and prognostic analysis

The median overall survival for all the patients was 12.32 months (95%CI, 12.01-12.63 months). Patients in HBsAg negative group were found to have better overall survival (12.56 months [12.23-12.89]) than those in HBsAg positive group (11.30 months [10.75-11.85]; p=0.001; Figure 1).

The results of univariate and multivariate analysis are shown in Table 2. Clinical characteristics, including gender (male vs female), age (<65 vs ≥65 years), ECOG performance status (<2 vs ≥2), histology (SCC vs non-SCC), liver metastasis (No vs Yes), treatment with chemotherapy (No vs Yes) and HBsAg status (positive vs negative) were incorporated into the univariate and multivariate analysis. By univariate analysis, patients who had ECOG performance status of <2, non-SCC, were absent of liver metastasis, received chemotherapy

Table 2. Univariate and Multivariate Analysis of Variables Correlated to Overall Survival

Characteristics		univariate analyses HR(95%CI)	p	multivariate analyses HR(95%CI)	p
Gender	Female	1	0.429	1	
	Male	1.086(0885,1.331)		0.206(0.981,1.484)	0.076
Age(years)	<65	1	0.635	1	0.949
	≥65	1.050(0.858,1.285)		0.993(0.806,1224)	
ECOG performance status	≥2	1	0.002	1	0.017
	<2	0.723(0.589,0.886)		0.778(0.632,0.957)	
Histology	Non-SCC	1	0.001	1	0.212
	SCC	1.495(1.191,1.876)		1.166(0.916,1.485)	
Liver metastasis	No	1	<0.001	1	0.001
	Yes	1.648(1.337,2.032)		1.447(1.170,1.791)	
Chemotherapy	No	1	<0.001	1	<0.001
	Yes	0.254(0.199,0.323)		0.286(0.224,0.367)	
HBsAg status	positive	1	0.001	1	0.034
	negative	0.638(0485,0..839)		0.740(0.560,0.978)	

*ECOG, Eastern Cooperative Oncology Group; SCC, squamous cell carcinoma; HBsAg, hepatitis B surface antigen

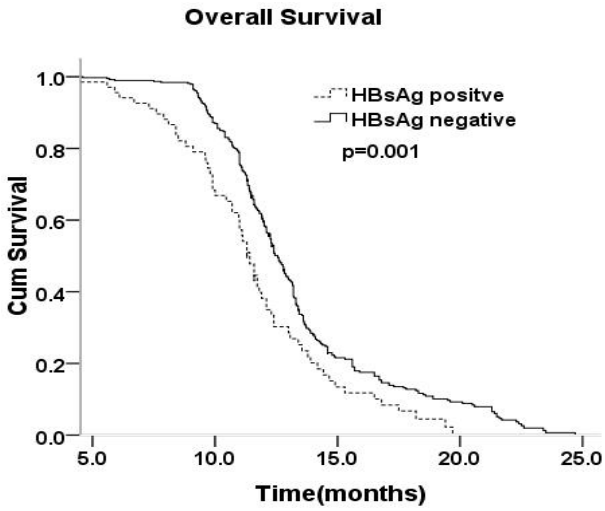

Figure 1. Kaplan-Meier Overall Survival Estimates for Patients with Advanced Non Small Cell Lung Cancer According to HBsAg Status. HBsAg: hepatitis B surface antigen

or were negative for HBsAg were shown to have superior OS (p=0.002, p=0.001, p<0.001, p<0.001 and p=0.001, respectively). Subsequently, COX multivariate analysis revealed that ECOG performance status, liver metastasis, treatment with chemotherapy and HBsAg statue remained as independent prognostic factors for OS (p=0.017, p=0.001, p<0.001 and p=0.034, respectively).

Discussion

To our knowledge, this is the first study to evaluate the prognostic significance of HBV infection in advanced NSCLC patients, suggesting that HBsAg-negative patients were demonstrated to be significantly correlated with favorable OS (12.56 months [12.23-12.89]) than HBsAg-positive counterpart (11.30 months [10.75-11.85]; p=0.001), and HBsAg status remained as an independent prognostic factor for OS by multivariate analysis (HR 0.740 [0.560, 0.978], p=0.034).

