Management of viral hepatitis in patients with haematological malignancy and in patients undergoing haemopoietic stem cell transplantation: recommendations of the 5th European Conference on Infections in Leukaemia (ECIL-5)

*Vincent Mallet, Florian van Bömmel, Christopher Doerig, Sven Pischke, Olivier Hermine, Anna Locasciulli, Catherine Cordonnier, Thomas Berg, Darius Moradpour, Heiner Wedemeyer, Per Ljungman, on behalf of ECIL-5**

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Université Paris Descartes, Sorbonne Paris Cité, Paris, France (Prof V Mallet MD); **Institut Pasteur, Institut National de la Santé et de la Recherche Médicale Unité 1223, Paris, France** (Prof V Mallet); **Hepatology Service, Assistance Publique–Hôpitaux de Paris, Groupe Hospitalier Cochin Port-Royal, Paris, France** (Prof V Mallet); **Hepatology Section, University Hospital Leipzig, Leipzig, Germany** (F van Bömmel MD, Prof T Berg MD); **Division of Gastroenterology and Hepatology, Centre Hospitalier Universitaire Vaudois, University of Lausanne, Lausanne, Switzerland** (C Doerig MD, Prof D Moradpour MD); **University Medical Center Hamburg–Eppendorf, First Department of Medicine, Hamburg, Germany** (S Pischke MD); **Department of Haematology, Paris Descartes University, Imagine Institute, Necker Hospital, Paris, France** (Prof O Hermine MD); **Ematologia e Trapianto di Midollo, Ospedale SanCamillo, Roma, Italia** (Prof A Locasciulli MD); **Hannover Centre for Internal Medicine, Hannover, Germany** (Prof H Wedemeyer MD); **Haematology Department, Henri Mondor Hospital, Assistance Publique–Hôpitaux de Paris, and Paris-Est Créteil University, Créteil, France** (Prof C Cordonnier MD); **and Karolinska University Hospital, Department of Haematology and Karolinska Institutet, Department of Medicine, Huddinge, Stockholm, Sweden** (Prof P Ljungman MD)

Summary

Viral hepatitis affects millions of people worldwide, and host immunity is the key determinant of patient outcome. Viral hepatitis can be life threatening in patients with haematological malignancy, including haemopoietic stem cell transplant recipients, because of the virus itself, or through a need to decrease the dose of chemotherapy. A past or currently infected haemopoietic stem cell donor could also transmit viral hepatitis. The burden of viral hepatitis in patients with haematological malignancies and the weak evidence on which previous guidelines are based has prompted the European Conference on Infection in Leukaemia (ECIL-5) to convene a group of experts in the fields of viral hepatitis and of haematological malignancy to specifically address previously unconsidered issues and grade the available quality of evidence according to the Infectious Diseases Society of America grading system. The group recommends that all patients should be screened for hepatotropic viruses before haematological treatment and that patients or haemopoietic stem cell donors with markers of past or current viral hepatitis should be assessed by an expert. Screening, vaccination, and treatment rules are reported in this Review.

Introduction

Treatment of patients with haematological malignancies has changed greatly in recent decades. A growing number of patients undergo haemopoietic stem cell transplantation (HSCT), including older patients and patients with comorbid conditions.[1,2]

In the WHO European Region, an estimated 13·3 million (1·8% of 898·6 million adults) have hepatitis B virus (HBV) and 15 million (2·0% of 732·1 million adults) have hepatitis C virus (HCV) and two-thirds of HBV and HCV patients are migrants or live in eastern Europe.[3,4]

Increasing numbers of patients with haematological malignancies or potential haemopoietic stem cell (HSC) donors are being found with markers of active or resolved HBV or HCV infection. Hepatitis E virus (HEV) is also thought to be prevalent in high-income countries, placing HSC recipients and donors at risk of acquiring and transmitting HEV.

Host immunity is the key determinant of the natural course of viral hepatitis. These infections could be life-threatening in patients with haematological malignancy, because of the effects of the virus itself, or through a need to decrease the dose of chemotherapy.

All patients with haematological malignancy should undergo screening for hepatotropic viruses before chemotherapy or HSCT or in the setting of hepatitis; those with markers of past or current viral hepatitis should undergo expert evaluation (tables 1 and 2). A past or currently infected HSC donor can transmit viral hepatitis. Donors should therefore be screened for hepatotropic viruses before HSC harvesting.

In this Review, HSCT refers only to allogeneic HSCT because graft-versus-host disease (GvHD), the possibility to transfer infections and specific immunity from the donor to the recipient, does not exist with autologous HSCT.

The burden of viral hepatitis and the weak evidence on which previous guidelines are based has prompted the European Conference on Infection in Leukaemia (ECIL-5) to convene a group of experts in the fields of viral hepatitis and of haematological malignancy to specifically address previously unconsidered issues.[5–9] We aimed to conduct a review of the literature on hepatitis viruses in patients with haematological malignancy to address the current gaps in knowledge and to provide simple guidelines for non-expert physicians. The final considerations and recommendations of the ECIL-5 Viral Hepatitis Group are summarised in this Review.

Guideline development overview

The ECIL is a joint initiative of the Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation (EBMT), European Organisation for Research and Treatment of Cancer (EORTC), Immunocompromised Host Society (ICHS), and European Leukaemia Net (ELN). The objective of ECIL is to develop evidence-based guidelines for the management of infectious complications in patients with haematological malignancy, mainly patients with leukaemia and HSCT recipients.

