Follow-up of Chronic HBV Infected Patients Planned Chemotherapy Due to Solid Organ Malignancy

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ABSTRACT
The aim of this study was to screen the patients with solid organ malignancy for HBV (Hepatitis B virus) infection before the start of chemotherapy and follow up in the oncology department of our setting. All cases admitted to oncology department for chemotherapy were screened prospectively for HBV infection and reactivation between March 2013-September 2014. A total of 225 patients were included in the study and divided into 3 groups; Group I: having recovered past HBV infection: 43 patients (19.1%), Group II: isolated Anti-HBcAg total positive: 20 patients (8.9%) and Group III: chronic HBV infection with 10 patients (4.4%). HBV reactivation developed in one (5.9%) of 17 patients in group II, and two (28.6%) of seven patients in group III while under lamivudine prophylaxis. Neither hepatitis flare by HBV reactivation nor HBV-related death were observed in our study. In the moderate endemi city areas like Turkey for HBV infection, all patients must be screened for HBV before starting of chemotherapy.

Keywords: Chemotherapy; HBV Reactivation, Solid Cancer

ÖZET
Solit Organ Malignitesi Nedeniyle Kemoterapi Planlanan Kronik Hepatit B Enfeksiyonu Hastaların Takibi
Bu çalışmada kurumumuzun onkoloji bölümüne solid organ malignitesi nedeniyle kemoterapi tedavisi planlanan hastaların HBV (Hepatit B Vırus) enfeksiyonu açısından takınsı ve takibi amaçlanmıştır. Mart 2013 - Eylül 2014 tarihleri arasında kemoterapi için onkoloji bölümüne başvuran tüm olgular, HBV için prospektif olarak taramış ve reaktivasyon açısından takip edilmiştir. Çalışmaya 225 hasta dahil edilmiş ve üç gruba ayrılmıştır; Grup I: Geçirilmiş HBV enfeksiyonu: 43 hasta (19.1%), Grup II: İzole Anti-HBcAg total pozitif: 20 hasta (8.9%) ve Grup III: Kronik HBV enfeksiyonu : 10 hasta (4.4%). HBV reaktivasyonu grup I’de 17 hastanın birinde (5.9%) görülmüşken grup III’te yedi hastanın kısında lamivudin profilaksi altında gelişmiştir. Çalışmamızda HBV reaktivasyonunun bağlı hepatit tablosu veya HBV’ye bağlı ölüm gözlenmemiştir. Türkiye gibi HBV enfeksiyonu açısından orta endemisite olan bölgelerde, kemoterapi tedavisi öncesi tüm hastalar HBV enfeksiyonu açısından taramalıdır.

Anahtar Kelimeler: Kemoterapi, HBV reaktivasyonu, Solid kanser
INTRODUCTION

The rate of HBV reactivation in patients undergoing cytotoxic chemotherapy ranges between 14-72%.\(^1\)\(^-\)\(^7\) In patients who are started immunosuppressive treatment due to malignancy, the evaluation of HBV serologic markers before the chemotherapy period and the determination of the roadmap according to this result is the main approach being applied in the world.\(^8\)\(^,\)\(^9\) However, in a provisional clinical opinion for the American Society of Clinical Oncology on HBV infection screening in patients, it is declared that HBV serological marker control is missed quite commonly. As a result of this missed group, the patients who have inadequate prophylaxis discontinue chemotherapy in more than 40% of hematologic malignancies and more than 60% of solid organ malignancies while about 25% develop hepatic failure due to HBV reactivation.\(^10\)

At least some of the immunosuppressive drugs weaken immune system through different mechanisms such as depleting the patient’s antibody-producing B cells or stimulating HBV replication by effecting glucocorticoid responsive element in the enhancer region of the HBV genome. Also tumor necrosis factor (TNF) is effective in reducing HBV clearance and transcription, and therefore TNF inhibition is directly associated with enhanced HBV replication.\(^11\)\(^-\)\(^14\) Beside traditional chemotherapeutic agents, biologic agents and glucocorticoids, some recent immunosuppressive agents such as mechanistic target of rapamycin (mTOR)-inhibitors and tyrosine kinase inhibitors are thought to be related with HBV reactivation.\(^15\)

The aim of this study was to screen the patients with solid organ malignancy for HBV infection before the start of chemotherapy in the oncology department of our setting. Our additional purposes were to define the risk groups for HBV reactivation and thereafter starting lamivudine prophylaxis to eligible patients to prevent from HBV reactivation and hepatitis.