HBV infection is endemic in some developing countries, including China, affecting nearly 15% of the population (Zhao et al., 2001; Sun et al., 2002; Lu et al., 2010). Meanwhile, Lung cancer is the most commonly diagnosed cancer and the leading cause of cancer death among men and women in China, contributing to 0.5 million deaths each year (Xie et al., 2012; She et al., 2013; Deng et al., 214; Liu et al., 2014). In light of this high prevalence of lung cancer and HBV infection in certain areas, lung cancer patients who are concurrently infected with HBV are frequently seen. Hence, the question whether HBV has a potential influence on lung cancer is raised. Unfortunately, little is known about the interaction of lung cancer and HBV infection. HBV reactivation, characterized by an increase in HBV DNA levels as compared with baseline levels and manifested by varying degrees of hepatitis, is a well-recognized complication in HBV carriers with cancer receiving chemotherapy, contributing to severe morbidity and mortality (Yeo et al., 2006; Hoofnagle et al., 2009; Chen et al., 2012; Tang et al., 2013). Until recently, it was reported that HBV reactivation was found in 19.3% of HBsAg seropositive patients with advanced NSCLC treated with systemic chemotherapy, similar to other types of cancer (Lin et al., 2014). Subsequently, a large body of retrospective studies investigated the prognostic influence of HBV on cancer survival. HBsAg-positive hepatocellular carcinoma was found to have more unfavorable clinical course and worse survival than HBsAg-negative one (Hatanaka et al., 2007). Similarly, our study revealed that HBsAg-negative patients were significantly associated with favorable OS (12.56 months [12.23-12.89]) than HBsAg-positive counterpart (11.30 months [10.75-11.85]; p=0.001), and HBsAg-positive status remained as an independent unfavorable prognostic factor for OS by multivariate analysis (HR 0.740 [0.560, 0.978], p=0.034). In contrast, metastatic colorectal cancers patients with HBV infection were found to survive longer than those without infection (Song et al., 2001). Differences in the overall survival were not seen in pancreatic cancer patients with or without HBsAg positive status, while patients infected with actively replicative HBV showed better survival than inactive HBsAg carriers (Wei et al., 2013). Based on evidence available, inconsistent results regarding the prognostic impact of HBV infection on cancer survival are difficult to be thoroughly illustrated. However, it is reasonable to believe that the type of cancer and degree of HBV activity should be considered while interpreting these findings.

The mechanism of the prognostic impact of HBV infection on cancer survival is not well understood. Firstly, it is well accepted that HBV reactivation is a well-described complication which could lead to severe hepatitis and death (Yeo et al., 2006; Hoofnagle et al., 2009; Chen et al., 2012; Tang et al., 2013; Lin et al., 2014). Nonetheless, the rate of HBV reactivation is rather low due to the introduction of prophylactic antiviral therapy in HBV carriers before the administration of chemotherapy (Yeo et al., 2006; Hoofnagle et al., 2009). In our study, death from HBV reactivation and fulminant hepatitis was not found, similar to the previous reports by Wei et al (Wei et al., 2013). Secondly, liver metastasis itself represents unfavorable prognosis in many types of cancers (Wu et al., 2012; Li et al., 2013). Lower rate of liver metastasis was seen in metastatic colorectal cancers infected with HBV than those without infection, leading to longer survival (Song et al., 2001; Qiu et al., 2011). While higher incidence of liver metastasis in pancreatic cancer was found in HBsAg-positive group than HBsAg -negative group, contributing to similar survival (Wei et al., 2013). Our result revealed that the difference in the HBsAg status was not significantly associated with the difference in the incidence of liver metastasis, but could influence survival outcome. Hence, the prognostic value of HBsAg status could not be simply explained through HBV reactivation or liver metastasis. It was reported that HBV was detected in diverse cell types, including endothelial cells, mucosal epithelial cells, macrophages/ monocytes and hematopoietic precursors, implying that HBV was likely to exist in the lung (Mason et al., 1993). Chronic exposure to HBV was probable to give rise to alteration in cellular immunity, leading to tumorigenesis

and promoting cancer aggressiveness (De et al., 2010; Engels et al., 2010; Srivatanakul et al., 2010; Li et al., Zhu et al., 2011; Li et al., 2013; Jiang et al., 2014). It is inferred that alteration in cellular immunity due to chronic HBV stimulation may be involved in influencing biological behavior of cancer cells. The mechanism of how HBV status affect the prognosis of advanced NSCLC is not well understood, more researches about the clinical data and laboratory mechanism are both needed.

Our study was limited by the retrospective nature, considering inevitably missed information and limited number of cases, more data and work are needed in future.

In conclusion, our study found that HBsAg-positive status was an independent prognostic factor for OS in patients with advanced NSCLC. Future prospective studies are required to confirm our findings.

References

Chen XQ, Peng JW, Lin GN, Li M, Xia ZJ (2012). The effect of prophylactic lamivudine on hepatitis B virus reactivation in HBsAg-positive patients with diffuse large B-cell lymphoma undergoing prolonged rituximab therapy. *Med Oncol*, **29**, 1237-41.

De Mitri MS, Cassini R, Bernardi M (2010). Hepatitis B virus-related hepatocarcinogenesis: molecular oncogenic potential of clear or occult infections. *Eur J Cancer*, **46**, 2178-86.