The methodology of the ECIL conferences has been previously described.[10] In brief, the ECIL organising

	Screening tests required
Patients with haematological malignancies, including candidates for HSCT	
HBV (AI)	HBsAg, anti-HBc, and anti-HBs Nucleic acid testing if HBsAg or anti-HBc positive
HCV (AII)	Anti-HCV Nucleic acid testing if anti-HCV positive Nucleic acid testing in the presence of risk factors Nucleic acid testing should be preferred if programmed HSCT
HEV (AII)	Nucleic acid testing
HAV (AIII)	Anti-HAV IgG
HDV (BII)	Anti-delta if HBsAg positive Nucleic acid testing if anti-delta positive
HSCT donors	
HBV (AII)	HBsAg, anti-HBc, and anti-HBs Nucleic acid testing if HBsAg or anti-HBc positive
HCV (AII)	Anti-HCV Nucleic acid testing in the presence of risk factors
HEV (AII)	Nucleic acid testing
HAV (BII)	Anti-HAV IgM in the presence of abnormal liver function tests
HDV (BIII)	Anti-HDV if HBsAg positive Nucleic acid testing if anti-HDV positive

Recommendations were formulated after discussion of the scientific literature review within the group and graded for quality of evidence (I–III) and strength of recommendation (A–C) using the Infectious Diseases Society of America grading system. ECIL-5=European Conference on Infection in Leukaemia. HSCT=haemopoietic stem cell transplant. HAV=hepatitis A virus. HBV=hepatitis B virus. HBc=hepatitis B core. HCV=hepatitis C virus. HDV=hepatitis D virus. HEV=hepatitis E virus.

Table 1: **ECIL-5 screening rules for patients with haematological malignancies and for HSCT donors**

	Diagnostic recommendation
HBV (AII)	HBsAg, nucleic acid testing
HCV (AIII)	Nucleic acid testing
HEV (AIII)	Nucleic acid testing
HAV (AII)	Anti-HAV IgM; nucleic acid testing if host treated with depleting antibodies
HDV (AII)	Nucleic acid testing
Adenovirus, cytomegalovirus, EBV, HSV, VZV*	Nucleic acid testing

Recommendations were formulated after discussion of the scientific literature review within the group and graded for quality of evidence (I–III) and strength of recommendation (A–C) using the Infectious Diseases Society of America grading system. ECIL-5=European Conference on Infection in Leukaemia. HSCT=haemopoietic stem cell transplant. HAV=hepatitis A virus. HBV=hepatitis B virus. HCV=hepatitis C virus. HDV=hepatitis D virus. HEV=hepatitis E virus. EBV=Epstein-Barr virus. HSV=herpes simplex virus. VZV=varicella-zoster virus. *Covered in the ECIL 2–4 guidelines.

Table 2: **ECIL-5 viral diagnostic recommendations for patients with haematological malignancy and acute hepatitis**

committee convened a group of independent international experts identified on the basis of knowledge and publications about viral hepatitis inside or outside of the context of haematological malignancy or immune-depression. Under the guidance of a designated leader, the group defined the relevant issues, questions, and outcomes to be addressed, and assessed these before the consensus conference through a review of the scientific literature with the objective to prepare proposals concerning the management of patients with haematological malignancies, including HSCT recipients (and their donors), with markers of past or current viral hepatitis. The main search terms used were "hepatitis A virus", "hepatitis B virus", "hepatitis C virus", hepatitis E virus", "liver fibrosis", "cirrhosis" AND "stem cell transplantation" or "bone marrow transplant" or "leukemia" or "lymphoma" or "myeloma" or "haematological malignancy" or "cancer" or "transplant recipients". PubMed and Web of Science searches (Jan 1, 1966, to Sept 15, 2013) were conducted. Cited and citing references of each identified article were checked. Recommendations were formulated after discussion of the scientific literature review within the group and graded for quality of evidence (I–III) and strength of recommendation (A–C) using the Infectious Diseases Society of America grading system.[11,12]

The consensus conference was convened at ECIL-5 (Sophia Antipolis, France) on Sept 19–21, 2013, and attended by 52 experts from 16 European countries as well as Russia, Israel, and Turkey. Delegates were specialists in haematology, oncology, microbiology, infectious diseases, and clinical research and selected on the basis of skills and active participation in the host organisations. The group presented the findings of the scientific literature review and the proposed recommendations in an initial plenary session. After panel debate, the recommendations were revised as necessary and discussed again in a second plenary session, and a final consensus was reached on the quality of evidence and the strength of each recommendation. A second PubMed and Web of Science search (Sept 15, 2013, to Jan 15, 2016) was conducted during the publication process of the ECIL-5 recommendations.

HBV infection

Landmarks in the natural history of HBV infections

The risk of developing chronic HBV infection is related to immune maturity. A chronic course develops in 95% of newborns, but in fewer than 10% of adults with acute HBV infection.[13]

Although the course of chronic HBV infection might be variable and can move from active to inactive states and then revert back to active liver disease years later, there is a general agreement that HBV infection runs in four phases which follow one another: the immune tolerant phase, the immune active phase, the inactive phase, and the recovery phase.[9]

Correspondence to:
Prof Vincent Mallet, Assistance Publique–Hôpitaux de Paris, Hôpital Cochin, Unité d'hépatologie, 75014 Paris
vincent.mallet@cch.aphp.fr

Slide sets from ECIL-5 covering these aspects are available via the websites of the organisations involved in the ECIL (European Group for Blood and Marrow Transplantation [EBMT], European Organisation for Research and Treatment of Cancer [EORTC], Immunocompromised Host Society [ICHS], ECIL and European Leukaemia Net [ELN]) see www.kobe.fr/ecil

