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Hepatitis B management during immunosuppression for haematological and solid organ malignancies: an Australian consensus statement

Abstract

Introduction: Individuals with chronic hepatitis B virus (HBV) infection or past exposure to HBV infection have a substantial risk of reactivation during immunosuppressive cancer therapy. HBV reactivation can lead to liver failure, cancer treatment interruption or death. Clinical concordance with screening and treatment guidelines is inconsistent in practice, and existing international guidelines are not specific to the Australian context. We developed an Australian consensus statement with infectious diseases, hepatology, haematology and oncology specialists to inform hepatitis B screening and antiviral management for immunocompromised patients with haematological and solid organ malignancies in Australia.

Main recommendations: Recommendations address four key areas of HBV infection management for immunocompromised patients with haematological and solid organ malignancies: who to test for HBV infection, when to start antiviral agents, when to stop antiviral agents, and how to monitor patients during cancer therapy. We recommend testing all patients undergoing cancer treatment for hepatitis B (including HBV surface antigen [HBsAg], HBV core antibody [anti-HBc], and HBV surface antibody) before cancer treatment. Individuals with chronic HBV infection (HBsAg positive) or past exposure (HBsAg negative and anti-HBc positive) receiving higher risk chemotherapy require antiviral prophylaxis using entecavir or tenofovir.

Changes in management as a result of this statement: This consensus statement will simplify the approach to testing and prophylaxis for HBV infection during cancer therapy, and harmonise approaches to discontinuing and monitoring individuals which have been highly variable in practice. We advocate for broader Medicare Benefits Schedule and Pharmaceutical Benefits Scheme access to HBV testing and treatment for patients undergoing cancer therapy.

It is estimated that 239 000 Australians were living with chronic hepatitis B virus (HBV) infection in 2015 (1.0% population prevalence), with the number of people affected steadily increasing.[1] Of these, only 62% of patients have been diagnosed, and 15% are receiving guideline-based care.[1] In addition, over 10% of all Australians — about 2.3 million individuals — are estimated to be HBV surface antigen (HBsAg) negative and HBV core antibody (anti-HBc) positive through previous resolved infection.[2]

Most Australians living with chronic HBV infection were born overseas in endemic areas, particularly Asia and the Pacific, southern Europe and Africa. In addition, Aboriginal and Torres Strait Islander people, who constitute 2.8% of the total population, are estimated to represent 9% of people living with chronic HBV infection. Other priority populations include people with a history of injecting drugs, men who have sex with men, and people born in Australia whose parents migrated from endemic areas. These risk factors lead to substantial heterogeneity in the prevalence of

chronic HBV infection across Australia, with more than 2% of the population estimated to be living with chronic HBV infection in some areas of Sydney, Melbourne and the Northern Territory, and less than 0.5% of the population affected in other areas.[1]

Hepatitis B virus reactivation during cancer therapy

Haematological and solid tumour malignancies are a major cause of illness in Australia,[3] and chemotherapy is a common treatment for these illnesses. In 2014–15 there were 440 561 hospitalisations for chemotherapy, with many more patients receiving treatment outside of hospital (eg, outpatient or day centre).[3] Individuals undergoing immunosuppressive cancer therapy and with serological markers for HBV infection are at risk of HBV reactivation. Given the number of people undergoing cancer therapy and the prevalence of HBV in Australia, several thousand people are likely to be at risk of HBV reactivation. Many of these individuals are also likely to be unaware of their HBV infection status.

