Recommendations for screening, monitoring, prevention, prophylaxis and therapy of Hepatitis B virus reactivation in patients with haematological malignancies and patients who underwent haematological stem cell transplantation – a position paper


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Title

Recommendations for screening, monitoring, prevention, prophylaxis and therapy of Hepatitis B virus reactivation in patients with haematological malignancies and patients who underwent haematological stem cell transplantation – a position paper


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Abstract

Scope - Hepatitis B virus (HBV) infection reactivation is associated with high morbidity and mortality in patients with haematological malignancy and/or haematopoietic stem cell transplantation (HSCT) however information on this issue is limited. The scope of this position paper is to provide recommendations on HBV screening, monitoring, prophylaxis, treatment and vaccination in the patients described above.

Methods – These recommendations were developed from one meeting of experts attended by different Italian scientific societies as well as from a systematic literature review (through December 31, 2016) on HBV infection in haematological patients and in patients who underwent HSCT published in the same issue of this journal. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology was used to provide a grading of each recommendation’s quality.

Questions addressed - These recommendations provide the answers to the following questions: 1. HBV screening and monitoring: Who should be screened before starting chemotherapy (CHT)? Which screening tests should be used? Should HBV-DNA detection be used to monitor HBV reactivation before starting antivirals? What is the best timeline to monitor HBV reactivation?; 2. Prophylaxis in HBsAg-positive patients: Which antiviral drugs should be used to treat HBsAg-positive patients? How long should antiviral prophylaxis be given to HBsAg-positive patients?; 3. Prophylaxis in patients with resolved HBV infection: Which patients with resolved HBV-infection should receive antiviral prophylaxis? Which antiviral drug should be used? How long should antiviral prophylaxis be given?; 4. HBV infection management strategy in autologous (auto-HSCT) and allogeneic HSCT (allo-HSCT): Which HSCT recipients should receive antiviral prophylaxis? Which antiviral drug should be used? How long should antiviral prophylaxis be given?; 5. Should third generation anti-HBV drugs be preferred to first or second generation antiviral drugs in the treatment of HBV reactivation with or without hepatitis flare in haematological patients; 6. Immunization against HBV in patients with haematological malignancies and/or patients who underwent HSCT: Should patient with haematological malignancies and/or those who underwent HSCT be vaccinated? Which HBV vaccination schedule should be adopted?

Recommendations – Hematologic patients should be screened for HBV (HBsAg plus anti-HBc, and HBV DNA in HBV-positive) before CHT. HBV DNA levels should be monthly
monitored in all HBV-positive patients who do not receive prophylaxis. HBsAg-positive haematologic patients and those undergoing HSCT, should be receive third-generation antivirals as prophylaxis. Anti-HBc-positive lymphoma patients and those receiving HSCT should receive antiviral prophylaxis. All HBV-negative haematologic patients should be vaccinated for HBV.

The acquisition of data from well-designed studies is desirable in the near future.
Introduction

Hepatitis B virus (HBV) reactivation in haematological patients has been associated with chemotherapy (CHT) interruption, frequent hospitalization, progression to hepatic failure and death (1). All of these conditions are largely preventable by the corrective measures of screening and prophylaxis. The grade of HBV reactivation risk for haematological treatments and the length of immunosuppression are not always clearly quantifiable. Despite suggestions of experts from existing international guidelines and given the lack of controlled studies, many areas remain unclear, primarily concerning which haematological patients are at a higher risk of HBV reactivation and the type and duration of HBV reactivation monitoring, prophylaxis or pre-emptive therapy. These topics deserve further attention.

This document constitutes the recommendations of the SIMIT (Italian Society of Infectious Diseases), the SIE (Italian Society of Haematology), the GITMO (Italian Group of Bone Marrow Transplantation) and the SIV-ISV (Italian Society of Virology). Here, the authors summarize the current evidence on HBV screening, monitoring, prophylaxis and therapy of HBV reactivation in patients with haematological malignancies and/or patients who underwent haematological stem cell transplantation (HSCT). Finally, it highlights the current gaps in knowledge on this topic.
Methods