	HBsAg-positive-patients		HBsAg-negative and anti-HBc-positive patients	
	Highest reported rate of HBV reactivation*	Antivirals at day 1 of immunosuppressive protocol	Highest reported rate of HBV reactivation*	Antivirals at day 1 of immunosuppressive protocol
HSCT[29,30]	High	Yes	High	Yes
Anti-CD20 antibodies[31–33]	73%	Yes	41%	Yes
Chemotherapy[26,34–36]	71%	Yes	9%	No
Anti-TNF antibodies[37]	39%	Yes	5%	No
Corticosteroids[38–40]	25%	Yes	1–5%	No
Methotrexate[40,41]	5%	Yes	Low	No
Azathioprine[40]	Low	Yes	Low	No

ECIL-5=European Conference on Infection in Leukaemia. HSCT=haemopoietic stem cell transplant. HBV=hepatitis B virus. *Rate of HBV reactivation is highest among HBsAg negative and anti-HBc-positive patients without anti-HBs born in area of high HBV endemicity where a mother-to-child mode of transmission prevails.

Table 3: **ECIL-5 treatment recommendations for patients with haematological malignancy and HBV markers**

People who clear HBsAg can be assigned as being in the recovery phase, and could achieve seroconversion to anti-HBs. In the natural course, 0·5–0·8% of infected people will clear HBsAg per year, especially those who were inactive carriers for a long time and older patients.[14] Anti-HBc antibodies are still detectable in these individuals.

Even in patients with HBsAg seroconversion, HBV probably persists lifelong in the nucleus of hepatocytes in the form of covalently closed circular (ccc)DNA. The HBV cccDNA represents the basis for HBV reactivation, and the basis for occult HBV infections, which are defined by the presence of HBV DNA in the liver and presence or absence of HBV DNA in serum without detectable HBsAg.[15,16]

Mechanisms of HBV reactivation

Immune responses, including CD4 helper T cells and CD8 cytotoxic T cells, determine the outcome of HBV infection.[17,18] A humoral response to HBV infection contributes to the control of the inactive carrier state and to the recovery phase.[19] Any impairment of the immune system, such as during chemotherapy, HSCT, or B-cell depletion, could induce HBV reactivation.

The first description of HBV reactivation was made in 1975 by Wands and colleagues[20] who suspected an association between increases in HBsAg titres together with elevation in serum transaminases and chemotherapy given for lymphoproliferative diseases.

It has then been established that HBV reactivation was related to a treatment-induced loss of immune control.[21,22] Response elements to corticosteroids that enhance HBV replication are also reported.[23] Hepatitis, including reported cases of fulminant hepatic failure, typically occurs after immune system reconstitution, de-novo recognition, and destruction of HBV-infected hepatocytes.[21,24] Fibrosing cholestatic hepatitis might also be a consequence of HBV reactivation. Fibrosing cholestatic hepatitis is caused by massive overproduction of HBV particles and proteins,[25] and shows a biochemical cholestatic profile with marked elevation of serum bilirubin, alkaline phosphatase, and gamma glutamyl transpeptidase.

Overall, the reported case-fatality rate of HBV reactivation is high in patients with haematological malignancy as a consequence of HBV-related hepatic failure, including in the setting of fibrosing cholestatic hepatitis, or of chemotherapy dose reduction.[26]

Definitions of HBV reactivation

The definition of HBV reactivation varies in the scientific literature, which makes any comparison of HBV reactivation rates across studies difficult.[7,8,27] The latest studies define HBV reactivation as a ten-fold increase in HBV DNA level in HBsAg-positive individuals and as a sero-reversion of HBsAg in HBsAg-negative and anti-HBc-positive individuals. However, reappearance of HBsAg is mostly preceded by a reappearance of HBV DNA.

Risk factors for HBV reactivation in patients receiving immunosuppressive treatments

The risk of reactivation primarily depends on the stage of HBV infection and the type of immunosuppressive regimen. HBsAg-positive people are at high risk of HBV reactivation during most immunosuppressive treatments, and there is a clear association between HBV reactivation risk and dosing and duration of immunosuppressive treatment. By contrast, HBsAg-negative and anti-HBc-positive people are at low risk during most immunosuppressive therapies with the important exceptions of HSCT and anti-CD20 antibodies. Other factors like age or gender contribute less to the risk of HBV reactivation.[28] An approach to summarise the most important risk factors for HBV reactivation for HBsAg-positive, HBsAg-negative, and anti-HBc-positive patients is shown in table 3. Detection of anti-HBs antibodies in HBsAg-negative and anti-HBc-positive individuals has been reckoned as a protective factor against HBV reactivation. However, the influence of anti-HBs on reactivation is small, especially under anti-CD20 antibodies or after HSCT.[29,42–46]

HBV reactivation in HBsAg-positive people receiving cytotoxic chemotherapy

In 1991, Lok and colleagues[34] demonstrated that 18 (67%) of 27 HBsAg-positive patients and 10 (14%) of 73 HBsAg-negative and anti-HBc-positive patients developed alanine transaminase elevations following administration of chemotherapy for non-Hodgkin lymphoma; this was later confirmed by others.[26,34] Reported rates of HBV reactivation following chemotherapy are similar in area of the world of lower HBV endemicity.[35,36]

These rates might be underestimated, as in most studies HBV DNA levels were only measured in the setting of overt HBV reactivation. A median delay of 16 weeks (range 4–36) was reported between chemotherapy initiation and HBV reactivation in HBsAg-positive patients.[47]

Combining chemotherapy with other immunosuppressive agents (anti-CD20 antibodies or corticosteroids) potentiates the risk of HBV reactivation.[49]

HBV reactivation in HBsAg-positive people receiving immunosuppressive treatments

Rituximab increases the risk of developing HBV reactivation and associated liver failure and death when given in association with corticosteroids or chemotherapy.[31] HBV reactivation under rituximab monotherapy has been reported.[32] The US Food and Drug Administration has issued box warnings for the anti-CD20 antibodies rituximab, and ofatumumab, a humanised anti-CD20 monoclonal antibody, because of an increased risk of HBV reactivation.[33] The lower number of HBV reactions reported under ofatumumab is probably due to its more recent licensing.