HBV reactivation is defined as a tenfold increase in HBV DNA levels from baseline in HBsAg positive individuals and as seroreversion to HBsAg positivity in HBsAg negative and anti-HBc positive individuals,[4-6] although reappearance of HBV DNA often occurs before HBsAg.[7] HBV reactivation has potentially serious consequences including hepatitis flares associated with elevated alanine aminotransferase (ALT), increased mortality due to liver failure, and interruptions to cancer therapy that contribute to lower cure rates and overall survival.[8,9]

HBV reactivation during cancer therapy has been reported in many HBsAg positive patients with haematological malignancies[10,11] as well as in HBsAg positive patients with solid tumours such as breast,[12,13] lung,[14,15] gastrointestinal,[16] liver,[17] and head and neck.[8,18] Patients with resolved or past HBV infection (HBsAg negative and anti-HBc positive) also remain at risk for HBV reactivation,[9] particularly patients with haematological malignancies undergoing therapy with rituximab or other B cell-depleting therapies and novel biological agents.[19,20]

Existing international guidelines

Major international organisations, including the American Gastroenterological Association,[4] the American Association for the Study of Liver Diseases,[21,22] the Asian Pacific Association for the Study of the Liver,[23] the European Association for the Study of the Liver,[5] the European Conference on Infections in Leukaemia[7] and the American Society of Clinical Oncology,[24] have produced recommendations for the testing and management of HBV infection in patients undergoing cancer therapy.

Objectives of this consensus statement

The purpose of this consensus statement is to make recommendations for the testing and management of HBV in Australian patients undergoing therapy for haematological and solid tumour malignancies. This statement is limited to cancer therapy for haematological and solid tumour malignancies because these patients have the highest risk of HBV reactivation, due to cumulative drug, disease and patient factors, and there is inconsistency of practice in this area. Other indications for immunosuppressive therapy, such as rheumatological conditions and solid organ transplantation, are beyond the scope of this statement. “Cancer therapy” refers to anticancer systemic treatments for haematological and solid tumour malignancies. Such systemic treatments usually fall into the categories of conventional cytotoxic chemotherapy, hormonal agents, or targeted therapy or immunotherapy, in contrast to local therapies such as surgery or radiotherapy. This statement is intended for a broad audience with an interest in the care of patients undergoing cancer

therapy and patients with chronic HBV infection. This includes medical specialists, nurses and pharmacists in cancer or hepatitis services, and general practitioners with a special interest.

The goals of this consensus statement are to prevent HBV reactivation in all patients during and after cancer therapy, and for there to be no preventable mortality and no interruptions to cancer therapy due to HBV reactivation.

Methods

This consensus statement was developed by medical specialists with expertise in infectious diseases, hepatology, haematology, oncology and paediatrics, and representatives from the Australasian Society for Infectious Diseases (ASID), the Gastroenterological Society of Australia (GESA), the Haematology Society of Australia and New Zealand (HSANZ), the Medical Oncology Group of Australia (MOGA), and the Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM).

This consensus statement was prepared using a consultative process involving the steering committee and working parties (online Supporting information). Recommendations presented in this consensus statement were developed through a review of existing guidelines and published literature (using MEDLINE and EMBASE) up to October 2017, and tailored to the Australian context by referring to local epidemiology and Medicare Benefits Schedule and Pharmaceutical Benefits Scheme funding rules. Levels of evidence for the recommendations were assessed according to the GRADE system[25] for international comparability. In accordance with GRADE, the quality of evidence was classified as high (A), moderate (B) or low (C), and the strength of recommendations was classified as strong (1) or weak (2).

Recommendations were developed by working groups focused on each of the key questions. Consensus was reached through discussion within each working group. If disagreements arose, further discussion and justification of opinions occurred until a consensus was achieved and the steering committee was responsible for the final recommendation decision. This final consensus statement was reviewed externally — and later formally endorsed — by the following medical societies: ASID, GESA, HSANZ, MOGA and ASHM.

During external consultations, explicit recommendations were developed and agreed upon for paediatric populations with input from a focused specialist working group. There were no changes to other consensus recommendations from this process.

Recommendations

Recommendations address four key areas of hepatitis B management for immunocompromised patients, including children, with haematological and solid organ malignancies: who to test for hepatitis B infection, when to start antiviral agents, when to stop antiviral agents, and how to monitor patients during cancer therapy. The recommendations summary is shown in Box 1. The full statement is available online at ASID (www.asid.net.au), GESA (www.gesa.org.au), ASHM (www.ashm.org.au), HSANZ (www.hsanz.org.au) and MOGA (www.moga.org.au).

