

dL, PT-INR 1.4–1.6) found that early administration of lamivudine significantly reduced the incidence of hepatic failure and mortality.²⁷⁸ A retrospective study of lamivudine therapy for fulminant or severe hepatitis B with PT-INR ≥ 2.0 found that 82.4% (14/17) of patients in the treated group survived and cleared HBsAg within 6 months, whereas the survival rate in the historical control group not administered lamivudine was only 20% (4/20), with a significant difference seen between groups ($P < 0.001$).²⁷⁷ Other studies have demonstrated the efficacy of lamivudine in the treatment of fulminant hepatitis B, with no reports of problems with safety, such as adverse reactions.^{298,299} Although there are no clear guidelines for when to stop NA therapy, negative conversion of HBsAg is usually the indicator for treatment cessation.

Administration of NAs is the mainstay of treatment of acute exacerbation of the carrier state. The viral load is already high at the time of onset of fulminant hepatitis, by which stage a therapeutic response to NAs is unlikely, necessitating commencement of NA therapy before the onset of severe or fulminant hepatitis B. Although subject numbers were low, the "Prospective study of the efficacy of lamivudine" in patients with acute exacerbation of the carrier state, conducted by an MHLW study group, found that 71% (5/7) patients administered lamivudine when a prothrombin time declined to $\leq 40\%$ died, but all patients administered lamivudine when a prothrombin time was $\geq 60\%$ survived. They therefore recommended that lamivudine should be administered to patients with acute exacerbation of the carrier state without delay, before the prothrombin time goes below 60%.³⁰⁰ On the other hand, in patients with acute exacerbation of chronic hepatitis B, lamivudine should be administered before the total bilirubin level exceeds 5 mg/dL.³⁰⁰ The cessation criteria for NA therapy in patients with acute exacerbation of the carrier state are the same as for chronic hepatitis B.

Even when liver transplantation is indicated, early NA therapy is effective in preventing recurrent HBV infection following transplantation. Post-transplant HBsAg positive conversion is considered less common after transplantation for HBV-associated acute hepatic failure than for chronic liver disease, although it is difficult to predict post-transplant recurrence. At present, the standard prophylactic regimen in HBsAg positive recipients is to commence NA therapy prior to transplantation, then introduce high titer hepatitis B immunoglobulin (HBIG) intraoperatively, and continue NA + HBIG dual therapy postoperatively.^{301,302}

Of the NAs, a number of studies have demonstrated that lamivudine ameliorates acute liver failure.^{277,278,298,303} Although evidence is scarce, amelioration of acute liver failure has also been suggested for entecavir and tenofovir.^{304–306} Caution is required when administering entecavir to jaundiced patients with acute hepatic dysfunction, as a post-administration rise in transaminases may occur. Adefovir therapy is not recommended, as it has only weak antiviral activity, and is nephrotoxic. Caution is also required with the use of tenofovir, as latent nephrotoxicity has been reported.

6.2.4 IFN

IFN is occasionally administered in combination with a NA when treating fulminant hepatitis B in Japanese patients, because it often occurs in HBV carriers.³⁰⁷ There is, however, a dearth of evidence clearly demonstrating the usefulness of IFN in the treatment of fulminant hepatitis.^{308,309} Caution for adverse effects including worsening liver function and bone marrow suppression is required in administering IFN to these patients, either using a low dosage or using IFN- β in an intravenous formulation to avoid hemorrhagic complications. When fulminant hepatitis occurs in an HBV carrier, it is important to suppress persistent hepatic inflammation as quickly as possible, for which corticosteroids are administered in combination with antiviral therapy. A clinical trial of the usefulness of corticosteroid pulse therapy in combination with NA therapy in the treatment of fulminant hepatitis B is currently being conducted by an MHLW study group.

Recommendations

- *Antiviral therapy for fulminant hepatitis B should be commenced as soon as possible using NAs, whether it is a rapidly progressive acute infection or acute exacerbation of the carrier state.*
- *NAs should be administered immediately to patients with severe acute hepatitis B, aiming to commence therapy before the prothrombin time goes below 40% in patients with severe acute hepatitis B, and before the prothrombin time goes below 60% in patients with acute exacerbation of the carrier state.*
- *IFN may be administered in combination with NAs. However, careful attention should be paid to possible exacerbation of hepatic dysfunction or the development of decline of blood cell counts during treatment.*