This position paper was developed from one meeting (Rome July 2015) that involved a team of experts from the SIMIT, the SIE, the GITMO and the SIV-ISV. It is based on a systematic literature review (2). The initial article underwent several rounds of review by authors. The results of our systematic review (2) were evaluated by Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (35) to provide a systematic method of grading both the strength of the recommendation (weak or strong) and the quality of evidence (very low, low, moderate and high). According to GRADE criteria, evidence from randomized controlled studies, initially considered of high quality, were rated down if there were risk of bias, inconsistence of results, indirectness of evidence, imprecision of results and publication bias. On the other hand, evidence from some observational studies, initially considered of low quality, were rated at high quality if a large magnitude of effect. Moreover, observational studies were considered to provide relevant information on the outcome of patients with haematological malignancies.
HBV screening and monitoring: Who should be screened before starting chemotherapy (CHT)? Which screening tests should be used? Should HBV-DNA detection be used to monitor HBV reactivation before starting antivirals? What is the best timeline to monitor HBV reactivation?

(see literature systematic review paper pages...)

The purpose of HBV screening and monitoring is to identify haematological patients with HBV infection who may benefit from receiving antiviral drugs (such as prophylaxis or pre-emptive therapy) and to check for possible reactivation of HBV replication.

a. **Who should be screened before starting CHT? Which screening tests should be used?**

All patients with a diagnosis of haematological malignancy and/or patients who have received HSCT should be screened for HBV infection prior to beginning CHT. Screening practice allows the early identification of patients with pre-existing HBV infection (resolved or chronic) who may benefit of antiviral prophylaxis or pre-emptive antiviral treatment.

There are no prospective, randomized studies on HBV screening in patients with haematological malignancy to establish the advantages of one screening approach over another (HBsAg plus anti-HBc, and HBV DNA in anti-HBc positive subjects), and therefore there is no agreement among international guidelines on which screening tests should be used (4-8).

We suggest that HBV screening should include serological assays for HBsAg, anti-HBc and anti-HBs. Patients identified as HBsAg-positive/anti-HBc-positive or HBsAg-negative/anti-HBc-positive+/-anti-HBs-positive should be tested for quantitative HBV DNA (strong recommendation; moderate quality of evidence).

b. **Should HBV-DNA detection be used to monitor HBV reactivation before starting antivirals? What is the best timeline to monitor HBV reactivation?**

All haematological patients receiving CHT and/or immunotherapy and patients who underwent HSCT with resolved or chronic HBV infection who have not received prophylaxis should be monitored monthly for HBV-DNA detection (strong recommendation, moderate quality of evidence).

In patients with chronic HBV infection receiving antiviral prophylaxis, monitoring for reactivation should be performed before the end of prophylaxis, periodically thereafter and...
most likely also during the prophylaxis period (strong recommendation, high quality of evidence).

In patients with resolved HBV infection receiving antiviral prophylaxis there are no data supporting HBV-DNA monitoring for reactivation (no recommendation, knowledge gap).

Comment - An unresolved issue is the timing of HBV reactivation monitoring in patients with resolved HBV infection and chronic haematological diseases (chronic lymphocytic leukaemia [CLL], chronic myeloid leukaemia [CML], multiple myeloma [MM]), receiving CHT (i.e., BCR-ABL tyrosine kinase inhibitors for CML) throughout their lifetimes. This condition might put them at risk of HBV reactivation for a long time, if not for life.

Prophylaxis in HBsAg-positive patients: Which antiviral drugs should be used to treat HBsAg-positive patients? How long should antiviral prophylaxis be given to HBsAg-positive patients?

(see literature review paper pages....)

The incidence of HBV reactivation in HBsAg-positive haematological patients who are not treated with antivirals and who undergo CHT is 10-50% and is associated with elevated mortality rates (9-11).

Which antiviral drugs should be used to treat HBsAg-positive patients?

All HBsAg-positive patients, regardless HBV DNA levels, should receive anti-HBV drugs. The efficacy of lamivudine is hampered by the development of mutations in the tyrosine-methionine-aspartate-aspartate (YMDD) motif of the HBV polymerase gene, resulting in lamivudine resistance (12). Furthermore, the most recent studies have reported incidences of HBV reactivation (breakthrough) ranging from 20 to 30% in HBsAg-positive lymphoma patients receiving prophylaxis with lamivudine (13-16).