The probability of HBV reactivation under corticosteroids is dependent on dose and time, and most of the evidence comes from patients without haematological malignancy.[39,40] Single case reports point out however that even very low doses of corticosteroids could increase the risk of HBV reactivation in HBsAg-positive people.[49] The use of glucocorticoids together with chemotherapy doubles the risk of HBV reactivation.[38]

Only isolated cases of HBV reactivation under antimetabolites have been reported, and in most cases these drugs were taken concomitantly with corticosteroids. Therefore, the risk associated with these agents alone is probably low.[50] Methotrexate might lead to HBV reactivation slightly more often than azathioprine, in about 5% of HBsAg-positive patients at 1 year of treatment.[40,51]

A review[37] of 257 patients with active or recovered HBV infection treated with anti-tumour necrosis factor α agents reports HBV reactivation in 39% of patients. HBV reactivation seemed to be more frequent during treatment with infliximab than with other tumour necrosis factor α inhibitors.[52]

HBV reactivation was reported in a few cases under other biological agents, including proteasome inhibitors and anti-CD52 monoclonal antibodies, such as bortezomib and alemtuzumab.[53,54] Nevertheless, they should be expected to bear a low to moderate risk of HBV reactivation.[53,54]

HBV reactivation in HBsAg-negative and anti-HBc-positive people

In general, the prevalence of HBV reactivation is lower in HBsAg-negative and anti-HBc-positive patients than in HBsAg-positive patients. However, the number of HBsAg-negative and anti-HBc-positive patients greatly exceeds HBsAg-positive patients, and due to the uncommon screening for anti-HBc antibodies before chemotherapy, HBV reactivation in anti-HBc-positive only individuals is often late diagnosed and fatal.[55]

As in HBsAg-positive individuals, the risk for HBV reactivation depends on the type of immunosuppression. Because of the heterogeneous study designs, it is difficult to compare the prevalence of HBV reactivation in HBsAg-negative and anti-HBc-positive subjects. During chemotherapy, the rate of HBV reactivation has been reported to be 9% in HBsAg-negative and anti-HBc-positive patients with anti-HBs antibodies, and 5% in HBsAg-negative and anti-HBc-positive patients without anti-HBs antibodies.[34]

Treatment with anti-CD20 monoclonal antibodies represents an important exemption as it directly targets humoral control of HBV infection at this stage. HBsAg-negative and anti-HBc-positive patients who receive rituximab are at high risk of HBV reactivation (25–40%).[38] A meta-analysis reviewing nine studies reported that HBsAg-negative and anti-HBc-positive patients with lymphoma who received rituximab had rates of HBV reactivation more than twice compared with those of controls receiving chemotherapy without rituximab.[56] As anti-HBs levels might still be protective for some time after destruction of B cells, HBV reactivation could become apparent many months, or even 1 year, after rituximab treatment, reaching up to 41·5 months in some studies.[45–47,57]

The risk of HBV reactivation under infliximab was reported as around 5% in the largest meta-analysis.[37] As in HBsAg-positive patients, bortezomib and alemtuzumab carry a risk of HBV reactivation in HBsAg-negative and anti-HBc-positive patients.[53,54] Calcineurin inhibitors inhibit T-cell proliferation and favour HBV reactivation, especially in the context of HSCT.[58,59]

Cases of HBV reactivation in HBsAg-negative and anti-HBc-positive patients have rarely been described during treatment with azathioprine or methotrexate, and the risk is probably low.[41] A case of fatal hepatic failure related to HBV reactivation in an HBsAg-negative and anti-HBc-positive patient receiving low dose methotrexate for rheumatoid arthritis has been reported.[60]

HBV reactivation and HSCT

Because of the profound immune suppression associated with chemotherapy conditioning before allogeneic HSCT and (in most cases) implementation of a new immune system that is naive to HBV after HSCT, the risk of severe complications, including fibrosing cholestatic hepatitis, related to HBV reactivation is very high in HBsAg-positive patients.[25,61,62]

The risk of HBV reactivation is also high in HBsAg-negative and anti-HBc-positive patients, and the delay between HSCT and HBV reactivation can be long, reported as 40% at 4 years of treatment in the largest study[42] and up to 85% at 3 years in small case series.[29,42–43]

Risk factors for HBV reactivation in patients undergoing HCST are low anti-HBs titres, use of multiple chemotherapeutic agents, GvHD, and duration of immunosuppression.[63,64] Allogeneic HSCT might lead more frequently to HBV reactivation than autologous HSCT in patients without antiviral prophylaxis.[65]

Vaccination of HBV seronegative patients is recommended in the general population.[7] Higher vaccine doses might be required to achieve anti-HBs response in immunocompromised patients. Vaccination of HBsAg-negative and anti-HBc-positive patients with a standard three-dose regimen after HSCT might reduce the rate of HBV reactivation.[66] Immunocompromised patients with anti-HBc antibodies and without anti-HBs antibodies might achieve protective immunity (anti-HBs antibodies ≥10 IU/L) through vaccination against HBV. This was shown in HIV-infected patients with detectable anti-HBc, in whom four double doses (40 µg) of hepatitis B vaccine administered at 0, 1, 2, and 6 months led to an anti-HBs antibody response in 74–82% of patients.[67]

To sum up, HBV reactivation is a frequent and late complication in HBsAg-negative and anti-HBc-positive allogeneic HSCT recipients. Lifelong HBV monitoring is mandatory in this setting.