6.3 HBV reactivation

Reactivation of HBV refers to a rise in the hepatitis B viral load caused by immunosuppression or chemo-

therapy in a patient with HBV infection. Reactivation of HBV is classified into reactivation from the carrier state and reactivation in a patient with resolved HBV infection (HBsAg negative, and anti-HBc antibody or anti-HBs antibody positive). Hepatitis associated with reactivation in a patient with resolved HBV infection is called "de novo hepatitis B". Not only is severe disease common in cases of hepatitis associated with reactivation of HBV, but also treatment of concurrent conditions is made difficult by the onset of hepatitis, so it is extremely important to prevent the onset of hepatitis itself. The basic strategy for prevention and treatment of HBV reactivation associated with powerful immunosuppressant or chemotherapy regimens should follow the guidelines summarized below, based on the "Guidelines for the prevention of hepatitis B virus reactivation in patients receiving immunosuppressive therapy or chemotherapy (Revised version)"^{310,311} produced by an MHLW study group (Fig. 7). An MHLW study group currently conducting a multicenter nationwide prospective clinical trial of preemptive antiviral therapy to prevent HBV reactivation during treatment of malignant lymphoma with rituximab has published the results of interim analyses.³¹² As for HBV reactivation caused by immunosuppressive and anti-cancer therapies rather than rituximab, the MHLW "HBV Reactivation through Immunosuppressive and/or Anti-cancer Therapies" research group has also reported its results.³¹³ Furthermore, the Japan College of Rheumatology has published "A proposal for management of rheumatic disease patients with hepatitis B virus infection receiving immunosuppressive therapy".³¹⁴

6.3.1 Risk of reactivation

The risk of reactivation of HBV is mainly governed by the HBV infection status and the degree of immunosuppression. The HBV infection status is classified into chronic active hepatitis, inactive carrier, and resolved infection. This corresponds to the risk of reactivation in descending order. There is no evidence available concerning asymptomatic carriers in the immune tolerance phase, the incidence of further activation of HBV, or whether NA therapy can prevent activation. The risks of HBV reactivation and the onset of hepatitis or fulminant hepatitis vary with the exact immunosuppressant or chemotherapy agents used, and the incidences of these events are unclear. When immunosuppressive therapy or chemotherapy including powerful agents such as rituximab is administered, careful attention should be paid to the possibility of reactivation in HBsAg positive patients

including inactive carriers, and patients with resolved infection. When standard immunosuppressive therapy or chemotherapy is administered, reactivation in HBsAg positive patients including inactive carriers is the main problem, but caution is also required with in patients with resolved HBV infection, as there have been reports of HBV reactivation in such patients with HBV DNA levels <2.1 log copies/mL, either administered corticosteroid monotherapy, or administered standard chemotherapy for the treatment of solid malignancies.³¹⁵ Risk factors for HBV reactivation in HBsAg positive patients are HBeAg positive status and high HBV DNA levels. Although most patients with resolved HBV infection are positive for both anti-HBc and anti-HBs antibody, some are either anti-HBc antibody positive or anti-HBs antibody positive alone. Although anti-HBs antibody act to suppress HBV reactivation, reactivation is still possible in patients positive for anti-HBs antibody alone.³¹⁵⁻³¹⁷

HBV reactivation is commonly associated with hepatitis, which can vary from mild and transient hepatitis to severe and fatal. The onset of hepatitis associated with HBV reactivation is not always during immunosuppressive therapy or chemotherapy, but may occur after its interruption or cessation. In particular, severe hepatitis associated with HBV reactivation has been reported after cessation of corticosteroid and methotrexate therapy.³¹⁸⁻³²¹ Moreover, conditions such as fibrosing cholestatic hepatitis (FCH) may present when viral replication is increased in the immunosuppressed state.^{322,323}

6.3.2 Screening (Fig. 7)

Screening for HBV infection should be performed in all patients undergoing immunosuppressive therapy or chemotherapy, irrespective of whether abnormalities of hepatic function are evident or not. HBsAg levels should be measured in all patients prior to commencement of treatment. In HBsAg positive patients, HBeAg, anti-HBe antibody, and HBV DNA levels should also be measured. A real-time PCR should be used for measurement of HBV DNA levels. In HBsAg negative patients, anti-HBc antibody and anti-HBs antibody should also be measured. Patients positive for anti-HBc or anti-HBs antibody are diagnosed as patients with resolved HBV infection. However, this excludes those positive for anti-HBs antibody alone due to prior hepatitis B vaccination. The next step for patients with resolved HBV infection is measurement of HBV DNA levels. For measurement of HBsAg, anti-HBc antibody and anti-HBs antibody, a highly sensitive test such as the CLIA or CLEIA method should be used. If HBV infection is diagnosed, the past history of hepatitis should be elicited, and screening for