The use of third generation antivirals (entecavir or tenofovir) is recommended in HBsAg-positive haematologic patient regardless of HBV DNA levels (strong recommendation, moderate quality of evidence).

Currently, entecavir and tenofovir, drugs with high genetic barriers to resistance, are preferred to lamivudine for the treatment of haematological patients with chronic HBV infection regardless of their HBV DNA levels (entecavir: strong recommendation, high quality of evidence, tenofovir; strong recommendation, moderate quality of evidence).
Comment - Both entecavir and tenofovir have excellent safety profiles without myelosuppressive effects (17, 18). Renal function and previous lamivudine use can guide the choice of antiviral drug in HBsAg-positive haematological patients. In the case of patients with severe renal impairment, entecavir may be a better treatment option than tenofovir as it has a low risk of inducing proximal tubular dysfunction and renal insufficiency (19). However, tenofovir is preferred to entecavir if a patient has previously received lamivudine therapy because a certain rate of resistance is expected (20).

How long should antiviral prophylaxis be given to HBsAg-positive patients?
Antiviral prophylaxis should be initiated at least 1 week prior to or in concomitance with starting CHT. It should be continued for the duration of CHT and should be administered for at least 12-24 months after CHT withdrawal (*strong recommendation, moderate quality of evidence*).

Subsequent monitoring for delayed HBV reactivation after the cessation of antiviral prophylaxis is essential (*strong recommendation, high quality of evidence*).

Comment - The duration of antiviral treatment after CHT interruption is the subject of debate because currently there are no randomized studies evaluating the optimal duration of post-CHT treatment. In particular, whether entecavir and tenofovir should be administered for a defined time or indefinitely in patients with active hepatitis depends on the baseline HBV DNA levels (>4 log_{10} copies/ml), on aminotransferase levels and on the degree of fibrosis/cirrhosis (21). The disappearance of HBV DNA and HBsAg associated with the appearance of anti-HBs are indicative of resolved infection and allow the suspension of antiviral therapy. For HBsAg-positive patients who undergo HSCT, there is a debate about how long to continue antiviral treatment because of the paucity of data on the optimal duration of therapy; however, it is quite clear that subsequent monitoring for delayed HBV reactivation after the cessation of antiviral prophylaxis is reasonable.

Prophylaxis in patients with resolved HBV infection: Which patients with resolved HBV-infection should receive antiviral prophylaxis? Which antiviral drug should be used? How long should antiviral prophylaxis be given?
(see literature review paper pages.....)

HBV reactivation in patients with resolved hepatitis (HBsAg-negative/anti-HBc-positive/anti-HBsAg-positive or negative) is an issue of growing relevance in the context of...
immunocompromised patients and, in particular, in the setting of haematological malignancies. The incidence of HBV reactivation in this category of patients not receiving antiviral prophylaxis has been reported to be between 4.1% and 41.5% (22-27).

Which patients with resolved HBV infection should receive antiviral prophylaxis? Which antiviral drug should be used? How long should antiviral prophylaxis be given?

a. Patients with lymphoma and resolved HBV infection

In patients with lymphoma and resolved HBV infection, entecavir and tenofovir should be considered the drug of choice for HBV prophylaxis, lamivudine can be considered an alternative drug option (weak recommendation, moderate quality of evidence).

Comment - Two randomized studies in which first-line prophylaxis with entecavir and tenofovir was used to prevent HBV reactivation in patients with haematological malignancy and resolved hepatitis were published (24, 27). No controlled studies were published on lamivudine use in the same category of patients. Lamivudine is a safe and well-tolerated drug in immunocompromised patients with resolved hepatitis, even if its use must be carefully monitored for the possible emergence of resistant viral strains. However, the potential risk of lamivudine resistance development is small in patients with resolved HBV infection and undetectable HBV DNA and in those who are expected to receive antiviral prophylaxis for less or more than six months. Therefore, although economic studies (costs and resource use) were not identified on this topic, given that lamivudine has the lowest cost, it is reasonable choose the least expensive antiviral drug in this setting.

Antiviral prophylaxis should be initiated at least 1 week prior to or in concomitance with starting CHT and should be administered at least for 12 months after CHT interruption (strong recommendation, moderate quality of evidence).