Who to test for hepatitis B infection

We recommend that all patients undergoing therapy for haematological and solid tumour malignancies are tested for hepatitis B infection. Testing all patients before cancer therapy can identify patients who may benefit from antiviral prophylaxis, allow for assessment of chronic HBV infection complications, and permit contact tracing of family members for chronic HBV infection and link them to care. Alternative approaches are to screen only patients at high risk of HBV infection or to screen only patients who, if serological testing were positive, would be prescribed antiviral prophylaxis. This would reduce the number of HBV tests performed, but may miss cases if HBV risk factors are not identified or if patients are not tested for HBV before low intensity immunosuppression and their cancer therapy was subsequently intensified. A Canadian analysis of pre-treatment HBV serological testing in patients with lymphoma

receiving rituximab-based chemotherapy found that a "test all" approach was associated with a tenfold lower rate of HBV reactivation than "test only high risk" or "test none" approaches. The "test all" approach is associated with the highest one-year survival rate and is the most cost effective.[26] Suboptimal testing rates have been observed in pre-treatment oncology patients based on the "test only high risk" approach.[24] The cost-effectiveness of universal screening among patients with haematological malignancies has not yet been determined in the Australian context. However, even outside the context of impending immunosuppression, international evidence suggests that screening for hepatitis B may be cost effective down to a population prevalence of 0.3%;[27] the estimated prevalence in the Australian population is 1.0%.[1] In view of these considerations, a "test all" approach is strongly recommended.

We recommend that HBsAg, anti-HBc and hepatitis B surface antibody (anti-HBs) tests are performed when testing for hepatitis B infection (Box 2). Risk of HBV reactivation in the setting of cancer therapy depends on HBV serological status. When found that, in the context of HBV screening, a positive HBsAg test indicates a diagnosis of chronic HBV infection. HBV reactivation during cancer therapy has been reported in many HBsAg positive patients with haematological malignancies[10,11] and HBsAg positive patients with solid tumours.[8,12-18] Patients may have serological evidence of past HBV exposure leading to an HBsAg negative and anti-HBc positive state. Globally, individuals with past exposure far outnumber those with chronic HBV infection. Although HBV DNA may not be detectable in serum, HBV may persist in hepatocytes and other tissues in the form of covalently closed circular DNA, putting individuals at risk of HBV reactivation during some cancer therapy regimens.[28,29]

The presence of anti-HBs is not completely protective against HBV reactivation in patients who are HBsAg negative and anti-HBc positive. There is some weak evidence that an anti-HBs titre of less than 100 IU/L is associated with higher risk of HBV reactivation than a higher anti-HBs titre. [30,31] Routine testing of anti-HBs can identify non-immune individuals who are susceptible to HBV infection. Those who are at risk of infection are eligible for government-funded vaccination, although vaccine funding outside the national immunisation schedule may only be provided at the state level.

When to start antiviral agents

We recommend that all HBsAg positive patients with haematological or solid tumour malignancy undergoing therapy should receive antiviral prophylaxis. Reactivation of HBV replication with increase in serum HBV DNA and ALT levels has been reported in 16–80% of hepatitis B carriers undergoing chemotherapy.[10,32] Hepatitis flares are often asymptomatic, but icteric hepatitis, clinical hepatic decompensation and death have been reported. HBV reactivation is well documented in patients with haematological malignancies, in particular those treated with rituximab-based chemotherapy.[33,34] Several prospective, randomised controlled trials[11,17,35-37] and multiple published case series have demonstrated the effectiveness of antiviral prophylaxis — therapy started before or at the same time as starting cancer therapy — in preventing HBV reactivation in HBsAg positive patients receiving cancer therapy.

