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Full Length Article

# Prevalence and chemotherapy-induced reactivation of occult hepatitis B virus among hepatitis B surface antigen negative patients with diffuse large B-cell lymphoma: Significance of hepatitis B core antibodies screening

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**KEYWORDS**

Hepatitis B virus;
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HBV-DNA;
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Occult HBV reactivation;
Diffuse large B-cell lymphoma

**Abstract** *Background:* Occult hepatitis B infection (OBI) is characterized by negative hepatitis B surface antigen (HBsAg) and detectable hepatitis B virus (HBV)-DNA in the liver and/or serum, with or without hepatitis B core antibody (anti-HBc). Anti-HBc is the most sensitive marker of previous HBV. HBV reactivation in patients under immunosuppressive treatment is life-threatening, occurring in both overt and occult HBV especially in hematological malignancies.

*Aim of the work:* To evaluate the prevalence and chemotherapy-induced reactivation of OBI among hepatitis B surface antigen negative patients with diffuse large B-cell lymphoma (DLBCL) patients and to determine the significance of anti-HBc screening among this group of patients before receiving chemotherapy.

*Patients and methods:* This cross-sectional study included 72 DLBCL patients negative for HBsAg, HBsAb and hepatitis C virus antibodies (anti-HCV). Patients were subjected to investigations including anti-HBc. All patients underwent alanine transaminase (ALT) monitoring before each cycle of chemotherapy and monthly for 12 months after the end of chemotherapy. Patients with suspected OBI were tested for HBV-DNA using real-time polymerase chain reaction (PCR).

*Results:* Anti-HBc was detected in 10 of 72 HBsAg negative sera (13.89%) (95% confidence interval 6.9–22.2%). Five of the 10 anti-HBc positive patients in this study had OBI reactivation.

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*Conclusion:* The study concluded that anti-HBc screening is mandatory before chemotherapy. HBsAg-negative/anti-HBc-positive patients should be closely observed for signs of HBV reactivation through the regular monitoring of ALT. Prophylaxis lamivudine is recommended for anti-HBc positive patients before chemotherapy.



## Introduction

Hepatitis B virus (HBV) infection is a major health problem, affecting about 2 billion people worldwide despite of the effective vaccination. There are 350 million HBV carriers worldwide and about one million die annually from HBV-related liver disease [1]. The prevalence of HBV infection varies in different parts of the world (< 1–15%) [2]. Intermediate endemicity of HBV infection had been recorded in Egypt [3].

Occult HBV infection (OBI) is characterized 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]. Anti-HBc is the most sensitive marker of previous HBV infection [5]. Anti-HBc is the first antibody to appear and present in all different phases of HBV. Anti-HBc may persist longer than hepatitis B surface antibody (anti-HBs) or hepatitis B envelope antibody (anti-HBe); however, it is not protective. Anti-HBc IgM may help in the diagnosis of the acute HBV and also during flares [6].

HBV reactivation in patients under immunosuppressive treatment is life-threatening occurring in both overt and occult HBV infection [7,8]. The risk of HBV reactivation is high with marked immunosuppression, especially in hematological malignancies chemotherapy (21–67%), bone marrow transplantation and monoclonal antibody therapy [9,10]. Under these conditions, HBV reactivation is associated with a mortality rate close to 20%, due to hepatic failure [11].

Diffuse large B-cell lymphoma (DLBCL) is the most common non-Hodgkin's lymphoma (NHL). Standard treatment for newly diagnosed DLBCL is anthracycline-based chemotherapy regimen, usually cyclophosphamide, doxorubicin, vincristine, and prednisone with or without rituximab [12].

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 diffuse large B-cell lymphoma (DLBCL) patients and to determine the significance of anti-HBc screening among this group of patients before receiving chemotherapy.

## Patients and methods

This cross-sectional study included 72 patients with diffuse large B-cell lymphoma (DLBCL) before receiving chemotherapy. Patients of this study were selected from the Hematology Unit, Internal Medicine Department, Faculty of Medicine, Tanta University and Tanta Cancer Center from May 2012 to October 2014. All patients included were negative for HBsAg, HBsAb and antibody for hepatitis C (anti-HCV). This study was conducted in accordance with the guidelines of the declaration of Helsinki 1975 and its subsequent amendments (1983). Participation in the study was voluntary after an informed written consent was obtained from the patients prior to the study.

All the patients were asked questions regarding age, sex, blood transfusion, past surgical procedures, intravenous drug abuse, jaundice, admission to fever hospital, and history of HBV vaccination.

Patients with recent jaundice, recent hospitalization due to fever, pregnancy, 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. Patients with HCV, human immunodeficiency virus (HIV), any hematological malignancy other than DLBCL or previous immunosuppressive treatments of any kind were also excluded.

Prior to start of the DLBCL treatment every patient underwent full history talking, complete physical examination, routine biochemistry assays including alanine transaminase (ALT) and aspartate transaminase (AST).

Diffuse large B-cell lymphoma (DLBCL) was diagnosed based on histopathological examination of lymph nodes and/or extranodal tissue biopsy specimen according to the Revised European-American Lymphoma (REAL) classification criteria revised by Harris [13]. Patients were staged according to the Ann Arbor staging system with Cotswolds modifications [14]. Ann Arbor staging was determined for all patients at the onset of DLBCL by physical examination, computed tomography scan (abdomen & pelvis, chest and neck) and bone marrow examination. The International Prognostic Index (IPI) was used for determining the prognosis of DLBCL [15]. Cheson's criteria were used to define the response to chemotherapy [16].

The standard protocol chemotherapy for DLBCL used in this study was CHOP [intravenous cyclophosphamide 750 mg/m$^2$, doxorubicin 50 mg/m$^2$, and vincristine 1.4 mg/m$^2$ (maximum dose: 2 mg) on day 1 and oral prednisone 100 mg/day on days 1–5] every 3 weeks for (6–8) cycles [17]. For patients with relapsed or progressed disease second line therapy ICE [24 h intravenous infusion ifosfamide 5000 mg/m$^2$ on day 2, intravenous carboplatin using the Calvert formula with maximum 800 mg on day 2 and intravenous etoposide 100 mg/m$^2$ on day 1–3] every 14 days or CEOP [intravenous cyclophosphamide 750 mg/m$^2$ on day 1, intravenous etoposide 50 mg/m$^2$ on day 1 and 100 mg/m$^2$ orally on day 2 and 3, intravenous vincristine 1.4 mg/m$^2$ IV (maximum dose: 2 mg) on day 1 and orally prednisone 100 mg/m$^2$ on day 1–10) every 3 weeks for patients candidate and non candidate for high dose therapy respectively [18,19].

All patients underwent total bilirubin and ALT monitoring during therapy before each cycle of chemotherapy and monthly for 12 months after the end of chemotherapy. If the patient experienced an ALT elevation more than threefold above the upper normal value, complete investigations including HBsAg, HBV-DNA levels, anti-HBc IgM, IgM hepatitis A virus antibody (anti-HAV) and HCV-RNA were performed to prove