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Hepatitis B Reactivation in Patients with Hematological and Solid Malignancies: A Retrospective Analysis of Single Center's Experience

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Abstract

Background: Hepatitis B reactivation might occur in patients with hematological and solid organ malignancies due to immunosuppressive effect of chemotherapy. **Methods:** Fourteen patients were evaluated retrospectively from their files to discuss the clinical manifestations, management, and avoiding of Hepatitis B reactivation within patients who receive immunosuppressive treatment. **Results:** These 14 HbsAg positive patients were being followed up and treated via oncological immunosuppressive chemotherapy. The ages of the patients were between 25 and 72. Seven of the patients were male, and the average follow up period for the patients was between 10 and 74 months. TV 0, 5 mg was started for seven of the patients before the chemotherapy and TFV 245 mg to one of the patients. LAM 100 was started for three patients whose basal HBV DNA was low. It has been analyzed that HBV DNA was negative in further observations. In follow up controls, we noticed HBV reactivation at two patients, LAM was given one of them and TFV was given the other one. One patient was applied allogeneic transplantation whose basal liver tests were normal and Hbsag was negative. Hepatitis B reactivation was detected after the first week of therapy. **Conclusions:** We offer testing in all patients undergoing cancer therapy for hepatitis B, HBsAg, core antibody (anti-HBc total), and anti-HBs before to start cancer therapy. Patients with higher risk of HBV reactivation require antiviral prophylaxis.

Keywords

Hepatitis B, Malignancies, Immunosuppression

1. Introduction

Hepatitis B reactivation might occur in patients with hematological and solid organ malignancies due to immunosuppressive effect of chemotherapy. Patients with a history of Hepatitis B who treated with immunosuppressive treatment are at risk for Hepatitis B reactivation and a serious hepatic attack, fulminant liver failure. This adverse condition can cause an interruption of chemotherapy, and can affect the success of primary solid cancer therapy. Several trials related to patients with solid tumors have suggested the efficacy of preventive anti-viral therapy. Many authors recommend testing all patients undergoing cancer treatment for hepatitis B in details such as hepatitis B surface antigen, hepatitis B core antibody, and hepatitis B surface antibody previous cancer therapy. Many authors recommend tenofovir or entecavir as preventive therapy, rather than lamivudine [1] [2] [3] [4].

HBV reactivations risk depends upon the kind of immunosuppressive drugs used. The risk of hepatitis B reactivation is at a great high with the use of protocols that contain anti-CD20 monoclonal antibodies and high dose glucocorticoids. And also hematopoietic cell transplantation has a great high risk of hepatitis B reactivation [1] [2] [3].

This study was performed in patients who underwent chemotherapy in South East Turkey where is an endemic location for hepatitis B virus, with an HBsAg prevalence of about 4% - 6% [2]. Our article retrospectively analyzed to discuss the clinical manifestations, management, and avoiding of hepatitis B reactivation within patients who receive immunosuppressive treatment.

2. Material Methods

14 patients were evaluated retrospectively from their files in Diyarbakır Memorial Hospital Clinic of Gastroenterohepatology between September 2013 and September 2019. Oncological or hematological cancer patients with HbsAg positive and were exposed to immunsuppressive chemotherapy were selected for analysis. These 14 HbsAg positive patients were being followed up and treated via oncological immunosuppressive chemotherapy.

3. Results

The ages of the patients were between 25 and 72, the average age was 51.5. Seven of the patients were male and the other 7 were female. The average follow up period for the patients were between 10 and 74 months.

HbsAg was positive in all of the patients. HbeAg and Anti-delta anticore were negative in all of the patients. Demographic and laboratory information of the patients are shown in **Table 1** and **Table 2**. Three of the patients were being followed up previously as inactive carriers. Other patients were newly diagnosed; their HbsAg tests were appeared out to be positive in studies before chemotherapy. None of the patients had liver cirrhosis in clinic, laboratory and imaging studies and none of them had antiviral treatment history. Prophylactic antiviral

Table 1. Patienst clinical and treatment characteristics.

