UK Chemotherapy Board

Position Statement on Hepatitis B Virus Screening and Reactivation Prophylaxis for Patients Planned to Receive Immunosuppressive SACT

The UK Chemotherapy Board would like to draw the attention of all health professionals involved in the prescribing and delivery of systemic anti-cancer treatment (SACT) to the national and international guidance published regarding hepatitis B virus (HBV) screening for patients planned to receive SACT. Our recommendation is that this guidance is followed and monitored to assure the safety of treatments administered.

Immunosuppressive SACT has the potential to cause flares and reactivation of HBV in patients who are currently infected or have previously been exposed to the virus. HBV reactivation can be transient but some cases lead to acute liver failure, hepatic decompensation and even death.

Many patients are unaware they have or have ever been exposed to HBV therefore screening is essential. HBV screening and prophylaxis for patients due to receive immunosuppressive therapy is outlined in guidance from the following bodies:

- National Institute for Health and Care Excellence (Clinical guidelines [CG165])
- European Association for the Study of the Liver (EASL HBV guideline 2017)
- American Association for the Study of Liver Diseases (AASLD HBV guideline 2018) (AASLD HBV guideline 2018)
- American Society of Clinical Oncology (Huang et al, Journal of Clinical Oncology 2020) (Huang et al, Journal of Clinical Oncology 2020)

It is evident that HBV screening practices vary between centres and in an effort to improve this, we would like to underline the importance of the above guidelines and strongly recommend patients are screened prior to initiating SACT treatment. Based on the type of immunosuppressant therapy, the risk of reactivation can be broadly divided into 3 risk groups (refer to Tables 1 and 2; details in attached St George's University Hospital guideline, Version 1.1, 18th March 2020):

- **High risk** (risk of HBV reactivation is ≥10 %)
- **Moderate risk** (risk of reactivation is between 1–10%),
- **Low risk** (risk of reactivation is < 1%)

We would like to highlight the following points taken from the international and national guidelines above:

1. All patients requiring SACT (excluding hormonal treatment) should be screened for HBV prior to commencing treatment by testing:
    a. Hepatitis B surface antigen (HBsAg)
    b. Hepatitis B core antibody (HBcAb)

2. The risk of hepatitis B reactivation should then be assessed by reviewing both the HBsAg and HBcAb status and the treatment regimen under consideration. The risk of HBV reactivation increases when a combination of immunosuppressant therapy is used. The patient's full medical history and current and past drug history must be considered when assessing risk.

3. All HBsAg-positive patients should be urgently referred to a hepatology specialist for further assessment and diagnosis of the phase of HBV infection. All these patients should start HBV prophylaxis prior to starting SACT.

4. Antiviral prophylaxis is given in the form of tenofovir or entecavir as these have a high barrier to HBV resistance. Prescribing of antivirals should be discussed with local hepatologists. For HBsAg positive patients, continue treatment for the duration of immunosuppressive SACT and at least 12 months after, except for B cell depleting agents which should continue for at least 18 months after- discontinuation of prophylaxis in this group must be guided by a hepatology specialist.

5. HBsAg negative, HBcAb positive patients are also at risk of HBV reactivation and HBV DNA levels should be measured. These patients should also be referred to a hepatology specialist and commence antiviral prophylaxis if receiving SACT associated with a high risk of HBV reactivation.

6. For moderate or low risk category patients, HBsAg, HBV DNA and ALT monitoring can be considered (rather than antiviral prophylaxis). However, if there are concerns regarding compliance with monitoring requirements, if the prescribing service is unable to provide monitoring or if there is an unknown risk of HBV reactivation for new immunosuppressant agents, antiviral prophylaxis is recommended. Duration of antiviral prophylaxis after treatment cessation is generally 12 months and should be guided by a hepatology specialist.

7. Although the risk of HBV reactivation associated with immune checkpoint inhibitors (ICI) is unclear, there have been case reports of HBV reactivation in ICI treated patients. These patients may also require high dose corticosteroids (prednisolone>20mg OD for >4weeks) if they develop immune related side effects which is associated with a moderate to high risk of HBV reactivation. Therefore, HBV positive patients due to commence ICI should also be commenced on antiviral prophylaxis.

All oncology departments should ensure consultants, trainees, pharmacists chemotherapy nurses and specialists nurses are aware of guidance on HBV screening for patients commencing SACT. Local guidelines with regular audit reviews should be in place to support this activity.

