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Original Article

To Study the Prevalence of Occult HBV Infection & Reactivation of HBV in Hematological Cancer Patients on & Before Cancer Chemotherapy

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Abstract

Background: *Occult hepatitis B infection is defined by negative hepatitis B surface antigen (HBsAg) and detectable hepatitis B virus (HBV DNA, with or without hepatitis B core antibody (anti-HBc). HBV reactivation is most commonly reported in patients receiving cancer chemotherapy for haematological malignancies or hematopoietic stem cell transplantation (HSCT) recipients.*

Objective: *In this study, we aimed to determine the prevalence & reactivation of occult HBV infection in hematological cancer patients on & before receiving chemotherapy.*

Methods: *The study was conducted in patients admitted in hematology department RGGGH, Madras medical college, Chennai for a time period from September 2018 to December 2018.Blood samples collected from newly diagnosed hematological malignancy and patients with diagnosed hematological malignancy on chemotherapy who were previously negative for HBsAg, were tested for HBsAg & anti-HBc antibodies. The samples that were negative for HBsAg but positive for anti-HBc also examined for HBV-DNA by polymerase chain reaction (PCR).*

Results: *Out of the 80 patients tested, 23 (28%) samples were positive for anti-HBc antibodies. HBV-DNA was detected in 5(6%) of anti-HBc positive samples. Reactivation of HBV occurred in 11% of patients. Reactivation was more frequent with chemotherapy drugs like Rituximab & daunorubicin. There was no significant difference in HBc antibody positivity based on gender, age, previous blood transfusions, biochemical parameters (ALT) (P>0.05).*

Conclusion: *The prevalence of occult HBV infection is 6% with isolated anti HBC positivity being 28%.Reactivation of HBV was seen in 9 patients (11%) Screening of occult HBV infection by HBsAg, HBV DNA and anti HB core antibody should be made mandatory before starting patients on immunosuppressants in cancer patients.*

Introduction

Hepatitis B virus (HBV) infection is a serious health problem in the world with nearly two billion people affected[1]. Implementation of hepatitis B surface antigen (HBsAg) screening in blood donors in the early 1970s has greatly reduced the transmission[2]. The natural history of HBV infection depends upon host factors such as integrity of immune system, age at primary infection, as well as viral factors including HBV genotype, viral mutations and viral load[3].

Occult HBV infection (OBI) is normally defined by negative serum hepatitis B surface antigen (HBsAg) and detectable HBV DNA in the liver and/or serum, with or without hepatitis B core antibody (anti-HBc)[4]. Several studies shows the risk of flaring up of chronic Hepatitis B (positive HbSAg) in patients treated by chemotherapy for hematologic and solid malignancies, with the highest risk of flare occurring when chemotherapy is discontinued. In these studies, the risk of reactivation of Hepatitis B is between 20% and 50%[5-7]. The diagnosis of OBI is difficult due to the presence of low amounts of viral DNA (<200 IU/mL) in the infected persons without detectable HBsAg[(8)]. The individuals with an OBI undergoing immunosuppression are generally at risk of HBV reactivation.

It is very obvious that the clinical &virological reactivation of occult HBV infection has been frequently revealed in various clinical settings, such as HIV infection, hematologic cancer, hematopoietic stem cell, and organ transplantation[(4,9)]. In these situations, the mortality rate in HBV reactivation is close to 20 percent, because of the liver failure or the development of the primary disease[(10,11)].

Hence, the aim of this study was to evaluate the prevalence and chemotherapy induced reactivation of OBI among hepatitis B surface antigen negative patients with hematological malignancies and to establish the significance of core antibody screening among this group of patients before receiving chemotherapy.

Methods

The study was conducted in patients admitted in hematology department RGGGH, Madras medical college, Chennai for a time period from September 2018 to December 2018.Newly diagnosed hematological malignancy and patients with diagnosed hematological malignancy on chemotherapy were included. All individuals were asked regarding age, sex, type of cancers, blood transfusion, jaundice and history of hepatitis B vaccination. Venous samples were tested for hepatitis B core antibody HBcAb and HBsAg using a commercially available enzyme-linked immunosorbent assay. HBV DNA was done for those patients with isolated HBcAb positivity and those who developed reactivation of HBV on treatment.

Patients with recent jaundice, recent hospitalization due to fever, recent delivery less than 12 weeks or close contact with a patient suffering from hepatitis in the last 6 months were excluded. Exclusion criteria also included acute or chronic HBV infection as marked by positive HBsAg and patients with HCV, human immunodeficiency virus (HIV) were excluded.