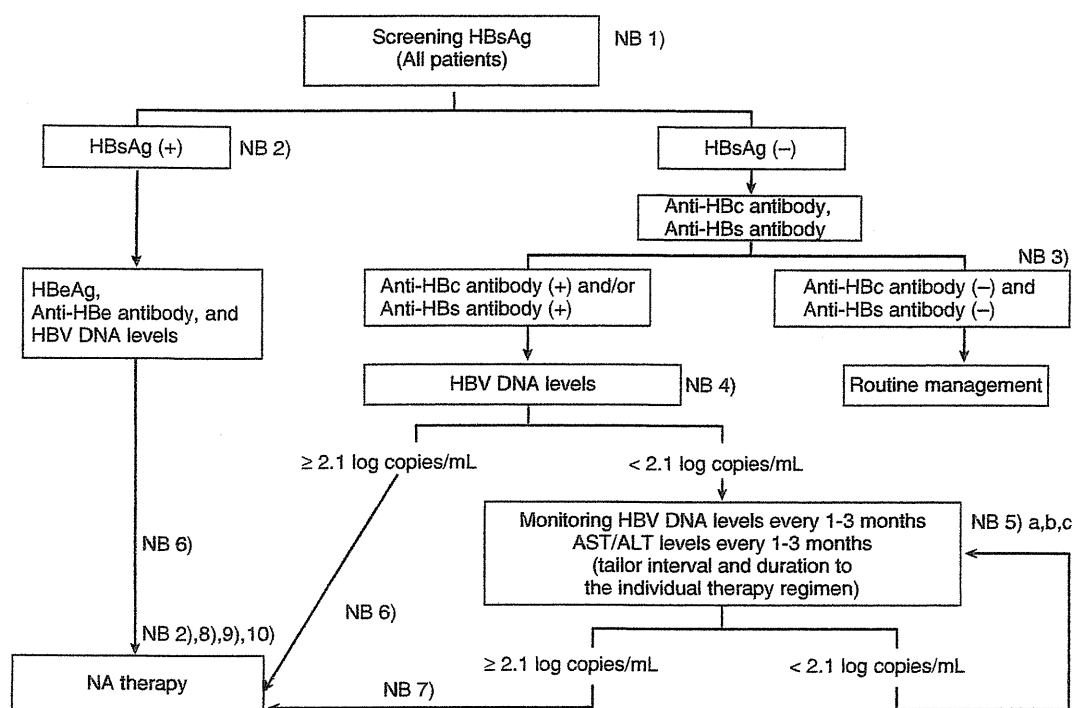


Figure 7 Guidelines for the prevention of hepatitis B virus reactivation in patients receiving immunosuppressive therapy or chemotherapy.

Addendum: Caution is required when administering powerful chemotherapeutic agents for hematological malignancies, as during or following completion of treatment some HBsAg positive or negative patients will develop hepatitis B due to reactivation of HBV, and some of these will go on to suffer fulminant hepatitis. Consideration should also be given to the possibility of HBV reactivation in association with standard chemotherapy for hematological malignancies or solid cancers, and immunosuppressive therapy for autoimmune diseases, such as rheumatic and collagen diseases. The incidences of HBV reactivation, hepatitis and fulminant hepatitis associated with standard chemotherapy and immunosuppressive therapy are not known, and there is a lack of evidence on which to base guidelines. Furthermore, prevention of fulminant hepatitis is not guaranteed with NA therapy.

NB 1) HBV carriers and patients with resolved hepatitis B should be screened prior to immunosuppressive therapy or chemotherapy. First HBsAg testing should be performed to determine whether they are an HBV carrier. HBsAg negative patients should be tested for anti-HBc antibody and anti-HBs antibody, to confirm past infection. Highly sensitive testing methods should be used for measurements of HBsAg, anti-HBc antibody and anti-HBs antibody.

NB 2) A hepatologist should be consulted concerning HBsAg positive patients. A hepatologist should preferably be consulted for all patients administered NAs.

NB 3) In some patients undergoing retreatment who did not undergo testing for anti-HBc or HBs antibody at the time of their initial chemotherapy, and in patients who have already commenced immunosuppressive therapy, antibody titers may be low, in which case measurement of HBV DNA levels is preferable.

