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Research Article

Effects of Hepatitis B Virus Infection Prognosis to Non-Small Cell Lung Cancer Survival

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Abstract

Objectives: Hepatitis B virus (HBV) infection and non-small cell lung cancer are both common diseases. These two diseases can often coexist. We planned to investigate the effects of HBV infection prognosis on NSCLC patients' overall survival (OS) times.

Methods: It was a retrospective study. The files of NSCLC patients who applied to our oncology department between January 2012 and December 2018 were scanned. Patients were divided into four groups in terms of HBV infection status; chronic Hepatitis B, hepatitis B recovery, vaccinated, and never HBV infected groups. All groups were compared for their OS times.

Results: Median OS was 12.86 months (95% confidence interval (CI), 10.54-15.18) for the whole group. Median OS times of not infected with HBV, spontaneous recovery, vaccinated, and chronic hepatitis B were 10.63, 13.03, 16.36, 7.16 months, respectively. There weren't any statistically meaningful differences between groups in terms of OS.

Conclusion: We hypothesized that the immune system might be more robust in patients with HBV spontaneous seroclearance (recovery) and the median OS might be better in metastatic NSCLC patients. This study's results did not meet our hypothesis. But the HBV vaccination ratio of patients was only 5.7%. In future studies effects of HBV vaccination to NSCLC prognonsis should be studied conducted more HBV vaccinated patient rate.

Keywords: Hepatitis B, prognosis, survival, non-small cell lung cancer

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There are nearly 400 million chronic hepatitis B (CHB) patients in the world. The prevalence of hepatitis B infection is between 2-8% and Turkey is in the middle endemic region.[1] When hepatitis B virus (HBV) infection occurs in an individual, the infection progresses in several different ways. It can be acute hepatitis or chronic active hepatitis or occult hepatitis or spontaneous recovery.[2] What determines these different prognoses? The most widely believed reason for the different prognoses of HBV infection is different immunity. Non-small cell lung cancer (NSCLC) is the most common type of cancer. There are a limited number of studies revealing the interaction of these two common diseases (HBV infection and NSCLC). Immunity is very important in the prognosis of metastatic NSCLC as well as in the prognosis of HBV. It has been shown that there is overall survival (OS) advantage in NSCLC patients with agents (programmed cell death receptor-1 (PD-1) blockers) that cause immune activation.[3] If strong immunity means both

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more HBV recovery and more OS in NSCLC, can we expect better OS in NSCLC patients with recovered HBV infection? This was the most fundamental question we sought to answer in this study.

In our previous study, we investigated the effect of chemotherapy on the prognosis of HBV infection and showed that chemotherapy causes HBV reactivation and adversely affects the prognosis of patients.[4] In this study, we aimed to reveal the effects of HBV infection prognosis on metastatic NSCLC patients' survival.

Methods

The files of patients with NSCLC who applied to our hospital between January 2012 and December 2018 were scanned. All patients conducted in this study were pathologically confirmed stage IV NSCLC. All patients had received chemotherapy. HBsAg, anti-HBsAb, anti-HBcIgGAb, anti-HBcIgMAb, HBeAg, and anti-HBe values were tested in all patients before or after diagnosis. The patients were divided into four groups. They were chronic Hepatitis B (HBsAg +, Anti HBsAg -, Anti HBcAg -), hepatitis B recovery (HBsAg -, Anti HBsAg +, Anti HBcAg +), vaccinated (HBsAg -, anti HBsAg +, anti HBcAg -), no HBV infection (HBsAg -, anti HBsAg -, anti HBcAg -) groups. We analyzed the OS, which was defined as the time elapsed from the diagnosis date of metastatic NSCLC to the date of death from any cause or study termination date. The statistical analyses were conducted using Statistical Package for Social Sciences (SPSS) version 22 (SPSS Inc, Chicago, IL). Univariate analysis was performed by using the Kaplan–Meier method to estimate the OS of different patient groups, and the groups were compared with the log-rank test. A p-value of <0.05 was considered statistically significant. Also, χ^2 or Fisher's exact test was used for independence between two variables when the comparing groups are independent and not correlated.