We recommend a simplified approach to prophylaxis for patients with prior HBV exposure (Box 3). We recommend that risk for HBV reactivation in patients who are HBsAg negative and anti-HBc positive is determined by the cancer therapy regimen (higher *v* lower risk), in contrast to some international guidelines that attempt to further quantify the risk of host immune system, disease and cancer treatment on HBV reactivation. Complicated algorithms are more difficult for practitioners to follow. Therefore, we recommend that HBsAg negative and anti-HBc positive individuals undergoing higher risk cancer therapy (haematopoietic stem cell transplantation; use of B cell-depleting, B cell active or anti-CD20 agents; acute leukaemia and high grade lymphoma therapy) should receive antiviral prophylaxis. With newer cancer therapies becoming available, new agents and classes might need to be classified as higher risk over time. Emerging classes of immunotherapy or target agents (eg, checkpoint inhibitors and tyrosine kinase inhibitors) have been reported to cause HBV reactivation via uncertain mechanisms. At this stage, they are not considered high risk drugs when used alone (ie, they should not prompt prophylaxis in HBsAg negative and anti-HBc positive individuals).

We recommend that HBsAg negative and anti-HBc positive patients undergoing lower risk cancer therapy (ie, all other regimens) do not require antiviral prophylaxis.

When starting HBV prophylaxis, antivirals should be commenced as soon as possible relative to the commencement of cancer therapy, but should not delay cancer therapy. Potent, high barrier to resistance nucleoside or nucleotide analogues (ie, entecavir or tenofovir) should be used for prophylaxis and treatment. Lamivudine carries substantial risk of developing resistance in chronic HBV infection, and with generic access to entecavir and tenofovir, these high barrier to resistance agents are similarly priced. We recommend that patients who are HBsAg positive are referred to a hepatitis specialist for ongoing care, particularly as medications may need to continue after cancer therapy. Serious medication side effects of tenofovir (including renal impairment, osteoporosis) and entecavir (including lactic acidosis) are rare, but they can influence the choice of medication, require monitoring during prolonged therapy, and highlight the need for specialist referral for people found to have chronic HBV infection. Antiviral prophylaxis for children should follow the same approach as for adults.

Patients without evidence of prior HBV exposure (HBsAg negative and anti-HBc negative) do not require antiviral prophylaxis. We suggest that these patients should be assessed for HBV immunity (using anti-HBs) and offered vaccination if anti-HBs titre is less than 10 IU/L at 6 months after completion of cancer therapy and when the underlying disease is controlled.

When to stop antiviral agents

Due to the complex nature of chronic HBV infection, patients who are HBsAg positive should be assessed by a hepatitis specialist to determine disease stage and need for treatment. This includes assessment for complications of chronic HBV infection and commencement of ongoing preventive health strategies as described in guidelines for the management of chronic HBV infection.[4,5,22,23] Assessment before cancer therapy will help determine who will require ongoing HBV treatment after immunosuppression. If patients fulfil the treatment criteria for chronic HBV infection, they should remain on therapy and follow standard management guidelines regardless of their malignancy.

The duration of HBV prophylaxis for people who do not otherwise have a treatment indication for HBV should be based on their degree of immunosuppression. We recommend that patients continue prophylaxis with a nucleoside or nucleotide analogue for 18–24 months after using B cell-depleting, B cell active or anti-CD20 agents or after haematopoietic stem cell transplantation. In this group, the optimal duration of prophylaxis is controversial and international guidelines differ in their recommendations. Double-blinded randomised controlled trials of entecavir and tenofovir prophylaxis in HBsAg negative and anti-HBc positive patients taking rituximab show that 12 months of therapy significantly reduces the risk of HBV reactivation and that HBV reactivation may occur up to 12 months after immunosuppression cessation.[9,36,38] Based on these data, overseas guidelines recommend at least 12–18 months of therapy after using B cell-depleting, B cell active or anti-CD20 agents, including during and after maintenance therapy,[4] to ensure all cases of reactivation are captured.[5] For the Australian context, we recommend continuing 18–24 months after immunosuppression after using B cell-depleting, B cell active or anti-CD20 agents, including during and after maintenance therapy. This is based on the recognition that timely review may not occur immediately after 12 months and that B cell-depleting therapies are rarely used in isolation, and risks are likely to be compounded by use in combination with other immunosuppressive therapies (such as occurs in non-Hodgkin lymphoma treatment). Therefore, 18–24 months represents a conservative timeframe to identify and treat HBV reactivation events. Stem cell transplantation is also associated with profound immunosuppression and B cell failure.[9]