The anti-HBc-positive stem cell donor

There is clear evidence that HBV could be transmitted by HBsAg-positive grafts to HBV-naive recipients or those who have lost protective immunity.[68] The subsequent infection is likely to be severe if the recipient has no HBV marker.[69] HBsAg-negative and anti HBc-positive grafts might also transmit HBV to recipients, albeit at lower frequency.[70] Detectable HBV DNA in the serum of the donor is a risk factor. Treatment of both the donor and the recipient and vaccination of the recipient could prevent HBV transmission.[71]

Alternatively, adoptive immunity against HBV might be transferred from anti-HBs-positive donors.[72] The immunisation of HBV-naive stem cell donors can induce HBV immunity in recipients within several days to weeks after transplantation.[73,74] Immunisation of stem cell donors is, theoretically, easy to perform and virtually risk free, although there might not be sufficient time to complete the vaccination schedule before stem cell harvesting. An accelerated schedule (days 0, 10, and 21) is a possible alternative.[75]

Antiviral treatments

The nucleoside analogues lamivudine, telbivudine, and entecavir, and the nucleotide analogues adefovir-dipivoxil and tenofovir-disoproxil-fumarate are licensed for HBV treatment.[6,7,34] These drugs suppress HBV replication and their effectiveness is monitored by quantifying HBV DNA in serum with a sensitive assay.[7] All of these substances are taken orally, once daily, and are generally well tolerated. The indications for antiviral treatment in immunocompetent individuals are based on serum HBV DNA levels, direct or indirect signs of necro-inflammation and fibrosis in the liver. Entecavir and tenofovir have the highest antiviral potency and are recommended as first-line treatment in all recent guidelines.[6,7,9] Even if highly active drugs are administered, reactivations might still occur, albeit at a low frequency.[76]

Timing and duration of antiviral treatment

A meta-analysis of five randomised controlled trials[77] reports a relative risk of HBV reactivation of 0·13 (95% CI 0·06–0·3) in patients receiving antivirals from day 1 of the immunosuppressive protocol compared with on-demand antiviral treatment. Current guidelines recommend maintaining patients under treatment until 12 months after cessation of therapy.[7] However, late reactivations (more than 1 year after cessation of haematological treatment) are reported in patients treated with anti-CD20 antibodies and allogeneic HSCT.[45,59]

HCV infection

Landmarks in the course of HCV infections

In non-oncology patients, anti-HCV antibodies are detected about 7–8 weeks after HCV infection, whereas HCV RNA can be detected after as little as 1–2 weeks. In chronic hepatitis C, both anti-HCV antibodies and HCV RNA can be detected. However, anti-HCV antibodies might not be detected in immunocompromised patients. In cases of spontaneous or treatment-induced viral elimination, anti-HCV antibodies persist in the absence of HCV RNA. Patients who have successfully eliminated HCV in the past are not at risk of reactivation under immunosuppressive therapy,[78] but reinfection with HCV is possible.

In the setting of HSCT, outcome of patients with chronic HCV infection seems to be similar to that of patients without HCV, although hepatitis exacerbations and rare cases of fibrosing cholestatic hepatitis have been described.[79–81] Reports on the course of chronic HCV infection in the paediatric population after HSCT are controversial: some indicating a prolonged benign course, without the development of significant liver fibrosis, even after 13–27 years of follow-up; others indicating a disease course similar to that in the adult population, where the development of cirrhosis and a worse outcome have been clearly documented after HSCT.[81–87] Liver monitoring and the treatment of chronic hepatitis C are therefore important elements in haematological patients.[85]

Increases in liver enzyme activity are common in HCV RNA-positive patients receiving chemotherapy, but such increases are usually mild to moderate. Some studies have suggested that chemotherapy does not increase the risk of clinically significant hepatotoxicity in HCV RNA-positive patients with haematological

Panel: **ECIL-5 recommendations for the management of HBV infection in patients with haematological malignancy**

The Infectious Diseases Society of America grading system for ranking recommendations includes three strengths of recommendation (grade A: good evidence to support a recommendation for or against use; grade B: moderate evidence to support a recommendation for or against use; grade C: poor evidence to support a recommendation) and three levels of quality of evidence (level 1: evidence from at least one properly, randomised, controlled trial; level 2: evidence from at least one well designed clinical trial, without randomisation; from cohort or case-controlled analytic studies [preferably from more than one centre]; from multiple time series; or from dramatic results of uncontrolled experiments; level 3: evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees)

Indications for screening

- All patients needing chemotherapy or immunosuppressive therapy (A I)

Screening parameters

- HBsAg, anti-HBc, anti-HBs; HBV DNA if anti-HBc detected
- Expert evaluation of all anti-HBc patients is recommended (A I)