NB 4) Patients with resolved HBV infection should be screened using real-time PCR measurement of HBV DNA levels.

NB 5)

a. Caution is required when treating patients with resolved HBV infection with rituximab + corticosteroid or fludarabine chemotherapy, or when they undergo hematopoietic stem cell transplantation, as these patients are at high risk of HBV reactivation. HBV DNA levels should be monitored on a monthly basis during treatment, and for at least 12 months afterward. Long-term monitoring is required for hematopoietic stem cell transplant recipients.

b. Although the incidence is low, there is a risk of HBV reactivation with standard chemotherapy regimens. HBV DNA levels should be measured every 1-3 months, with the interval and duration tailored to the individual therapy regimen. It is best to err on the side of caution with patients undergoing treatment for hematological malignancies.

Figure 7 Continued

c. There is also a risk of HBV reactivation associated with immunosuppressive therapy using corticosteroids, immunosuppressant agents, or molecular targeted therapy with immunosuppressant or immunomodulator activity. HBV DNA levels should be monitored on a monthly basis in patients on immunosuppressive therapy for at least 6 months after commencement or alteration (including cessation) of treatment. After 6 months, the interval and duration should be tailored to the individual therapy regimen.

NB 6) Administration should be commenced as soon as possible, before commencement of immunosuppressive therapy or chemotherapy.

NB 7) Administration should be commenced as soon as the HBV DNA levels exceed 2.1 log copies/mL, during or after immunosuppressive therapy or chemotherapy. If this occurs during treatment, it is preferable to consult with a hepatologist, and not immediately cease the immunosuppressant or antineoplastic agent with immunosuppressive activity.

NB 8) Entecavir is the recommended NA.

NB 9) Cessation of NA therapy can be considered if the following criteria are met.

In patients who were HBsAg positive at the time of screening, when the criteria for cessation of NA therapy in cases with chronic hepatitis B are met.

In patients who were anti-HBc antibody and/or anti-HBs antibody positive at the time of screening:

- 1 NA therapy has been continued for at least 12 months after completion of immunosuppressive therapy or chemotherapy.
- 2 ALT (GPT) levels have been normalized during this period (excluding causes of elevated ALT levels other than HBV).
- 3 negative conversion of HBV DNA has occurred during this period.

NB 10) Patients should be carefully monitored, including measurement of HBV DNA levels, for at least 12 months following completion of NA therapy. Monitoring methods depend on package inserts of each NA. NA therapy should be immediately resumed if HBV-DNA levels exceed 2.1 log copies/mL during monitoring period.

chronic liver disease performed, including abdominal ultrasonography. In HBV DNA positive patients, testing for HBV genotype, precore mutations and core promoter mutations is desirable.

Recommendations

- **Screening for HBV infection should be performed in all patients undergoing immunosuppressive therapy or chemotherapy, who are at risk of HBV reactivation.**
- **Screening for HBV infection should be performed in a systematic fashion, using a highly sensitive test, and include measurement of levels of HBsAg, anti-HBc and anti-HBs antibodies, and HBV DNA.**

6.3.3 Basic strategy for prevention and treatment of reactivation

When immunosuppressive therapy or chemotherapy, with the associated risk of HBV reactivation, is administered to patients with chronic active hepatitis, NA therapy should be commenced beforehand as possible. Immunosuppressive therapy is considered safe in patients with chronic hepatitis under cover of antiviral therapy.³²⁴ When immunosuppressive therapy or chemotherapy, with the associated risk of HBV reactivation, is administered to HBsAg positive inactive carriers, prophylactic NA therapy should be commenced without delay beforehand. Patients with resolved HBV infection and HBV DNA levels ≥ 2.1 log copies/mL on pretreatment screening should be administered prophylactic NA

therapy beforehand, as for inactive carriers. Patients with resolved HBV infection and HBV DNA levels < 2.1 log copies/mL on pretreatment testing should undergo regular monitoring of HBV DNA levels during and after their immunosuppressive therapy or chemotherapy. If HBV DNA levels exceed 2.1 log copies/mL during monitoring, preemptive NA therapy should be commenced immediately. The interval between tests should be of the order of 1–3 months, although the monitoring duration and intervals can be adjusted in accordance with the nature of the immunosuppressive therapy or chemotherapy.