	Age	Sex	Liver Cirrhosis	Malignancy	Chemotherapy	Antiviral Therapy	Follow up (Month)
1. patient	59	f	no	Breast	TRANSTUZUMAB-PERTUZUMAB	ETV 0.5	16
2. patient	70	m	no	Gall Bladder	Gemcitabine + cddp	ETV 0.5	30
3. patient	44	f	no	Breast	AC	ETV 0.5	39
4. patient	60	f	no	Periton	Pacl + Carbo	ETV 0.5	27 (ex)
5. patient	60	m	no	Prostate	Zoladex + docetaxel + enzalutamid +zometa	ETV 0.5	
6. patient	55	m	no	Rectum	5 FU, folfox-4	ETV 0.5	39
7. patient	66	m	no	Lung	Gemcitabine	Lam 100 mg + TFV 245 mg	41 (ex)
8. patient	72	f	no	NHL (Large cell)	5 years before, 6 cure chop Now R-ICE	TFV 245 mg + Lam 100 mg	72
9. patient	25	f	no	Giant cell tm of bone	Proliakordexa	ETV 0.5 mg	40
10. patient	44	f	no	NHL	BMT	ETV 1 mg	10
11. patient	46	f	no	Breast	AC-Gemcitabine-Carboplatin-Doxataksel	TFV 245 mg	50
12. patient	70	m	no	Laryngeal-Lung	Gemcitabine-Daksotaksel-cisplatin	Lam 100 mg	48
13. patient	49	m	no	Testicular	CDDp-Carboplatin	Lam 100 mg	74
14. patient	61	m	no	Prostate		Lam 100 mg	72

Table 2. Patients baseline laboratory results.

	HBV DNA (IU/mL)	HBsAg	HBeAg	Anti-delta	PLT	INR	AST (IU/L)	ALT (IU/L)	TBİL (mg/dL)
1. patient	189.746	positive	negative	negative	220,000	1.1	28	38	0.11
2. patient	2539	positive	negative	negative	187,000	1.0	11	12	0.34
3. patient	0	positive	negative	negative	340,000	1.2	26	28	0.28
4. patient	1220	positive	negative	negative	365,000	1.0	33	55	0.33
5. patient	12	positive	negative	negative	293,000	1.0	31	42	0.18
6. patient	0	positive	negative	negative	420,000	0.9	17	3	0.24
7. patient	184,000	positive	negative	negative	178,000	1.2	269	289	0.89
8. patient	59,051.199	positive	negative	negative	365,000	1.6	1350	1700	8.45
9. patient	246	positive	negative	negative	312,000	1.1	18	21	0.13
10. patient	1223.000	positive	negative	negative	229,000	1.7	2200	2120	11.2
11. patient	84	positive	negative	negative	397,000	1.1	11	11	0.64
12. patient	34	positive	negative	negative	178,000	1.2	23	27	0.21
13. patient	0	positive	negative	negative	196,000	0.9	34	29	0.44
14. patiant	0	positive	negative	negative	21,000	1.0	15	14	0.13

treatment started before chemotherapy and continued until the sixth month after the end of the chemotherapy. The use of drugs was ended if liver tests were normal and HBV DNA was negative in the tests of the sixth months.

ETV 0.5 mg was started for seven of the patients before the chemotherapy and TFV 245 mg to one of the patients. Apart from the first patient, HBV DNA values of these eight patients were negative or were less than 2000 IU. Basal HBV DNA value of the first patient was 189,746 IU. Liver tests of these eight patients were in normal values and HBV DNA values were negative. LAM 100 was started for three patients whose basal HBV DNA was low. It has been analyzed that HBV DNA was negative in 48, 72 and 74 month observations (**Table 2**).

Based on the normal liver tests LAM 100 mg was started for patient number 7 whose previous HBV DNA was 200 IU. It has been observed that liver tests were elevated in seventeenth month. HBV DNA was 184,000 IU. TFV 245 mg was added to the treatment. HBV DNA became negative in the following period.

Patient number eight had 6 doses of CHOP with the diagnosis of NHL five years ago. In that period, TFV 245 mg was started. In January 2019, R-ICE treatment was applied because of nux. ALT: 700 Tbil 8.45 HBV DNA 59.051.199 IU values were detected at the third week of the treatment. 100 mg LAM was added to TFV 245 mg treatment. ALT Tbil values of the patient became normal. HBV DNA became negative in the second month.

Allogeneic transplantation was applied to patient number 10 because of Non-Hodgkin Lymphoma (NHL). Basal liver tests were normal and HbsAg were negative. However, Anti-HBc-IgG was not tested at the basal evaluation. The patient came to us with icteric sclera and skin after the first week of allogeneic transplantation therapy. The values of the patient were: Anti-HBc-IgG positive HBV DNA 1223.000 IU AST 2200 ALT 2120 Tbil 11.2. 1 mg ETV was started for the patient. Tbil was elevated to 21 and INR was elevated to 3, 2 in the following period. Patient was sent to liver transplantation center for close follow up. However, liver tests and bilirubin became normal with medical treatment. HBV DNA became negative.