PATIENTS and METHODS

All patients who admitted to Ege University Faculty of Medicine Tulay Aktaş Oncology Hospital for chemotherapy due to solid organ malignancy and who have not received chemotherapy for the last six months or before, were screened prospectively for HBV between March 2013-September 2014. HBV serologic markers were studied with Architect kit (Abbott, USA) on Architect i2000SR. HBV DNA Abbott M2000rt real-time PCR instrument was run with RealArt HBV PCR Kit (Abbott, USA). The lower limit for HBV-DNA positivity was 10 IU / ml.

The patients were called by phone and invited to the outpatient unit. The written consent form was obtained from all patients who accepted to participate in the study. All patients were recorded in the standard case report form. Patients who participated in the study were divided into three groups according to their serological results; Group I: patients with past HBV infection, Group II: patients with isolated anti-HBc total positivity and Group III: patients with chronic HBV infection. In group I (past HBV infection) patients were followed up monthly by screening AST, ALT, HBsAg and anti-HBsAg in terms of possible reactivation during chemotherapy. In group II (isolated anti-HBcAg total positive); lamivudine prophylaxis 100 mg 1x1 / day was started to the patients who had a detectable initial HBV DNA level (≥10 IU / ml) or became HBV DNA positive and/or HBsAg positive in the follow-up. Patients who were negative for HBV DNA in group II were followed up monthly by screening AST, ALT, HBsAg, HBV DNA and anti-HBsAg. In Group III (chronic Hepatitis B infection), all patients were initially screened for HBV DNA, HBeAg and anti-HBeAg in addition to other tests, and lamivudine prophylaxis 100 mg 1x1 / day was started. Group III patients were followed up monthly by screening AST, ALT, HBsAg, anti-HBsAg, HBeAg, anti-HBeAg and HBV DNA levels in terms of possible HBV reactivation while they were under lamivudine prophylaxis. The following definitions were used for HBV reactivation and hepatitis flare due to HBV (4, 16-20):

HBV Reactivation:

1) HBsAg-positive patients
   * ≥10x increase in HBV DNA
   * Hepatitis B e antigen (HBeAg) becomes positive in HBeAg-negative patients

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2) HBsAg-negative, and anti-HBc-positive and/or anti-HBsAg-positive patients

* HBsAg becomes positive

* HBV DNA becomes positive in patients whose HBV DNA level was below the detectable limit.

Hepatitis flare is defined as a greater than 3-fold increase of serum alanine aminotransferase level that exceeded 100 IU/L. The data were recorded and evaluated in the Microsoft Office Excel program. SPSS version 20 was used in the statistical analysis of the study. In the analysis of the data, descriptive statistical methods, Mann Whitney U and t test (independent samples t test) were applied. This prospective and interventional study was approved by the Ethics Committee of Ege University (Code: 13-2/6 Date: 26/02/2013). Each patient was informed about the aims of the study and the signed informed consents were recorded in the patient’s medical files.

RESULTS

A total of 267 patients fulfilled the study inclusion criteria and invited to the study by a phone call. Forty-two patients were excluded because of not intending to participate, inaccessibility or missing communication information. Two hundred and twenty five patients [mean age 57.8 ± 13.2 (20-82 years), 136 (60.4%) female, 89 (39.6%) male] were included in the study.

The main malignancy types of patients included in the study were breast cancer (66 patients, 29%), colon cancer (34 patients, 15.1%), lung cancer (14 patients, 6.2%), stomach cancer (11 patients, 4.8%), pancreatic cancer (11 patients, 4.8%) and ovarian cancer (8 patients, 3.5%) (Figure 1).

When the patients included in the study were examined according to the serological results of HBV; a total of 118 (52.4%) had no HBV infection and 34 (15.1) were immunized. Remaining patients were divided into three groups; Group I: past HBV infection: 43 patients (19.1%), Group II: isolated anti-HBcAg total positive: 20 patients (8.9%) and Group III: chronic HBV infection with 10 patients (4.4%). A total of 8 patients (Group I: 2, Group II: 3, Group III: 3) discontinued the visits during the follow up. The mean follow-up duration of the patients (Group I, II and II) during the chemotherapy period was 120.68 ± 71.76 (30-450) days.