Before start of the cancer therapy each patient underwent history taking, complete physical examination, routine biochemistry assays including alanine transaminase (ALT), aspartate transaminase (AST), total and direct bilirubin. Patients with HBV infection as labeled by positive HBsAg were excluded.

Venous blood samples for occult hepatitis B infection (OBI) were obtained from all patients for HBsAg, antiHBc antibody. Samples were tested for hepatitis B core antibody (HBcAb) and HBsAg using a commercially available enzyme-linked immunosorbent assay. In patients positive for anti HBc antibody, HBV DNA was performed using PCR.

Patients who were HBsAg negative, HBc antibody positive and serum HBV DNA positive (>50 IU/mL, according to kit inc) were labelled as occult hepatitis B infection (OBI). Reactivation was defined when there was evidence of HBsAg

seroreversion (the reappearance of HBsAg) with an increase in HBV DNA levels when compared with baseline HBV-DNA levels (>2000 IU/mL) in the absence of history, clinical or laboratory features of all other possible etiological factors of hepatitis[12].

Statistical Analyses- The SPSS software version 16.0 and chi-square test were used for data analysis. The significance level was $P<0.05$.

Results

There were a total of 80 patients. There were 80 patients included in the study. 47 (58%) male & 33(41%) females were included. The mean age group was 40.65±15.9. There was no significant difference in HBc antibody positivity based on age, gender, duration of disease, previous blood transfusions (BT) or biochemical parameters (ALT) levels ($P>0.05$) (Table 1,2,3,4 & 5).

High risk medication (like rituximab, daunorubicin) was given to 54(67.6%) of patients and moderate risk (imatinib) given to to 21 (26.2%) (Table 6 & 7). There was higher prevalence of occult HBV infection in patients who were given high risk medications (statistically not proved)

Of the total 80 patients, isolated anti HBC positivity was seen in 23 patients (28%). HBV DNA was positive in 5 of 23 patients and negative in 18 patients (22.5%). Reactivation of HBV was seen in 9 patients (11%) (Table 8)

Table 1: Association between Age with Occult HBV

Variable	Occult HBV	No Occult HBV	t Test	P Value
Age in years (Mean±SD)	46.8±14.1	38.2±16.1	-2.26	0.026

Table 2: Association between Gender with Occult HBV

Gender	Occult HBV N (%)	No Occult HBV N (%)	Total N (%)	Chi-square Test	p value
Male	11 (47.8)	36 (63.2)	47 (58.8)	1.59	0.2
Female	12 (52.2)	21 (36.8)	33 (41.2)		
Total	23 (100)	57 (100)	80 (100)		

Table 3: Association between Duration with Occult HBV

Variable	Occult HBV	No Occult HBV	Z test	P value
Duration in Months (Median, IQR)	4 (3-6)	6 (3-12)	-1.361	0.174

Table 4: Association between Blood Transfusion with Occult HBV

Blood Transfusion	Occult HBV N (%)	No Occult HBV N (%)	Total N (%)	Chi-square Test	P value
Yes	22 (95.7)	50 (87.7)	72 (90)	1.15	0.28
No	1 (4.3)	7 (12.3)	8 (10)		
Total	23 (100)	57 (100)	80 (100)		

Table 5: Association between ALT with Occult HBV

ALT	HBV Occult N (%)	No Occult N (%)	Total N (%)	P value
Significant Rise	0 (0)	5 (0)	5 (6.2)	0.314
No Significant Rise	23 (100)	52 (91.2)	75 (93.8)	
Total	23 (100)	57 (100)	80 (100)	

Table 6: Association between Risk with Occult HBV

Risk	Occult HBV N (%)	No Occult HBV N (%)	Total N (%)
Low	3 (13.0)	2 (3.5)	5 (6.2)
Moderate	5 (21.7)	16 (26.1)	21 (26.2)
High	15 (65.3)	39 (68.4)	54 (67.6)
Total	23 (100)	57 (100)	80 (100)

Table 7: Association between various chemotherapeutic agents with Occult HBV

Main drug	Occult HBV N (%)	No Occult HBV N (%)	Total N (%)
Adriamycin	9 (39.1)	20 (35.1)	29 (36.2)
Bortezumab	4 (17.4)	2 (3.5)	6 (7.5)
Cyclophosphamide	1 (4.3)	2 (3.5)	3 (3.8)
Daunorubicin	2 (8.7)	6 (10.5)	8 (10)
Dexamethasone	1 (4.3)	4 (7)	5 (6.2)
Imatinib	2 (8.7)	13 (22.8)	15 (18.8)
Rituximab	4 (17.4	10 (17.5)	14 (17.5)
Total	23 (100)	57 (100)	80 (100)