A survey conducted by an MHLW study group found that increased HBV DNA levels were not necessarily detected in patients with resolved HBV infection, after HBV DNA levels (real-time PCR) were < 2.1 log copies/mL and amplification reaction signals were detected in pretreatment monitoring, or HBV DNA levels were < 2.1 log copies/mL and amplification reaction signals were detected in monitoring during treatment. They concluded that HBV reactivation can be diagnosed when HBV DNA levels exceed 2.1 log copies/mL, and it is reasonable to commence NA therapy at that point.³¹³

The usefulness of prophylactic lamivudine therapy prior to chemotherapy in HBV carriers has been demonstrated in prospective studies.^{325–328} Although few in number, some studies have shown prophylactic entecavir and tenofovir therapy to be useful.^{329–331} The

genetic barrier to resistance to lamivudine is low, so resistant strains are likely to appear if the virus has a high capacity to proliferate, or the period of administration is long, and at present entecavir therapy is recommended.

The criteria for cessation of NA therapy are the same as for cessation of NA therapy in HBsAg positive patients. For anti-HBc or anti-HBs antibody positive patients, NA therapy should be continued for at least 12 months after completion of immunosuppressive therapy or chemotherapy, although NAs may be ceased during this period if continued ALT normalization and HBV DNA negative conversion are seen. However, close follow-up including HBV DNA monitoring is necessary for at least 12 months after cessation of NA therapy.

Recommendations

- *When immunosuppressive therapy or chemotherapy, with the associated risk of HBV reactivation, is administered to HBsAg positive inactive carriers, or patients with resolved HBV infection and HBV DNA levels ≥ 2.1 log copies/mL on pretreatment screening tests, NA therapy should be commenced without delay.*
- *Patients with resolved HBV infection and HBV DNA levels < 2.1 log copies/mL on pretreatment screening tests should undergo regular monitoring of HBV DNA levels during and after their immunosuppressive therapy or chemotherapy. If HBV DNA levels exceed 2.1 log copies/mL during monitoring, preemptive NA therapy should be commenced.*
- *Entecavir is the recommended NA.*
- *The criteria for cessation of NA therapy are the same as for cessation of NA therapy in HBsAg positive patients. For patients with resolved HBV infection, NA therapy should be continued for at least 12 months after completion of immunosuppressive therapy or chemotherapy, although cessation of NAs may be considered during this period if continued ALT normalization and HBV DNA negative conversion are seen.*
- *Close follow-up including HBV DNA monitoring is necessary for at least 12 months after cessation of NA therapy. If HBV DNA levels exceed 2.1 log copies/mL during the follow-up period, NA therapy should be recommended immediately.*

6.3.4 Liver transplantation

HBV reactivation is a potential problem in recipients of a liver transplant from an HBsAg negative and anti-HBc antibody positive donor. In a report from a time before prophylactic HBIG administration became standard, HBV reactivation occurred in 15 out of 16 recipients

of liver transplants from anti-HBc antibody positive donors, one of whom died from FCH.³³² It is preferable to exclude anti-HBc antibody positive donors, but a strategy is needed when transplantation of a liver from such a donor cannot be avoided. One such strategy is to administer HBIG during the transplantation procedure, and maintain anti-HBs antibody levels postoperatively. Postoperative administration of NA therapy, or NA+HBIG combination therapy, is also considered useful.^{333,334} Early commencement of NA therapy following HBV reactivation has also been reported to be effective.³³⁵

6.3.5 Transplantation of other organs

HBV reactivation is seen in a high proportion (50–94%) of HBsAg positive patients undergoing transplantation of kidneys and other organs.^{336–339} Following HBV reactivation, rapid progression is seen from chronic hepatitis B to liver cirrhosis, which becomes the cause of death. Prophylactic NA therapy is recommended for HBsAg positive and/or anti-HBc antibody positive patients, commencing prior to the transplantation procedure.

6.3.6 Hematopoietic stem cell transplantation

HBV reactivation is seen in a high proportion ($\geq 50\%$) of HBsAg positive patients undergoing of hematopoietic stem cell transplantation.³⁴⁰ The rate of HBV reactivation is 14–20% in patients with resolved HBV infection.^{341,342} The risk of HBV reactivation is higher with allogeneic bone marrow transplantation than with autologous bone marrow transplantation. This is thought to be due to the need for long term corticosteroid and immunosuppressant therapy for graft-versus-host disease (GVHD) with allogeneic transplantation. Characteristic of reactivation in patients with resolved HBV infection undergoing hematopoietic stem cell transplantation is the delayed onset of HBV reactivation, influenced by immunosuppressant therapy and delayed immune reconstitution.^{343,344} The median interval between transplantation and HBsAg positive conversion is long at 19 months (range 6–52 months),³⁴⁵ necessitating long term HBV DNA monitoring after transplantation.