In group I, there was no HBV reactivation and/or hepatitis. In group II, there was occult HBV infection in one (5.9%) case while HBV reactivation developed in one (5.9%) other patient. Lamivudine prophylaxis was started to these two patients. In group III, three were already receiving antivirals, lamivudine prophylaxis was started in seven patients before their chemotherapy regimen. Two (28.6%) of seven patients developed HBV reactivation on lamivudine prophylaxis. During the HBV reactivation, the HBV DNA levels of the first and the second patient were found 10 IU/ml and 37 IU/ml, respectively. HBV DNA levels were detected again negative in both patients’ follow-up. During the follow up neither hepatitis flare by reactivation of HBV nor HBV-related death were observed in our study (Figure 2).

The mean age of the patients with HBV reactivation was 60 ± 7.5 (52-67 years) and one (33.3%) was female and two (66.6%) were male. There was no statistically significant difference between the mean age of patients with HBV reactivation and without reactivation (p≥ 0.05). In patients with HBV reactivation, one had lung cancer, one had breast cancer and one had primary unknown malignancy. When HBV reactivation rate was evaluated according to patients’ (Groups II and III) type of malignancy, HBV reactivation rate was higher in patients diagnosed with breast cancer (1 of 5, 20%). When the chemotherapy regimens of three patients were evaluated; the first case had received docetaxel and cyclophosphamide, second had docetaxel and cisplatin and the third case had received etoposide and cisplatin. HBVDNA level was nega-
tive in all three cases before the chemotherapy and lamivudine resistance could not be analysed.

When the group of patients (group II and III) followed-up with HBV reactivation were examined according to chemotherapy agents, reactivation was seen in two of four patients receiving docetaxel (50%), one of three patients receiving cyclophosphamide (33.3%), two of three patients receiving cisplatin (66.3%). The follow-up duration of the patients (group II and III) during the chemotherapy period was 173.3 ± 83.3 (100-270) days. Two of three patients (66.3%) who developed HBV reaction died during follow-up. The causes of death of these patients were complications secondary to malignancies but not hepatitis flare by reactivation of HBV or HBV-related. Nevertheless, it is attracting attention that when group II and III were evaluated, the mortality rate was relatively lower in patients without HBV reactivation group (5 of 21 patients, 23.8% vs 2/3, 66.6%, p= 0.19).

**DISCUSSION**

In spite of improvements in the diagnosis and management of HBV infection, HBV reactivation is still a vital and preventable problem that may cause severe morbidity and mortality in immunocompromised patients. Risk analysis is the most important strategy for prevention of HBV reactivation. Previous reports identified host factors, viral factors (HBsAg status, high HBV DNA level, HBeAg seropositivity, cccDNA, low anti-HBsAg level), type of malignancy (lymphoma, breast cancer) and immunosuppressive therapy (B cell depleting agents (eg, rituximab, ofatumumab), anthracycline derivatives (eg, doxorubicin, epirubicin), corticosteroids (10-20 mg prednisone daily or equivalent).
for > 4 weeks] as risk factors for HBV reactivation.\textsuperscript{16,21-24} Male gender and younger age are the most significant host-related variables for HBV reactivation. Yeo et al. evaluated prospectively 626 cancer patients undergoing chemotherapy, 78 patients with HBsAg-positive were followed and 3 of 15 patients with HBV reactivation were female and 12 were male.\textsuperscript{4} Despite the relatively small number of patients in our study, findings are compatible with the literature, two of three patients (66.6\%) with HBV reactivation were male and one (33.3\%) was female.

When solid tumor patients with HBV reactivation are evaluated according to malignancy types, it has been noticed that the incidence of reactivation is increased in some malignancies. HBV reactivation is more common in patients with breast cancer than other solid tumors. The rate of HBV reactivation in HBsAg positive patients with breast cancer is reported to range between 25-40\%. HBV reactivation was observed in one of five patients (20\%) with breast cancer in our study. This frequent occurrence of HBV reactivation in patients with breast cancer is thought to depend on the widespread use of agents that have been shown to enhance HBV DNA expression, such as corticosteroids and anthracyclines.\textsuperscript{3,25} The most important issue in terms of risk of HBV reactivation is the type of chemotherapy agents used. Yeo et al. evaluated cancer patients with HBV reactivation according to chemotherapy agents prospectively. They determined that chemotherapy regimens of the patients with HBV reactivation (n= 15) contained the following agents respectively; 11 (73\%) steroids, nine cyclophosphamide (60\%), nine (60\%) anthracyclines, seven (47\%) vinca alkaloids, four (27\%) etopside, three (20\%) fluorouracil and two (13\%) taxanes.\textsuperscript{5} In the literature, there are studies reporting HBV reactivation in patients who received anthracyclines, alkylating agents, fluorouracil, docetaxel or epirubicin in their chemotherapy regimen.\textsuperscript{36-28} In our study, HBV reactivation developed in patients who received cisplatin, docetaxel, or cyclophosphamide in their chemotherapy regimens and therefore we suggest that such patients should be monitored more closely.