Table 1: Immunosuppressive therapy risk groups for HBsAg positive patients

Reproduced and amended with permission from St George's University Hospitals Hepatitis B Reactivation Policy Version 1.1, 18th March 2020. This is an example list and will not include all treatments used in practice.

Risk of reactivation	Immunosuppressive therapy	Prophylaxis
High risk	B-cell depleting agents including; rituximab, ocrelizumab, epratuzumab, ofatumumab,ibritumomab. Bone marrow transplant, Haemopoietic stem cell transplant or Solid organ transplant High risk cytokine modulators; Ustekinumab and JAK inhibitors including; baricitinib, tofacitinib. More potent TNF-α inhibitors including; infliximab, adalimumab, certolizumab, golimumab. High-dose corticosteroids (prednisolone>20mg OD for >4weeks). Anthracyclines including; doxorubicin, epirubicin. Local therapy for HCC including; TACE. Immunomodulatory drugs (IMiDs) such as lenolidamide	Anti-viral prophylaxis with tenofovir or entecavir
Moderate risk	Systemic chemotherapy Cladribine Moderate risk cytokine modulators; abatacept, ixekizumab, mogamulizumab, natalizumab, sarilumab, secukinumab, tocilizumab, vedolizumab Less potent TNF-α inhibitors including; etanercept. Immunophilin inhibitors including; cyclosporine. Tyrosine-kinase inhibitors including; imantnib, nilotinib. Proteasome inhibitors such as; bortezomib. Moderate-dose corticosteroids (prednisolone 10mg OD for >4 weeks).	Anti-viral prophylaxis with tenofovir or entecavir
Low risk	Antimetabolites including; azathioprine, 6-mercaptopurine, methotrexate. Fingolimod Short-term low dose corticosteroids. Intra-articular steroid injections (extremely low risk).	Anti-viral prophylaxis with tenofovir or entecavir Or Monitor HBsAg, HBV DNA and ALT every 3 months
Unknown risk	Immune checkpoint inhibitors such as; anti-PD-L1 (e.g. nivolumab), anti-PD-1 (e.g. pembrolizumab) and anti-CTLA4 (e.g. ipilimumab).	Anti-viral prophylaxis with tenofovir or entecavir To prevent potential treatment interruption

Table 2: Immunosuppressive therapy risk groups for HBsAg negative, HBcAb positive patients
Reproduced and amended with permission from St George's University Hospitals Hepatitis B Reactivation Policy Version 1.1, 18th March 2020. This is an example list and will not include all treatments used in practice.

Risk of reactivation	Immunosuppressive therapy	Prophylaxis
High risk	B-cell depleting agents including; rituximab, ocrelizumab, epratuzumab, ofatumumab, alemtuzumab, ibritumomab. Bone marrow transplant, Haemopoietic stem cell transplant or Solid organ transplant. Immunomodulatory drugs (IMiDs); lenalidomide, pomalidomide, thalidomide	Anti-viral prophylaxis with tenofovir or entecavir
Moderate risk	High-dose corticosteroids (prednisolone>20mg OD for >4weeks). Anthracyclines including; doxorubicin, epirubicin. Local therapy for HCC including; TACE. Systemic chemotherapy Cladribine Cytokine modulators; abatacept, , ixekizumab, mogamulizumab, natalizumab, sarilumab, secukinumab, tocilizumab, ustekinumab, vedolizumab, TNF-α inhibitors including; infliximab, adalimumab, certolizumab, etanercept,golimumab. JAK inhibitors including;baricitinib, tofacitinib. Immunophilin inhibitors including; cyclosporine. Tyrosine-kinase inhibitors including; imatinib, nilotinib. Proteasome inhibitors such as; bortezomib.	Anti-viral prophylaxis with tenofovir or entecavir Or *Monitor HBsAg, HBV DNA and ALT every 3 months
Low risk	Moderate and low dose prednisone (10mg prednisolone OD for > 4 weeks or intra-articular steroid injections). Fingolimod Antimetabolites including; azathioprine, 6-mercaptopurine, methotrexate.	NA not required and monitoring not mandatory
Unknown risk	Immune checkpoint inhibitors such as; anti-PD-L1 (e.g. nivolumab), anti-PD-1 (e.g. pembrolizumab) and anti-CTLA4 (e.g. ipilimumab).	Anti-viral prophylaxis with tenofovir or entecavir To prevent potential interruption of treatment.

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