Table 8: Prevalence of Occult HBV & reactivation of HBV

Variable	Anti HBC +ve	HBV DNA +ve	HBV Reactivation
Percent	23(28%)	5(6%)	9(11%)

Discussion

This study highlights the importance of screening occult HBV infection in hematological malignancy before & during chemotherapy. In OBI, HBV reactivation may be due to the disease process per se and autoimmunity[13,14]. The mortality rate of hepatitis in HBV reactivation is around 20 percent[12]. Hence this study aimed at prevalence of occult HBV & reactivation of HBV in hematological cancer patients before & during chemotherapy in a tertiary care center which caters a quite large number of patients from the state

In our study the prevalence of occult HBV infection is 6% with isolated anti HBC positivity being 28%.This is higher when compared to other studies[15,16]. In a study by Sodhi et al[17] the incidence of OBI was 1.9% (13 out of 690) which was less compared to our study. In a study by Yeo et al[17] with study among 104lymphoma patients observed 46 patients out of 104 (44.2%) were HBsAg negative/anti-HBc positive.

In an observational study of hematological cancer patients, Francisci et al[19] reported the incidence of HBV reactivation was 18%. In Egypt a study by Elkady et al[20] showed that 18 (34%) out of 53 HBsAg-negative patients with hematologic malignancies were found to be positive for anti-HBc. Five of the 53 (9.4%) patients with hematologic malignancies experienced HBV reactivation.

The reasons of the differences of several investigations for the occurrence of OBI could be due to geographical variations in prevalence of HBV, population characteristics, immunosuppressive conditions, HBV genotypes, study volume, unclear definition of OBI and also, the differences in the sensitivity of the techniques utilized for the identification of the HBV DNA, such as the PCR primer selection methods[8].

In our study reactivation of HBV was 11% (9 out of 80) which was higher compared to other studies. In a study by Orhan *et al*[21]. in Turkey which included 1826 patients, 59 (3.2%) cases were HbSAg positive and after chemotherapy, nine patients suffered from reactivation of Hepatitis B.A meta-analysis of 26 studies[22] reported that reactivation (in chronic HBV, without prophylaxis) ranged from 4% to 68% (median, 25%). Prophylaxis reduced the risk for HBV reactivation [odds ratio (OR): 0.12, 95% confidence interval (CI) 0.06–0.22], HBV- related hepatitis (OR: 0.18, 95% CI 0.10–0.32) and chemotherapy interruption (OR: 0.10, 95% CI 0.04–0.27).

In our study there was no significant difference in HBc antibody positivity based on age, gender, duration of disease, previous blood transfusions (BT) or biochemical parameters (ALT) levels Occult HBV infection is transmitted through blood transfusion in cancer patients, except if the blood that is transfused is analyzed for anti-HB core antibody and HBV DNA[17,23]. Occult HBV infection is the largest cause of transfusion-transmitted HBV infection in many countries

It is important to note that occult HBV patients

may develop HBsAg seroreversion, with subsequent HBV reactivation after chemotherapy, particularly in the cases of serious immunosuppression, such as patients of hematopoietic stem- cell transplantation and also those patients getting rituximab-based chemotherapy[24,25]

Conclusions

OBI is a significant challenge in clinical practice for specialists of different branches since the number of HBsAg-negative/anti-HBc-positive individuals (potential 'OBI carriers') is considerably higher than HBsAg-positive individuals worldwide. In our study the prevalence of occult HBV infection was 6% with isolated anti HBC positivity being 28%.The issue of HBV reactivation in patients undergoing systemic chemotherapy for hematological malignancies is underreported in the medical literature. Reactivation of HBV occurred in 11% of patients in our study. The most common drugs implicated in HBV reactivation in our study for which the frequency of HBV reactivation appears to be highest are rituximab, anthracyclines, vincristine, cyclophosphamide, etoposide and imatinib. Life-threatening or severe hepatitis related to HBV reactivation have been reported. Chemotherapy withdrawal is sometimes required, which may affect the prognosis of cancer.

Limitations of our study were smaller sample size & less HBV DNA monitoring. Hence large prospective trials are needed to have a clear understanding of the situation. Therefore screening for occult hepatitis B with HbsAg, total Anti Hbc and HBV DNA should be made mandatory before starting patients on immunosuppressants.

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