Vaccination

- Vaccination of anti-HBc-negative and anti-HBs-negative patients before and after HSCT is recommended (A I); double vaccine doses (40 μg) may be required to achieve an anti-HBs response in immunocompromised patients (at 0, 1, 2, and 6 months)
- Vaccination of anti-HBc-negative and anti-HBs-negative stem cell donors before HSC harvesting should be considered (B III); an accelerated single-dose (20 μg) 3-week (at 0, 10, and 21 weeks) schedule may be an alternative to the conventional 6-month protocols

Indication for treatment

- All HBsAg-positive patients (A I)
- Biological agents: all anti-HBc-positive patients (A II)
- Stem cell transplantation: all anti-HBc-positive patients (A I)
- All HBsAg-negative, anti-HBc-negative, and anti-HBs-negative recipients receiving anti-HBc-positive grafts (A III); vaccination and the addition of hepatitis B immune globulin can be considered in this setting (B III)

Start of antiviral treatment

- At the start of immunosuppressive therapy (A II)

Choice of antiviral drug

- Tenofovir or entecavir (A I); drug dosing should follow standard recommendations

Duration of antiviral treatment

- Until haematological cure is pronounced and 1 year after withdrawal of immunosuppressive treatment (B III)
- Antivirals may be given for longer periods in HSCT recipients with chronic GvHD and patients exposed to depleting antibodies (A III)

Treatment monitoring

- 3-monthly monitoring of HBV DNA and ALT; monthly monitoring of HBV DNA and ALT after the withdrawal of antiviral treatment (A II)

ECIL-5=European Conference on Infection in Leukaemia. HSCT=haemopoietic stem cell transplant. HBV=hepatitis B virus. GvHD=graft-versus-host disease. ALT=alanine aminotransferase.

malignancies.[88,89] However, most of these data were obtained before the introduction of rituximab.[90] The risk of acute flare-ups in patients undergoing chemotherapy for haematological malignancies seems to be higher in patients on rituximab-containing treatment regimens.[91,92] Flare-ups of liver disease and rare episodes of liver failure have also been described in HCV RNA-positive HSCT recipients.[93] However, the risk is small and, as HSCT can be life-saving, the presence of HCV RNA in the recipient does not constitute a contraindication for HSCT, particularly since the use of directly acting antivirals (DAAs).[91,92]

Assessment of liver fibrosis in HCV RNA-positive recipients is recommended, as close monitoring is essential in patients with known underlying fibrosis. Liver fibrosis is a risk factor for sinusoidal obstruction syndrome (SOS) and drug toxicity.[94] SOS-sparing regimens should be considered in HCV RNA-positive patients with significant liver fibrosis. Treatment for HCV should be considered as soon as possible after the successful treatment of haematological malignancy.

Treatment of HCV, present and future

Treatment regimens will vary with HCV genotype, degree of liver fibrosis and response to prior antiviral treatment. Until recently, interferon-alfa-based antiviral therapies were the only option available. The situation is rapidly changing, because a wealth of new DAAs are currently being approved or will be approved in the near future. Expert advice should be sought before the prescription of antiviral drugs, among others as drug–drug interactions have to be taken into account.

For more on **directly acting antivirals** see www.easl.eu or www.hcvguidelines.org

For more on **drug–drug interactions** see www.hep-druginteractions.org/

The HCV RNA-positive donor

In general, HCV RNA-positive donors should not be considered, because they will transmit HCV to the recipient. Such individuals are dismissed from unrelated donation. However, the risk:benefit ratio should be evaluated carefully if the only available family donor is HCV RNA positive.[95] Given the life-saving potential of HSCT and current progress in the treatment of HCV infection, an HCV RNA-positive (related) donor could be considered if no suitably matched HCV RNA-negative

donor is available, provided that this is acceptable under national law and local guidelines and the recipient is fully informed. There have been a few reports of successful treatment of HCV infection in the donor before stem cell harvesting.[96] Although feasible in some circumstances, the urgency of HSCT might limit this approach. The duration of antiviral treatment (12 weeks) could be a limiting factor. Harvesting stem cells once the HCV-infected donor has an undetectable HCV RNA by a sensitive technique could represent an acceptable alternative.[96,97]

Recommendations of ECIL-5 for HCV

Close monitoring of liver function tests and HCV RNA is recommended in HCV-infected patients receiving chemotherapy, depleting antibodies or undergoing HSCT (AIII; see panel for explanation of Infectious Diseases Society of America grading system for ranking).

HSCT with an HCV RNA-positive donor could be considered, if other donor options are considered inferior (BIII). In this case, the donor should be rapidly evaluated by an expert, and treatment with new DAAs should be considered.

For HCV-infected recipients, expert liver monitoring is recommended after HSCT (AIII).

Antiviral treatment should be considered for all HCV RNA-positive haematological patients, once the haematological disease has been brought under control (AIII).