There is not enough data about HBV reactivation in patients with solid tumors who has occult HBV infection. Saitta et al. evaluated 44 solid tumor patients with occult HBV infection prospectively during chemotherapy period and HBV reactivation was not reported in any of these patients.\textsuperscript{29} In our study, occult HBV infection was detected in one patient (5.9\%) in group II (isolated total anti-HBc positivity), HBV reactivation or hepatitis was not observed in clinical follow-up of this patient who was started lamivudine prophylaxis.

Patients with isolated total anti-HBcAg positivity have risk for reactivation during chemotherapy regimen, too. Borentain et al. evaluated 84 HBsAg-negative/anti-HBcAg positive patients with haematological and solid tumors. HBV reactivation rate was 8\% (7/84) and three of seven patients with HBV reactivation had haematopoietic stem cell transplantation, and four had received chemotherapy regimens including rituximab.\textsuperscript{30} In our study, group II (isolated total anti-HBc positivity), HBV reactivation was observed in one (5.9\%) of 17 patients which was consistent with the literature.

Lamivudine is the most commonly used antiviral drug used for the prevention of HBV reactivation. Preemptive lamivudine prophylaxis has been shown to be associated with 79-100\% reduction in HBV reactivation risk.\textsuperscript{31} Katz et al. meta-analyzed 21 studies that comprised a total of 324 patients in lamivudine group and 599 patients in the control group. They concluded that clinical (OR= 0.09; 95\% CI 0.05-0.15) and virological HBV reactivation rates (OR= 0.04; 95\% CI 0.01-0.14) as well as HBV-related mortality were significantly reduced (OR= 0.20; 95\% CI 0.09-0.45) in the lamivudine group.\textsuperscript{32} In our study, group III (chronic HBV infection), two patients with HBV reactivation had neither serious reactivation nor hepatitis clinic which may be associated with their below the detectable level of HBV-DNA levels at the beginning of chemotherapy. When evaluating the reactivation phases associated with HBV, lamivudine prophylaxis may have a possible mechanism of inhibiting new hepatocytes from infection by suppressing the increase of viral replication occurring in the first phase of the reactivation and preventing hepatocyte damage associated with the reconstitution of the second phase immune system. Chen et al. followed up 213 HBsAg-positive solid tumor
patients to compare the efficacy of entecavir with lamivudine in the prophylaxis of HBV reactivation undergoing chemotherapy. HBV reactivation was lower in entecavir group (0% vs. 7.0%). In patients with a baseline HBV DNA level ≥ 2000 IU/mL, no patient (0%) in entecavir group had HBV reactivation but HBV reactivation was observed 10 patients (15.9%) in lamivudine group. They declared both agents were equally efficient in the patients with HBV DNA levels < 2000 IU/mL but entecavir was superior to lamivudine in terms of reactivation incidence in the patients with ≥ 2000 IU/mL. In literature, the data about using tenofovir for prevention of HBV reactivation in patients receiving immunosuppressive therapy are rare. Koskinas et al. presented their real life experience with tenofovir and followed up 25 patients who received tenofovir prophylaxis during immunosuppressive therapy. There was no HBV reactivation in all 25 patients with tenofovir prophylaxis, and they expressed that tenofovir is highly effective in the prophylaxis of HBV reactivation in patients receiving immunosuppressive therapy. Considering these two reactivation patients (with HBV DNA level < detectable limit) that develop under lamivudine prophylaxis in our study. The presented cases in our study had been started lamivudine due to reimbursement problems. We think that it would be questioned to prefer drugs with a higher genetic barrier to resistance and strong antiviral activity such as entecavir or tenofovir in patients with lower HBVDNA levels, too.

CONCLUSION

In the moderately HBV endemic areas like Turkey, all patients must be screened for HBV before the start of chemotherapy. It is quite important to determine the risk factors and prefer suitable antiviral drugs for reducing morbidity and mortality due to HBV reactivation. Use of lamivudine vs entecavir or tenofovir even in cases with low level of HBVDNA should be analysed in larger cohorts.

Acknowledgement:

Authors thank Emine Sevim Kocakçz (English teacher) for English proofreading.

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