Deng W, Long L, Li JL, et al (2014). Mortality of major cancers in Guangxi, China: sex, age and geographical differences from 1971 and 2005. *Asian Pac J Cancer Prev*, **15**, 1567-74.

Engels EA, Cho ER, Jee SH (2010). Hepatitis B virus infection and risk of non-Hodgkin lymphoma in South Korea: a cohort study. *Lancet Oncol*, **11**, 827-34.

Hatanaka K, Kudo M, Fukunaga T, et al (2007). Clinical characteristics of NonBNonC- HCC: comparison with HBV and HCV related HCC. *Intervirology*, **50**, 24-31.

Hoofnagle JH (2009). Reactivation of hepatitis B. *Hepatology*, **49**, 156-65.

Jiang XF, Tang QL, Zou Y, et al (2014). Does HBV infection increase risk of endometrial carcinoma? *Asian Pac J Cancer Prev*, **15**, 713-6.

Li L, Wu B, Yang LB, Yin GC, Liu JY (2013). Chronic hepatitis B virus infection and risk of pancreatic cancer: a meta-analysis. *Asian Pac J Cancer Prev*, **14**, 275-9.

Li SL, Su M, Peng T, et al (2013). Clinicopathologic characteristics and prognoses for multicentric occurrence and intrahepatic metastasis in synchronous multinodular hepatocellular carcinoma patients. *Asian Pac J Cancer Prev*, **14**, 217-23.

Lin GN, Peng JW, Xiao JJ, Liu DY, Xia ZJ (2014). Hepatitis B virus reactivation in hepatitis B surface antigen seropositive patients with metastatic non-small cell lung cancer receiving cytotoxic chemotherapy: the efficacy of preemptive lamivudine and identification of risk factors. *Med Oncol*, **31**, 119.

Liu J, Yang XL, Li A, et al (2014). Epidemiological patterns of cancer incidence in southern China: based on 6 population-based cancer registries. *Asian Pac J Cancer Prev*, **15**, 1471-5.

Lu FM, Li T, Liu S, Zhuang H (2010). Epidemiology and prevention of hepatitis B virus infection in China. *J Viral Hepat*, **17**, 4-9.

Mason A, Wick M, White H, et al (1993). Hepatitis B virus replication in diverse cell types during chronic hepatitis B virus infection. *Hepatology*, **18**, 781-9.

Qiu HB, Zhang LY, Zeng ZL, et al (2011). HBV infection decreases risk of liver metastasis in patients with colorectal cancer: a cohort study. *World J Gastroenterol*, **17**, 804-8.

She J, Yang P, Hong Q, Bai C (2013). Lung cancer in China: challenges and interventions. *Chest*, **143**, 1117-26.

Sun Z, Ming L, Zhu X, Lu J (2002). Prevention and control of hepatitis B in China. *J Med Virol*, **67**, 447-50.

Song E, Chen J, Ou Q, et al (2001). Rare occurrence of metastatic colorectal cancers in livers with replicative hepatitis B infection. *Am J Surg*, **181**, 529-33.

Srivatanakul P, Honjo S, Kittiwatanachot P, el al (2010). Hepatitis viruses and risk of cholangiocarcinoma in northeast Thailand. *Asian Pac J Cancer Prev*, **11**, 985-8.

Tang Y, Sun LG, Liu CS, et al (2013). Clinical analysis of stages of HBV infection in 100 cases of lymphoma. *Asian Pac J Cancer Prev*, **14**, 959-62.

Wei XL, Qiu MZ, Chen WW, et al (2013). The status of HBV infection influences metastatic pattern and survival in Chinese patients with pancreatic cancer. *J Transl Med*, **11**, 249.

Wu C, Li F, Jiao SC (2012). Prognostic factors for survival of patients with extensive stage small cell lung cancer--a retrospective single institution analysis. *Asian Pac J Cancer Prev*, **13**, 4959-62.

Xie WC, Chan MH, Mak KC, Chan WT, He M (2012). Trends in the incidence of 15 common cancers in Hong Kong, 1983-2008. *Asian Pac J Cancer Prev*, **13**, 3911-6.

Yeo W, Johnson PJ (2006). Diagnosis, prevention and management of hepatitis B virus reactivation during anticancer therapy. *Hepatology*, **43**, 209-20.

Zhao SM, Li HC, Lou H, et al (2001). High Prevalence of HBV in Tibet, China. *Asian Pac J Cancer Prev*, **2**, 299-304.

Zhu F, Li HR, Du GN, Chen JH, Cai SR (2011). Chronic hepatitis B virus infection and pancreatic cancer: a case-control study in southern China. *Asian Pac J Cancer Prev*, **12**, 1405-8.