4. Discussion

This study performed in South East Turkey where is an endemic location for hepatitis B virus, with an HBsAg prevalence of about 4% - 6% [2], Hepatitis B reactivation might occur in patients with malignancies because of immunosuppressive effect of chemotherapy. So that patients with a story of Hepatitis B who treated with immunosuppressive treatment are at risk for Hepatitis B reactivation and a severe attack hepatitis B disease. This situation can conclude with elevated liver enzymes, fulminant liver failure [1] [4]. Furthermore, this negative situation (reactivation of hepatitis B) can cause an interruption of chemotherapy, delaying therapy of patient primary solid cancer. Although prophylactic antiviral therapy usage before chemotherapy has been recommended for patients with solid and hematological malignancies [5]-[9], many clinical studies related to patients with solid tumors have suggested the efficacy of preventive anti-viral therapy [10] [11]. In this article, we retrospectively analyzed naive 14 non-cirrhotic HBV positive patients with solid tumors. Our article review will discuss the clin-

ical manifestations, management, and avoiding of Hepatitis B reactivation within patients who receive immunosuppressive treatment.

In one study, where hepatitis B prevalence similar to our region, Kim *et al.* examined on 178 patients with breast cancer while chemotherapy performed. 97% of them were HBsAg negative, 35% had abnormal hepatic function. Yet, only in 1% of patients acute hepatitis has been developed during chemotherapy [3] [12]. In Kim study, 60% of the HBsAg positive patients developed liver abnormalities, and also 33% of them had a progression to acute hepatitis. Furthermore, the incidence of hepatitis because of Hepatitis B reactivation was 21% of all cases. In this study they advocated that those findings are similar with other studies which documented a 24% ~ 28% incidence of Hepatitis B reactivation; even if the patients and chemotherapeutic protocols were different [3] [11] [13]. In another study that Kim *et al.* researched, lamivudine treatment was performed the patients when Hepatitis B reactivation was found. But, Lamivudine treatment didn't affect fast enough, indeed, chemotherapy treatment had to be delayed in 78% of these patients that was 16% of all 111 patients. They retrospectively analyzed of 2431 patients with early breast cancer. Within these patients, 111 HBsAg positive female patients were accepted in their study. Thirty-seven patients (33.3%) cultivated acute hepatitis, of that 23 (20.7%) were associated with Hepatitis B reactivation. Those patients who diagnosed with hepatitis B reactivation were administered lamivudine at that case of hepatitis B reactivation [3] [14] [15] [16]. However, opposite of Kim et al., some researchers have suggested prophylactic therapy via lamivudine in patients who had solid tumors [10] [11]. In one essay on breast cancer, it was found that the patients in a prophylactic lamivudine group had a lesser incidence of hepatitis (12.9% vs. 59.0%), a decreased hepatitis B reactivation (6.5% vs. 31.1%) and decreased cessation of chemotherapy (16.1% vs. 45.9%) according to a control group [17]. In our study, ETV 0, 5 mg was started for seven of the patients before the chemotherapy and TFV 245 mg to one of the patients. Almost all these 8 patients' HBV DNA level was less than 2000 IU. We obtained good results in follow up. LAM 100 mg was started for three patients whose basal HBV DNA was low. It has been analyzed that HBV DNA was negative in follow-up results. In one patient who has normal basal liver tests, LAM 100 mg was started whose previous HBV DNA was 200 IU. It has been observed that liver tests were elevated in seventeenth month. HBV DNA was 184,000 IU. TFV 245 mg was added. HBV DNA became negative in the following period. On the other hand, another patient had 6 doses of CHOP with the diagnosis of NHL five years ago. In that period TFV 245 mg was started. In the fifth year of TFV treatment, because of NHL nux, R-ICE treatment was applied. In this period due to hepatitis B flare, 100 mg LAM was added to TFV 245 mg. HBV DNA became negative in the second month of the combination treatment.

Patients who receive anti-CD20 therapy and hematopoietic cell transplantation have a great high risk of hepatitis B reactivation, up to 20% [1]. In patients who are performed hematopoietic stem cell or solid organ transplantation are

under the risk even in the patients who are HBsAg-negative. In some studies reported that HBsAg negative patients who are treated with allogeneic transplant have risk of hepatitis B reactivation [1] [18]-[28] allogeneic transplantation was applied to our one patient because of NHL. This patient's basal liver tests were normal and HbsAg were negative. However, Anti-HBcIgG was not evaluated at the basal evaluation. The patient came to us with hepatic flare in the first week after allogeneic transplantation. One mg ETV was started and at follow up, liver tests and bilirubin became normal range with medical treatment and HBV DNA became negative.

In conclusion, we offer testing in all patients undergoing cancer therapy for hepatitis B, HBsAg, core antibody (anti-HBc total), and anti-HBs before to start cancer therapy. Patients with higher risk of HBV reactivation require antiviral prophylaxis.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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