6.3.7 Chemotherapy including rituximab

The risk of HBV reactivation is high with chemotherapy using rituximab or fludarabine for hematological malignancies, reported to be 20–50% in carriers and 12–23% in patients with resolved HBV infection.^{316,346} Prospective HBV DNA monitoring studies conducted in Japan and Taiwan found the risk of HBV reactivation to be

approximately 10% in patients with resolved HBV infection.^{312,347} For HBV reactivation associated with rituximab+corticosteroid combination therapy, the rate of fulminant hepatitis was high, and mortality also high in cases of fulminant hepatitis.^{288,348}

The Taiwanese group conducted a multicenter collaborative prospective clinical trial of monthly HBV DNA monitoring in patients with malignant lymphoma who underwent chemotherapy including rituximab.³⁴⁷ Using an HBV DNA cutoff value of 3.0 log copies/mL, they defined HBV reactivation as an increase in the HBV DNA levels at least 10 times greater than baseline. As a result, HBV reactivation was seen in 9.3% (14) of patients, in 5 of whom hepatic dysfunction was seen. Of these, serious hepatic dysfunction (ALT increase ≥ 10 times upper limit of normal) associated with HBV reactivation was seen in 2 patients, but it did not develop into fulminant hepatitis, and no deaths were reported.

In Japan, an MHLW study group is conducting a multicenter collaborative clinical trial with patients with malignant lymphoma who underwent rituximab+corticosteroid combination therapy with the aim of determining the usefulness of HBV DNA monitoring during treatment. They have published their interim analysis results.³¹² Using an HBV DNA cutoff value of 1.8 log copies/mL, they defined HBV reactivation as a HBV DNA levels above the cutoff value (greater than the signal detection sensitivity), and commenced NA therapy. HBV reactivation was seen in 16/187 patients, but there were no cases of hepatitis associated with HBV reactivation.

These results strongly suggest the necessity for highly sensitive HBV DNA monitoring and the immediate commencement of NA therapy as soon as HBV DNA becomes detectable. This supports the validity of the present MHLW guidelines for the management of HBV reactivation.

6.3.8 Standard chemotherapy

For standard chemotherapy regimens, the incidence of HBV reactivation is relatively high in inactive carriers, but only 1–3% in patients with resolved HBV infection.^{325,349,350} The incidence of HBV reactivation is higher for chemotherapy regimens that include corticosteroids or anthracycline anti-cancer agents.^{345,351,352} A prospective study conducted by an MHLW study group found that standard chemotherapy for solid cancers in patients with resolved HBV infection induced HBV reactivation (HBV DNA ≥ 2.1 log copies/mL) in 1 out of 36 patients. The HBV DNA levels in that patient was 2.4 log

copies/mL, and entecavir therapy was commenced immediately, with no evidence of the onset of hepatitis. Chemotherapy for hematological malignancies, not including rituximab, induced 1 case of hepatitis over the 3 month monitoring period.³¹³

In general, monitoring of HBV DNA levels in patients undergoing standard chemotherapy for solid cancers should be performed at intervals of 1–3 months, although the monitoring duration and intervals can be adjusted in accordance with the nature of the chemotherapy. More intensive surveillance is required for hematological malignancies. If reactivation occurs during chemotherapy, it is preferable to consult with a hepatologist, and not immediately cease the antineoplastic agent with immunosuppressive activity.