Use of HBV prophylaxis for 6 months after cessation of non-B cell-depleting immunosuppression is supported by several randomised controlled trials of lamivudine use for HBV prophylaxis.[9,11,37,39] There is limited evidence on the differences between continuing prophylaxis for 6 or 12 months. We therefore recommend that patients continue prophylaxis with a nucleoside or nucleotide analogue for 6–12 months after cessation of non-B cell-depleting cancer therapy.

After stopping antiviral treatment, we recommend that ALT, HBsAg and HBV DNA level should be tested every 3 months for at least 12 months.

How to monitor individuals

Monitoring suggestions are based on consensus opinion as there is little high quality evidence to inform recommendations. We suggest that patients receiving antiviral prophylaxis during cancer therapy should be seen 3 months after initiating therapy, and then every 3–6 months with ALT and HBV DNA testing to assess HBV reactivation. Adherence to treatment is critical and should be evaluated throughout therapy. We suggest that clinicians should consider HBV infection for any unexplained ALT elevation among patients receiving cancer therapy. Cases of HBV reactivation require urgent referral to a hepatitis specialist.

Changes in practice and policy

We advocate for these recommendations to be reflected in the Australian funding structure. The Pharmaceutical Benefits Scheme should cover the prescription of entecavir or tenofovir, both of which are now off patent for patients identified as at-risk of HBV reactivation during immunosuppressive cancer therapy. The Medicare Benefits Schedule should cover regular HBV DNA testing during and after cancer therapy. We acknowledge that the recommendations may not reflect current practice in all cancer and hepatitis services across Australia. We urge health care service administrators and specialists to think about systems and procedures to enable implementation of these best practice recommendations.

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[Insert Boxes]

[Box 1]

1 Recommendations summary

Consensus recommendations	GRADE quality of evidence*
1. Who to test for HBV infection	
1.1. We recommend that all patients undergoing therapy for haematological malignancy are tested for HBV infection	A1
1.2. We recommend that all patients undergoing therapy for solid tumours are tested for HBV infection	B1
1.3. We suggest that the treating haematologist or medical oncologist prescribing cancer therapy is responsible for hepatitis B testing	C2
1.4. We recommend that HBsAg, anti-HBc and anti-HBs are performed when testing for HBV infection	A1
1.5. We recommend hepatitis B testing in children should follow the same approach as for adults	C1
2. When to start antiviral agents	
2.1. We recommend that all HBsAg positive patients with haematological or solid tumour malignancy undergoing therapy should receive antiviral prophylaxis	A1
2.2. We recommend that risk for HBV reactivation in patients who are HBsAg negative and anti-HBc positive is determined by the cancer therapy regimen (higher risk *v* lower risk)	B1
We make the following recommendations for patients who are HBsAg negative and anti-HBc positive:	
▸ 2.3. Patients undergoing higher risk cancer therapy (haematopoietic stem cell transplantation; B cell-depleting, B cell active or anti-CD20 agents; acute leukaemia and high-grade lymphoma therapy) should receive antiviral prophylaxis	B1
▸ 2.4. Patients undergoing lower risk cancer therapy do not require antiviral prophylaxis	C1
2.5. We recommend that patients without evidence of prior HBV exposure (HBsAg negative and anti-HBc negative) do not require antiviral prophylaxis	C1
▸ We suggest that these patients should be assessed for HBV immunity (using anti-HBs) and offered vaccination if anti-HBs < 10 IU/L at 6 months after completion of cancer therapy and when the underlying disease is controlled	C2
2.6. We recommend that antiviral prophylaxis should be commenced as soon as possible relative to the commencement of cancer therapy, but should not delay cancer therapy	B1
2.7. We recommend the use of potent, high barrier to resistance nucleoside or nucleotide analogues (ie, entecavir or tenofovir) for antiviral prophylaxis	A1
2.8. We recommend that all HBsAg positive patients should be referred to a hepatitis specialist for routine assessment	C1
2.9. We recommend that antiviral prophylaxis for children should follow the same approach as for adults	C1
3. When to stop antiviral agents	
3.1. We recommend that HBsAg positive patients should be assessed at the start of cancer therapy to determine their phase of disease and ongoing need for hepatitis B treatment after immunosuppression	C1
3.2. We recommend that patients who fulfil treatment criteria for chronic hepatitis B regardless of their malignancy should remain on therapy and follow standard management guidelines	A1
3.3. We recommend that patients continue prophylaxis with a nucleoside or nucleotide analogue for 18–24 months after B cell-depleting, B cell active or anti-CD20 agents or haematopoietic stem cell transplantation therapy, provided they do not fulfil the criteria for hepatitis B treatment independent of immunosuppression status	B1
3.4. We recommend that patients continue prophylaxis with a nucleoside or nucleotide analogue for 6–	B1