Comment - Although there is an agreement on the optimal start time of prophylaxis in weeks before the beginning of CHT, little is known about the best time to discontinue HBV prophylaxis. The period of immune recovery is probably the best time to stop antiviral prophylaxis; however, the lack of reliable biological markers of immune recovery prevents the definition of the optimal duration of prophylaxis, particularly in patients with haematological malignancies. The incidence of delayed HBV reactivation after the cessation of antiviral prophylaxis in lymphoma patients with resolved HBV infection is unknown.
b. Patients with acute T cell leukaemia (ATL), MM, CLL and other haematological malignancies with resolved HBV infection

Haematological patients with ATL, MM and CLL with resolved HBV infection should undergo antiviral prophylaxis (weak recommendation, low quality of evidence).

Lamivudine should be the drug administered in patients with CLL for a 12-months duration of therapy, (weak recommendation, low quality of evidence), while there are no studies on HBV antiviral prophylaxis in ATL and MM patients (no recommendation, knowledge gap).

Comments – Three cases of HBV reactivation in HBsAg-positive CML patients and one case in a CML patient with resolved HBV infection during Bcr-Abl tyrosine kinase inhibitor (TKI) (i.e., imatinib, dasatinib,) treatment were published (28-31). Currently, there are no studies describing a better intervention strategy to monitor or prevent HBV reactivation in CML patients during TKI therapy. Regarding CLL, caution in the administration of Ibrutinib and idelalisib is suggested in HBV-positive patients, but the best intervention strategy is not yet known (32, 33).

Strategy of HBV infection management in autologous (auto-) and allogeneic haematopoietic stem cell transplantation (HSCT) 
(see literature review paper pages and tables)

HSCT, and in particular allogeneic HSCT (allo-HSCT), is a condition associated with a high risk for HBV reactivation, a lower rate reported in patients with resolved infection, while a higher rate was reported in HBsAg-positive recipients.

Which HSCT recipients should receive antiviral prophylaxis? Which antiviral drug should be used? How long should antiviral prophylaxis be given?

a. HBsAg-positive auto- and allo-HSCT recipients

All HBsAg-positive HSCT recipients should be treated independently of the presence or the level of HBV DNA (strong recommendation, moderate quality of evidence).

Antiviral treatment should be conducted with entecavir or lamivudine (strong recommendation, moderate quality of evidence)

Antiviral drugs should be started at least a week before the HSCT procedure and should be continued for at least one year (strong recommendation, moderate quality of evidence).
Comment - In HBsAg-positive patients undergoing HSCT, the only high-genetic-barrier antiviral drug used was entecavir, no data are available on tenofovir use in this kind of patients. Regarding the duration of antiviral treatment, given the high overall mortality of HSCT patients, very limited information was present in the published studies. However, it is reasonable to consider lifelong antiviral treatment in these patients. The disappearance of HBV DNA and HBsAg associated with the appearance of anti-HBs are indicative of resolved infection and allow the suspension of antiviral therapy.

b. Auto- and allo-HSCT recipients with resolved HBV infection

All anti-HBc-positive HSCT recipients should receive prophylaxis with lamivudine, independently of the presence of HBV DNA, for a time period of at least 18 months (strong recommendation, moderate quality of evidence).

Comments - Ideally the duration of antiviral prophylaxis should be based on immune recovery (i.e., increased CD4+ counts above 200-400 cells/mm^3), which can take years following allo-HSCT. Close monitoring of viremic rebound and sero-reversion should be performed when prophylaxis is discontinued. The timing of monitoring is not actually defined.

c. HBV-negative allo-HSCT recipient with an anti-HBV-positive donor

All HBV-negative allo-HSCT recipients with anti-HBc-positive/anti-HBs-positive or -negative (HBV DNA-negative) donors should receive prophylaxis with lamivudine (weak recommendation, moderate quality of evidence). The lamivudine prophylaxis duration is not defined (no recommendation, knowledge gap).