6.3.9 Immunosuppressive therapy for rheumatic and connective tissue diseases

It is characteristic of immunosuppressive therapy for autoimmune diseases, such as rheumatic and connective tissue diseases, that multiple immunosuppressant agents including methotrexate and corticosteroids are administered for long periods. Immunosuppressant agents known to be associated HBV reactivation include corticosteroids, immunosuppressant agents (azathioprine, cyclophosphamide, cyclosporine and mycophenolate mofetil), anti-rheumatic agents with immunosuppressive activity (methotrexate, tacrolimus, leflunomide and mizoribine), and biological agents such as anti-TNF- α agents.^{353,354} A prospective study conducted by an MHLW study group found that immunosuppressive therapy for rheumatic and connective tissue diseases in patients with resolved HBV infection induced HBV reactivation (HBV DNA ≥ 2.1 log copies/mL) in 6 out of 121 patients (2 patients with pretreatment HBV DNA < 2.1 log copies/mL, signal detected, 4 patients with pretreatment HBV DNA < 2.1 log copies/mL, signal not detected). The timing of reactivation was within 6 months after commencement of treatment in all cases.³¹³ Accordingly, HBV DNA monitoring at monthly intervals is desirable for at least 6 months after commencement or alteration of immunosuppressive therapy. There is insufficient evidence concerning monitoring more than 6 months after commencement or alteration of immunosuppressive therapy, so the monitoring duration and intervals can be adjusted in accordance with the nature of the treatment. If HBV reactivation occurs during immunosuppressive therapy, it is preferable to consult with hepatologist, and not immediately cease the immunosuppressant agent.

6.3.10 Novel molecular targeted therapies

Although evidence is lacking concerning the risk of HBV reactivation with novel molecular targeted therapies, there have been reports of hepatitis associated with several molecular targeted therapeutic agents.^{355–357} In particular, caution is required with molecular targeted therapeutic agents with immunosuppressive or immunomodulating activity, necessitating more intensive surveillance.

Recommendations

- *Monthly HBV DNA monitoring should be performed for patients undergoing hematopoietic stem cell transplantation or chemotherapy including rituximab, corticosteroids or fludarabine, during treatment and for at least 12 months after its completion.*
- *HBV DNA monitoring should be performed every 1–3 months for patients undergoing chemotherapy for hematological malignancies, not including rituximab, and standard chemotherapy for solid malignancies, although the monitoring duration and intervals can be adjusted in accordance with the nature of the treatment.*
- *Monthly HBV DNA monitoring should be performed at monthly intervals for patients undergoing immunosuppressive therapy for rheumatic or connective tissue diseases, for at least 6 months after commencement or alteration of treatment. After 6 months, the monitoring duration and intervals should be decided in accordance with the nature of the treatment.*

- *If HBV reactivation occurs during chemotherapy or immunosuppressive therapy, it is preferable to consult with a hepatologist, and not immediately cease the anti-neoplastic agent with immunosuppressive activity or immunosuppressant agent.*

6.4 Coinfection with HIV

6.4.1 Epidemiology

As we saw above in the section on acute HBV, coinfection with HBV and HIV infection may occur. HIV patients exhibit an HBsAg positive rate of 6.3%³⁵⁸ and anti-HBs antibody positive rate of around 60%.³⁵⁹ It has been reported that immunopathy associated with HIV can increase the likelihood of HBV infection becoming chronic by as much as 23%.³⁶⁰ Over 80% of HBsAg positive Japanese HIV-infected patients have HBV genotype A³⁶¹, which contributes to the higher HBsAg positive rates among HIV sufferers. Thus, coinfection with HIV can occur in patients with chronic hepatitis B as well as those with acute hepatitis B.

6.4.2 Basic principles

NAs are the mainstay of HBV therapy in patients coinfecting with HIV. Antiretroviral therapy (ART) for HIV infection involves a combination of three or more anti-HIV agents. Table 16 shows anti-HIV agents that are also active against HBV. Nucleoside analog reverse transcriptase inhibitors (NRTI) are generally used as two of the anti-HIV agents. They will normally have anti-HBV activity as well, to discourage the development of drug-resistant HBV.

Table 16 Anti-HIV drugs also active against HBV*

Common name	Product name	Code	Dosage	Remarks
Lamivudine	Epivir	3TC	300 mg once or twice daily	Reduce dosage for renal failure Different dosage to Zefix
Emtricitabine	Emtriva	FTC	200 mg	Reduce dosage for renal failure
Tenofovir disoproxil fumarate	Viread	TDF	300 mg	Reduce dosage for renal failure
Emtricitabine + tenofovir disoproxil fumarate	Truvada	TDF+FTC	One tablet	Reduce dosage for renal failure
Zidovudine + lamivudine	Combivir	AZT+3TC	Two tablets twice daily	Reduce dosage for renal failure Contraindicated if hemoglobin <7.5 g/dL
Abacavir + lamivudine	Epzicom	ABC+3TC	One tablet	Reduced dosage for renal failure Contraindicated in severe hepatic dysfunction

*All these of the above are classed as nucleoside analog reverse transcriptase inhibitors (NRTI). Other options include anti-HIV agents such as non-nucleoside reverse transcriptase inhibitors (NNRTI), protease inhibitors (PI), integrase inhibitors and CCR-5 inhibitors.