Results

In this study we conducted 265 (232 male, 33 female) metastatic NSCLC patients, 118 were alive and 87 were dead. The most common histology was adenocarcinoma (82%). 130 Patients had never been infected with HBV and, spontaneous HBsAg seroclearance occurred in 103 patients. The HBV vaccination ratio of patients was only 5.7% (15 patients). There were 17 patients in the CHB group. The rate of any comorbidity (diabetes mellitus and/or arterial hypertension and/or ischemic heart disease) was 46.5% (Table 1). Median OS was 12.86 months (95% confidence interval (CI), 10.54-15.18) for the whole group. Median OS times of not infected with HBV, spontaneous recovery, vaccinated, and chronic hepatitis B were 10.63, 13.03, 16.36, 7.16 months, respectively. All groups were compared in terms of the median OS with the pairwise Cox-Mantel test. There weren't any statistical differences between groups (Table 2).

Table 1. Charesteristics of patients.

Charesteristics	n (%)
Median age (year) (range)	62.0 (21.6-90.0)
Sex	
Female	33 (12.5%)
Male	232 (87.5%)
Histology	
Adenocarcinoma	217 (82%)
Squamoz	31 (12%)
Not other specified	17 (6%)
Hepatitis B status	
No enfection	130 (49.1%)
Recovery	103 (38.9%)
Vaccinated	15 (5.7%)
Chronic hepatitis B	17 (6.4%)
Comorbidity (DM, HT, IHD)	
Absent	142 (53.5%)
Present	113 (46.5%)

DM: Diabetes mellitus; HT: Arterial hypertension; IHD: Ischemic heart disease.

Discussion

Many factors can determine the prognosis in both small cell and non-small cell cancer.[5] Especially chronic infections may be effective in cancer prognosis by affecting the immune system. We hypothesized that the immune system might be more robust in patients with HBV spontaneous seroclearance (recovery) and the median OS might be better in metastatic NSCLC patients. This study's results did not meet our hypothesis. There are some studies in the literature showing the relationship between HBV infection and NSCLC. In a study, HBsAg-negative and positive NSCLC patients were compared, and it was shown that the median OS results were worse in HBsAg-positive NSCLC patients (12.56 vs 11.3 months, p=0.001). It was not clear why OS was worse in HBsAg-positive NSCLC patients in that study. It has been stated that the most likely reason is immunosuppression due to cancer itself or chemotherapy leading to HBV activation and thus active hepatitis B decreases OS.[6] In another study, HBV reactivation was observed at a rate of 19.3% after chemotherapy in patients with chronic hepatitis B and NSCLC. Acute activation of hepatitis B is reported to be associated with increased mortality. In addition, they stated, that chronic exposure to HBV suppresses cellular immunity and causes cancer to become aggressive.[7] Suehiro et al.[8] showed tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) receptor 3 (TRAIL-R3) was significantly upregu-

Table 3. Pairwise comparison of overall survival for metastatic non-small cell lung cancer in terms of hepatitis status (Log Rank (Cox-Mantel) test used)

	HBsAg-negative/ HBsAb-negative/ HBcAb-negative		HBsAg-negative/ HBsAb-positive		HBsAg-negative/ HBcAb-positive		HBsAg-positive/ HBcAb-positive	
	Chi-Square	p	Chi-Square	p	Chi-Square	p	Chi-Square	p
HBsAg-negative/HBsAb-negative/ HBcAb-negative	-	-	,588	,443	,108	,743	,059	,808
HBsAg-negative/HBsAb-positive	,588	,443	-	-	,403	,525	,765	,382
HBsAg-negative/HBcAb-positive	,108	,743	,403	,525	-	-	,193	,660
HBsAg-positive/HBcAb-positive	,059	,808	,765	,382	,193	,660	-	-

HBcAb: Hepatitis B core antigen; HBsAb: Hepatitis B surface antibody; HBsAg: Hepatitis B surface antigen.

lated in the livers of HBV-infected patients.

The HBV vaccination ratio of patients was only 5.7%. Routine HBV vaccination has been given to newborn babies since 1991 in our country. Since our NSCLC patients are mostly in advanced ages, the vaccination rate was found to be very low. Prechemotherapy HBV infection status screening rates increased in recent years.[4] In future studies effects of HBV vaccination to NSCLC prognonsis should be studied conducted more HBV vaccinated patient rate. Also, effects of HBV infection to immunotherapy of NSCLC should be investigated.

Disclosures

Ethics Committee Approval: Approval was obtained from the ethics committee of Karadeniz Technical University Ethics Committe. Protocol number is 2019/180, date is 08/11/2019.

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Conflict of Interest: None declared.

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