Scholars Journal of Applied Medical Sciences
Abbreviated Key Title: Sch J App Med Sci
ISSN 2347-954X (Print) | ISSN 2320-6691 (Online)
Journal homepage: https://saspublishers.com

OPEN ACCESS

Gastroenterology

Viral Hepatitis B and Chemotherapy

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DOI: 10.36347/sjams.2022.v10i05.019 | **Received:** 02.04.2022 | **Accepted:** 12.05.2022 | **Published:** 18.05.2022

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Abstract **Review Article**

Patients with chronic hepatitis B treated with chemotherapy or immunotherapy are at risk of viral reactivation, which can have serious or even fatal consequences [1]. Patients treated with chemotherapy for haematological disease have a known risk of hepatitis B virus (HBV) reactivation with an estimated incidence of 14-72% [2]. The majority of chemotherapy drugs can induce HBV reactivation in patients with HBs-positive antigen [3]. HBs testing should therefore be recommended prior to chemotherapy. Preventive antiviral treatment will reduce the risk of HBV reactivation.

Keywords: chemotherapy, hepatitis B virus (HBV), immunosuppressive, therapies.

INTRODUCTION

There is a significant risk of B-virus reactivation in patients receiving immunosuppressive therapy. The incidence of reactivation is not well known. B viral reactivation may range from minor transaminase elevations to fulminant hepatitis. B viral reactivation can occur during immunosuppressive therapy or in the months following its cessation. It is defined by a rise in B viral load followed by a rise in transaminases [4, 5]. Chemotherapy for haematological cancers was the first treatment incriminated. However, chemotherapy for solid cancers is also responsible for viral reactivation. This implies systematic screening for HBsAg and HBcAb in all patients to be treated with chemotherapy. A few cases of viral reactivation have also been reported after extensive radiotherapy. Immuno-suppressive treatments outside of oncology are also responsible for viral reactivation. These include biotherapies used in IBD, rheumatology and dermatology. Corticosteroids administered at a dose of more than 40 mg, even for less than a week, can also induce reactivation. It is therefore important to inform the patient about the risks of taking corticosteroids [7].

Risk of chemotherapy-induced HBV reactivation

Viral B reactivation can range from minor transaminase elevation to fulminant hepatitis.

B viral reactivation may occur during immunosuppressive therapy or in the months following its cessation. B viral reactivation is defined by an increase in B viral load followed by an increase in transaminases.

The various immunosuppressive therapies are identified as being at low (< 1%), moderate (1- 10%) or high (> 10%) risk of rVHB according to the various studies and analyses published in the literature (Table I) [8].

Table I: Risk of B viral reactivation according to the immunosuppressive therapy envisaged

Risk Immunosuppressive therapy	
High risk (>10%)	Anti-Lymphocyte B: rituximab, ofatumumab High dose corticosteroids Anthracyclines: doxorubicin, epirubicin
Moderate risk (1-10%)	Anti-TNF : Etanercept, adalimumab, infliximab Other anti-cytkoin drugs: abatacept, ustekinimab, natalizumab and vedolizumab Calcineurin inhibitors: Ciclosporin Tyrosine kinase inhibitors: imatinib and nilotinib Proteasome inhibitors: bortezomib Moderate dose corticosteroids
Low risk (<1%)	Antimetabolites, azathioprine, 6-mercaptopurine and methotrexate Low-dose corticosteroids Intra-articular injection of corticosteroids

1. Management of HBV reactivation

HBV testing

The screening strategy is therefore based on two criteria: the risk linked to immunosuppressive treatment and the risk linked to the host. However, the learned societies are not unanimous on the recommendations for screening and in particular on the impact of these two criteria. These recommendations are summarised in Table II, which is adapted from a review article proposed by ASCO in 2015 [9] and updated according to subsequent publications.

Table II: Summary of recommendations for hepatitis B screening and prophylaxis

TABLE IV Summary of recommendations for hepatitis B screening and prophylaxis (from [28])				
Learned society	Patient population	Screening recommenda tions	Serological tests	Prophylaxis
American Association for the Study of Liver Diseases (2009)	Patients receiving cytotoxic or immunosuppressive therapy	Screening of patients at high risk of HBV infection	HBsAg, anti-HBc	Lamivudine, telbivudine, tenofovir, or entecavir for all HBV carriers; continue for 6 months after cessation of oncology treatment
American Gastroenterological Association Institute (2015)	Patients to be treated with immunosuppressi ve therapy	Screening patients at risk of infection at HBV or at moderate to high risk of reactivation	HBsAg and anti- HBc	Antiviral prophylaxis in case of moderate risk to high; no routine prophylaxis in low-risk patients Low-risk resistance antivirals recommended over lamivudine; treatment to be continued for 6 months after cessation of immunosuppressive therapy
American Society of Clinical Oncology (2015)	Patients receiving immunosuppres sive therapy	Screen patients with risk factors for HBV infection for whom immunosuppressive therapy with risk of reactivation is planned	HBsAg and anti- HBc	Antiviral therapy if there is evidence of chronic infection
European Association For Study of the Liver (2017)	Patients receiving chemotherapy or immunosuppressi ve therapy	Screening of all patients before treatment	HBsAg, anti-HBsAb and anti-HBcAb	Routine antiviral therapy if HBsAg+ until 12 months after completion of treatment. Antiviral therapy if HBsAg - and anti-HBsAb + if medium or high risk of reactivation

In practice, a broad screening attitude for any patient before initiation of cancer treatment may be justified.

Treatment

Pre-emptive treatment with nucleoside or nucleotide analgesics should be initiated before the start of immunosuppressive therapy in any patient detected as HBsAg positive or with a positive viral load. In case of isolated anti-HBcAb positivity, HBV DNA testing should be performed and treatment should be initiated in case of positivity (occult hepatitis B). Pre-emptive treatment should be continued for the duration of treatment and for 12 months after cessation of treatment (18 months if treated with Ritixumab) [2].

Quarterly monitoring of transaminases and B viral load is recommended, as well as monitoring of the tolerance of nucleotide analogues (phophoraemia, creatinemia, proteinuria). Vaccination must be carried out before the start of the immunosuppressant for patients with negative HBV serology (HBsAg negative / anti-HBc negative / anti-HBs negative).

CONCLUSION

The majority of chemotherapy drugs and targeted therapies carry a risk of B viral reactivation. Screening for B-virus infection is recommended for all candidates for chemotherapy and targeted therapy. Entecavir and tenofovir are treatment options for prophylaxis of HBV reactivation in patients receiving systemic anti-cancer therapies. Antiviral prophylaxis should be maintained during the period of immunosuppression and for at least 12 months (18 months if the regimen includes Rituximab) after cessation of immunosuppressive therapy.

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