HCV-associated haematological malignancy

HCV as a cause of haematological malignancy

Chronic HCV infection is associated with a two-times to four-times increase in the risk of developing B-cell non-Hodgkin lymphoma.[98–101] HCV-associated B-cell non-Hodgkin lymphoma usually occurs after long-term (median of 25 years) HCV infection. HCV-associated B-cell non-Hodgkin lymphoma is more likely than HCV-negative counterparts to be marginal zone lymphomas and diffuse large B-cell lymphomas,[98] and are frequently found at extranodal sites.[99] Chronic HCV infection could give rise to low-grade B-cell clonal expansion, initially confined to the bone marrow, with the potential to progress to overt lymphoma in 10–20% of patients.[102,103] HCV-associated lymphomas are frequently associated with type II mixed cryoglobulinaemia.[102]

HCV-associated lymphoma raises questions about the role of antiviral treatment in reducing tumour burden and the liver toxicity associated with chemotherapy. Antiviral treatment, including interferon-free regimens,[104,105] has been shown to decrease the tumour burden in patients with low-grade HCV-related non-Hodgkin lymphoma.[106–108] The benefits of antiviral treatment in diffuse large B-cell lymphomas are less evident. Higher rates of liver toxicity after chemotherapy are observed in HCV RNA-positive patients,[90,109,110] but patients with diffuse large B-cell lymphomas are currently systematically treated as HCV-negative patients.[108,109,111] In this context, antiviral treatment could be administered in cases of HCV-positive B-cell non-Hodgkin lymphoma, after a successful chemotherapy regimen.[112] We therefore suggest that, in patients with diffuse large B-cell lymphomas, antiviral treatment should be proposed when the lymphoma is in remission, taking into account the risk–benefit ratio, which largely favours antiviral treatment since the advent of interferon-free regimens.

Recommendations of the ECIL-5 for HCV-associated haematological malignancy

Patients with B-cell non-Hodgkin lymphoma should be screened for HCV RNA, irrespective of planned chemotherapy (A II).

The eradication of HCV should be attempted in cases of HCV-associated B-cell non-Hodgkin lymphoma (B II).

HEV infection

Landmarks in the course of HEV infections

The family Hepeviridae consists of positive-stranded RNA viruses infecting a wide range of species. The Orthohepevirus group includes the HEV genotypes 1–4, strains capable of infecting humans, HEV1–2 being strictly human pathogens, whereas HEV3–4 are zoonotic. Infection with HEV is typically subclinical and self-limited. In individuals with comorbid conditions, HEV can cause severe liver disease and a range of extrahepatic manifestations have been recognised.[113] Nucleic acid testing should be preferred to diagnose HEV infection, as serological tests vary in sensitivity and specificity.[114]

The main route of HEV transmission is enteric: waterborne in developing (HEV1–2) countries and food-borne in industrialised (HEV3–4) countries.[113] Blood-borne transmission of HEV via red blood cells, platelets or plasma has also been demonstrated. The prevalence of HEV RNA in blood products is variable, depending on the region and screening technique considered. In Europe, the frequency of HEV RNA-positive blood products ranges between one in 760 and one in 15 000.[115–123] High viral load and paucity of anti-HEV antibodies in the blood product are risk factors for HEV transmission.[119] Current methods of pathogen reduction, including the use of intercept technology, a combination of synthetic psoralene amotosalen HCl treatment with ultraviolet A light illumination, might not prevent plasma-borne transmission of HEV.[118,124,125] Patients undergoing HSCT might be at risk of acquiring HEV through blood transfusions. Stem cell donors can also transmit HEV.[126]

Chronic HEV infection has been reported in immunocompromised individuals.[114,127] The poor development of HEV-specific T-cell responses is the most relevant risk factor.[128] Calcineurin inhibitors favour HEV replication, probably by inhibiting lymphocyte proliferation, and a reduction in calcineurin inhibitor dose can lead to HEV clearance in roughly one-third of patients.[129,130] In vitro, mTOR inhibitors can facilitate HEV replication, whereas

mycophenolate mofetil can inhibit HEV replication.[131,132] However, the relevance of these in-vitro observations to clinical decision making remains unclear.

Results of several series suggest that ribavirin monotherapy is effective against HEV.[133,134] A dose of 10 mg/kg bodyweight per day for 3 months seems to be appropriate for most patients.[135] There is, however, clinical evidence for the selection of resistant variants during therapy.[134,136] Information about the safety and efficacy of ribavirin in HSCT recipients with chronic HEV infection is limited. However, ribavirin has been safely used in HSCT recipients with HCV or respiratory syncytial virus infections.[85,137] It is therefore reasonable to assume that ribavirin is potentially safe and useful in these patients.

So far, detection of HEV RNA neither in the donor nor in the recipient can be considered as an absolute contraindication for HSCT. In these settings, antiviral therapy has to be considered on an individual basis. The safety of ribavirin in the peri-HSCT period is unknown. We therefore would recommend waiting for stable HSC engraftment in a HEV RNA-positive recipient before ribavirin administration.

Recommendations of ECIL-5 for HEV

Patients with haematological malignancies, including HSCT recipients, should be informed about the risks of food-borne HEV transmission (AIII).

For patients with chronic HEV infection, a decrease in the dose of immunosuppressive drugs could be considered (BIII).

For patients with chronic HEV infection, antiviral therapy with ribavirin could be considered (BIII).

HSCT donors, including those with normal transaminase levels, should be screened for HEV by nucleic acid testing (NAT) (BIII).

HAV infection

Landmarks in the course of HAV infections

The seroprevalence of anti-HAV antibodies among blood donors in Europe has decreased in the past few decades.[138] Due to the scarcity of chronic HAV infection, blood products and HSCT donors are not routinely tested for HAV. There is therefore a theoretical risk of HAV transmission by blood transfusion, blood products, or HSCT, which should theoretically increase with loss of herd immunity.[139] Enteric (faecal-oral) transmission via person-to-person contact within the household is the predominant way of spreading the disease; exposure in centres for babies and children or in institutions for mentally disabled people are other important risk factors.[140]

The natural course of HAV infection in immunocompromised patients is similar to that in immunocompetent patients, but can be severe in patients with pre-existing liver disease[141] and conditioning could be a risk factor. Infection with HAV in HSCT recipients can increase the risk of SOS,[142] and HAV has been associated with aplastic anaemia.[143]

Tests for anti-HAV IgM antibody can give false-negative results in immunocompromised patients, particularly those treated with depleting antibodies, and NAT should be preferred in this setting.[144]

Liver function tests should be performed in donors before harvesting stem cells. Donors with abnormal liver function tests should be tested for anti-HAV IgM. If HAV is detected, donation should be delayed until HAV RNA is no longer detectable in the donor.