In patients with very low CD4 counts (well below the normal range of 800–1200/ μ L), ART may cause exacerbation of hepatitis due to recovery of cellular immunity, in a phenomenon known as Immune Reconstitution Inflammatory Syndrome (IRIS). In the majority of cases, IRIS is observed within 16 weeks of starting ART. It can be difficult to distinguish between IRIS and drug-induced liver injury.

An issue with ART is the potential for drug-induced liver injury associated with the use of anti-HIV agents, particularly protease inhibitors (PI) and non-nucleoside reverse transcriptase inhibitors (NNRTI). The risk of liver injury generally decreases during ongoing ART,³⁶² it is however more likely in patients with advanced liver fibrosis, and particularly cirrhosis. Cessation of ART or a change in the agents used should be considered if liver injury is detected or hepatic function deteriorates.

Prolonged administration of tenofovir and/or adefovir can lead to renal damage.³⁶³ In the case of tenofovir, this may be irreversible.³⁶⁴ For this reason, changes in the drug regimen should be considered before the estimated glomerular filtration rate (eGFR) falls below 60% or phosphorus reabsorption falls below 70%.

6.4.3 Problems with treatment and responses

Before commencing ART including anti-HBV agents, it is important to check for a history of treatment with anti-HBV agents such as lamivudine, adefovir, entecavir or any of the anti-HIV drugs listed in Table 16. If any of these agents have been administered in the past, an infectious diseases specialist should be consulted regarding the choice of ART agents.

Functional hepatic reserve should also be evaluated prior to commencing ART including anti-HBV agents, given that IRIS can potentially exacerbate hepatitis in patients with a low hepatic reserve. Protease inhibitors and NNRTIs known to cause hepatic dysfunction should be avoided with these patients.

Entecavir is not recommended for patients coinfecting with HIV and HBV not being administered anti-HIV agents, as it can lead to the emergence of drug-resistant HIV.

All the abovementioned factors should be considered in selecting the ART regimen. The ART regimen should consist of a backbone of either tenofovir (TDF) with emtricitabine (FTC), or tenofovir (TDF) with lamivudine (3TC), together with a key drug (integrase inhibitor, NNRTI or PI).

Where IRIS occurs during ART including anti-HBV agents, it is usually only transient in nature. Although it is generally held that cessation of ART should be considered when transaminase levels reach more than five to ten times the baseline level, it is preferable to address the problem without interrupting ART.

If it proves necessary to cease administration of an anti-HIV drug with anti-HBV activity (such as lamivudine, emtricitabine, tenofovir or Truvada (emtricitabine+tenofovir)) due to adverse reactions associated with ART, there is a danger of recurrence or aggravation of hepatitis. Where possible, two anti-HBV agents should be administered instead. Consideration should be given to entecavir+adefovir combination therapy.

It is rare for treatment to be indicated for HBV alone, and "treatment of HIV infection not indicated or not wanted". If this situation does arise, Peg-IFN α -2a therapy should be considered.

Specific directions regarding coinfections with HBV and HIV are set out in the HIV Guidelines.^{365,366}

Recommendations

- *In patients with very low CD4 counts (well below the normal range of 800–1200/ μ L), ART may exacerbate hepatitis due to recovery of cellular immunity.*
- *When administering ART, we should take into consideration the potential for anti-HIV agents to cause drug-induced liver injury.*
- *Before commencing ART involving anti-HBV agents, it is important to check for a history of treatment with anti-HBV agents.*
- *Before commencing ART involving anti-HBV agents, it is important to evaluate functional hepatic reserve.*
- *The ART regimen should consist of a backbone of either tenofovir (TDF) with emtricitabine (FTC), or tenofovir (TDF) with lamivudine (3TC), together with a key drug (integrase inhibitor, non-nucleoside reverse transcriptase inhibitor or protease inhibitor).*
- *If it is necessary to cease administration of an anti-HIV drug with anti-HBV activity due to adverse reactions associated with ART, there is a danger of recurrence or aggravation of hepatitis. Where possible, two anti-HBV agents should be administered instead. Consideration should be given to entecavir+adefovir combination therapy.*

CONFLICTS OF INTEREST

THE MEMBERS OF Drafting Committee for Hepatitis Management Guidelines have received consultant

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