Should third generation anti-HBV drugs be preferred to first or second generation antiviral drugs in the treatment of HBV reactivation with or without hepatitis flare in haematological patients

There are no studies which directly compare the clinical efficacy of third generation antiviral drugs versus first or second generation of anti-HBV drugs in the treatment of HBV reactivation, with or without hepatitis, during immunosuppressive-CHT in haematological patients. However, the severe consequences of this condition in these patients (CHT interruption, frequent hospitalization, progression to hepatic failure and death) make the antiviral treatment of HBV reactivation indispensable. Therefore, the use of antivirals with high potency and high barrier to resistance (third generation anti-HBV drugs) is recommended (strong recommendation, knowledge gap).
Comment - In immunocompetent patients with chronic HBV infection, randomized studies demonstrated that the use of entecavir versus LMV, entecavir versus adefovir or tenofovir versus adefovir was associated with a higher rate of non-detectable HBV-DNA (34-38). In addition, in a network meta-analysis (39), the use of tenofovir showed a higher efficacy compared with lamivudine in inducing undetectable HBV-DNA levels in the treatment of immunocompetent patients with chronic HBV infection.

The duration of antiviral therapy in the immunocompromised patient is expected to be prolonged (even more than 12 months) due to the severity of HBV hepatitis manifestations and the need to continue immunosuppressive therapy. Reactivation of HBV in this kind of patients is usually related to high levels and prolonged virus replication despite antivirals use, thus promoting the selection of resistant strains during treatment with low genetic barrier antivirals, such as lamivudine. Entecavir and tenofovir have greater antiviral potency compared with lamivudine and their use is associated with low or absence selection of drug resistance mutations (40, 41). Recently, tenofovir alafenamide (TAF), a novel targeted prodrug of tenofovir, was tested in two randomized studies in treatment-naïve immunocompetent subjects with chronic hepatitis B and shown to be non-inferior and associated with less bone and renal adverse effects than tenofovir (42, 43).

Only a retrospective study (44) and two case series (45, 46) described the successful treatment with drugs with higher antiviral potency and high genetic barrier such as entecavir or tenofovir in haematological patients.

Immunisation against HBV in patients with haematological malignancies and/or patients who underwent HSCT

(see literature review paper pages ...)

Should patients with haematological malignancies and/or those undergoing HSCT be vaccinated?

All patients with haematological malignancies and/or patients undergoing HSCT who are HBV-negative at screening should undergo HBV vaccination and their anti-HBs titre should be periodically monitored (strong recommendation, low quality of evidence).

Which HBV vaccination schedule should be adopted?

A standard vaccination schedule (20 µg at 0, 4 and 6 months) is generally recommended; however, an intensive schedule with four single 20 µg HBV vaccine doses administered at
0, 2, 4 and 6 months may be an alternative to the conventional protocol with the ultimate aim to obtain a better vaccination response (strong recommendation, low quality of evidence).

Comment - In general, in adults with hematologic malignancies, including acute leukaemia and other myeloproliferative diseases, an anti-HBV vaccine should be administered 1-2 weeks before the initiation or 3 months after the completion of CHT (47). HBV vaccination of HBV-negative auto- or allo-HSCT patients should be performed before beginning the conditioning regimen. In the allo-HSCT setting, vaccination of donors for HBV-positive recipients is also suggested with the goal that the adaptive immune response from the HBV-vaccinated donor could protect the recipient from HBV reactivation (48).
Conclusions

The majority of the questions on HBV screening and monitoring, on HBV prophylaxis in patients with chronic or resolved HBV infection, and on the management of HBV infection in HSCT were addressed by recommendations with a moderate quality of evidence. HBV immunization and treatment of HBV reactivation were supported by studies with low quality of evidence. Gaps of knowledge remain on HBV reactivation monitoring in patients with resolved infection taking lamivudine and on the duration of prophylaxis in HSCT recipients from HBV positive donor. Moreover, to date, the scientific literature does not provide guidance (gap of knowledge) in ATL and MM patients with resolved HBV infection. There is a great need in the near future of high-quality studies, mainly RCTs, that provide clear indications on: 1. the risk of HBV reactivation in hematologic diseases other than lymphoma; 2. the risk of HBV reactivation as consequence of new target biologic treatments use; 3. the duration of HBV prophylaxis in either HBsAg-positive or anti-HBc-positive haematologic patients receiving CHT-immunotherapy or HSCT; 4. the duration of HBV DNA monitoring after antivirals withdrawn; 5. the best drug, or combination of drugs, for HBV hepatitis flare therapy; 6. the most protective HBV immunization schedule in haematological patients.
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