12 months after cessation of cancer therapy (that is not B cell-depleting, B cell active or anti-CD20 agents or haematopoietic stem cell transplantation therapy (see recommendation 3.3 above), provided they do not fulfil the criteria for hepatitis B treatment independent of immunosuppression status	
3.5. We recommend that ALT, HBsAg and HBV DNA level should be tested every 3 months after nucleoside or nucleotide analogue withdrawal for at least 12 months	B1
3.6. We recommend that the decision to stop antiviral agents in children should follow the same approach as for adults	C1
4. How to monitor individuals	
4.1. We suggest that patients receiving antiviral prophylaxis during cancer therapy should be seen 3 months after initiating antiviral therapy, and then every 3–6 months	C2
4.2. We suggest that ALT and HBV DNA should be used to monitor patients receiving antiviral prophylaxis during cancer therapy	C2
4.3. We suggest that patients' adherence to antiviral prophylaxis should be evaluated throughout therapy	C2
4.4. We suggest that clinicians should consider hepatitis B infection for any unexplained ALT elevation among patients receiving cancer therapy	C2
4.5. We recommend that all cases of HBV reactivation should be urgently referred to a hepatitis specialist for treatment	A1
4.6. We recommend that all children commenced on antiviral prophylaxis should be monitored using the same approach as for adults, in consultation with a hepatitis specialist (ideally with paediatric expertise)	C1

ALT = alanine aminotransferase. anti-HBc = hepatitis B core antibody. anti-HBs = hepatitis B surface antibody. HBV = hepatitis B virus. HBsAg = hepatitis B surface antigen. * GRADE quality of evidence classification: A = high; B = moderate; C = low; strength of recommendation: 1 = strong; 2 = weak.[25]

[Box 2]

2 Hepatitis B virus (HBV) test clinical questions

Test	Clinical question
Hepatitis B surface antigen (HBsAg)	Does the person have chronic HBV infection?
Hepatitis B core antibody (anti-HBc)	Has the person ever been exposed to HBV?
Hepatitis B surface antibody (anti-HBs)	Is the person immune to HBV?
Hepatitis B DNA by polymerase chain reaction	Does the person have any and how much HBV detectable (for those who are HBsAg positive)?

[Box 3; doy_mja18.01315_gr]

3 Hepatitis B virus management during cancer therapy summary recommendations

[Box 3 foot]

ALT = alanine aminotransferase. anti-HBc = hepatitis B core antibody. HBsAg = hepatitis B surface antigen. HBV = hepatitis B virus. HSCT = hematopoietic stem cell transplantation. * Including rituximab, obinutuzumab, ocrelizumab, ofatumumab and ibrutinib — this is not an exhaustive list as new agents will be introduced and more evidence about the risk of HBV reactivation comes to light. † Lower level of evidence for risk of HBV reactivation in acute leukaemia and high grade lymphoma therapy.