Recommendations of ECIL-5 for HAV

HSCT transplantation is not recommended if the donor or the recipient is viraemic for HAV (AIII). Vaccination should be considered in HAV IgG antibody-negative patients at risk (BII).

HDV infections

Landmarks in the course of HDV infections

The defective HDV infects only HBsAg-positive individuals and follows the same parenteral route as HBV. The prevalence of chronic HDV co-infection is estimated at 2·5–10% of HBsAg-positive patients in Europe.[145] The natural course of chronic hepatitis D is rapid progression to cirrhosis and liver-related complications. Anti-HDV antibodies are detectable in all individuals exposed to HDV. HDV replication requires HBsAg, and HDV propagation is detected by NAT for HDV RNA. HDV can still replicate even when HBV DNA is suppressed by nucleos(t)ide analog treatment, as HBsAg is still-positive in successfully treated HBV patients. Thus, nucleos(t)ide analogue treatment of HBV does not lead to suppression of HDV; liver disease can progress and patients might also be at risk when immunomodulatory therapies are initiated.

Pegylated interferon-alfa is the only recommended treatment for chronic HDV infection, with a success rate of 25–30% 24 weeks after therapy. However, late reactivations can occur even years after therapy[146] which should be considered if immunomodulating interventions are needed.

Recommendations of the ECIL-5 for HDV

Patients and HSC donors harbouring anti-HBc antibodies should be screened for HDV with anti-HDV serology, and for HDV RNA if anti-HDV antibodies are detected (AII).

HSCT transplantation is not recommended if the donor harbours HBsAg and anti-HDV antibodies or HDV RNA (AIII).

Patients with haematological malignancies and HBV and HDV co-infection should be managed in the same way as patients with HBV monoinfection (AI).

Future directions and gaps in knowledge

In ECIL-5, we agreed that there was a paucity of knowledge for prediction of liver failure after haematological treatment. For HBV, knowledge is limited for

mechanisms underlying HBV reactivation, duration of antiviral treatment after completion of haematological treatment, anti-inflammatory strategies for severe HBV reactivation, and vaccination protocols for patients with haematological malignancies, including HSCT recipients, and for stem cell donors. For HCV, there is insufficient knowledge for the role of direct antivirals in the treatment of patients with haematological malignancies, including those with HCV-associated lymphoma, and knowledge is limited for burden, clinical importance, and strategies for the management of HEV in patients with haematological malignancies. Additional studies should address the gaps in our knowledge regarding viral hepatitis (A to E) in haematology-oncology patients.

Contributors

VM recruited the experts, directed the group, and compiled the recommendations. All authors were involved in the literature search, development of recommendations, and conception of the manuscript. All authors revised the manuscript and gave final approval.

Declaration of interests

VM has been a scientific adviser or consultant for Gilead, Abbvie, MSD, JJ/Janssen-Cilag, and Bristol-Myers Squibb and has received payment for lectures through speakers' bureaus for Abbvie, Bristol-Myers Squibb, Gilead, JJ/Janssen-Cilag, Novartis, and Roche. FvB is on the speakers' bureau of, and received grants from Gilead and Roche; he is on the speakers' bureau of and received grants from Bristol-Myers Squibb. CD has been a scientific adviser for Gilead. SP has received payments for lectures from Falk Foundation, Merck and co, and Roche and he was reviewer for the Hong Kong Health Authority. TB advises, is on the speakers' bureau of, and received grants from Gilead, Roche, and Bristol-Myers Squibb. HW has received clinical research grants from the following companies: Abbott, Bristol-Myers Squibb, Gilead, Merck, Novartis, Roche, Roche Diagnostics, Siemens; has received consultancy fees from Abbott, Abvie, Biolex, Bristol-Myers Squibb, Boehringer Ingelheim, Gilead, ITS, JJ/Janssen-Cilag, Medgenics, Merck/Schering-Plough, Novartis, Roche, Roche Diagnostics, Siemens, Transgene, ViiV; has been a scientific adviser or consultant for Abbott, Abvie, Biolex, Bristol, Myers Squibb, Boehringer Ingelheim, Gilead, ITS, JJ/Janssen-Cilag, Medgenics, Merck/Schering-Plough, Novartis, Roche, Roche Diagnostics, Siemens, Transgene; has received payment for the development of educational presentations and speaker fees from Abbott, Bristol-Myers Squibb, Gilead, ITS, JJ/Janssen-Cilag, Merck/Schering-Plough, Novartis, Roche; and has received payment for lectures through speakers' bureaus for Abbott, Bristol-Myers Squibb, Gilead, ITS, JJ/Janssen-Cilag, Merck/Schering-Plough, Novartis, and Roche. DM has served as an advisory board member for AbbVie, BMS, Gilead, Janssen, MSD, and Roche and has received research and travel grants from BMS, Gilead, MSD, and Roche. PL has received research support from MSD. OH, AL, and CC declare no competing interests. The ECIL-5 meeting was supported by unrestricted grants from Astellas Pharma, Gilead Sciences, Merck, and Pfizer.

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