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MINIREVIEWS

Hepatitis B virus reactivation with rituximab-containing regimen

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Core tip: The deleterious effects of hepatitis B virus (HBV) reactivation in rituximab-containing chemotherapy regimens have been reported and the effect of lamivudine treatment in the prevention of HBV reactivation is also well documented. Once reactivated, HBV may lead to death due to hepatitis. In this review, we discuss the factors of preventive lamivudine treatment (especially in the course of HBV antibody), including to whom and for how long the drug should be given, based on case studies and reports that span rituximab's debut in 2002 on the Japanese market to June 2013.

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Abstract

Rituximab is recognized as a useful drug for the treatment of B-cell non-Hodgkin's lymphoma and its use has been extended to such diseases as idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, chronic rheumatoid arthritis and ANCA-associated vasculitides. One serious complication associated with its use is the reactivation of hepatitis B virus and the search for methods to prevent this occurrence has resulted in the rapid accumulation of knowledge. In this review, we discuss case analyses from our department and other groups and outline the current knowledge on the topic and the remaining issues.

Key words: Rituximab; Hepatitis B virus; Reactivation; Chemotherapy; Lamivudine; Non-Hodgkin's lymphoma

INTRODUCTION

Rituximab, which is a mouse-human chimeric antibody that targets CD20, was introduced to treat B-cell non-Hodgkin's lymphoma and has improved outcomes in this patient group[1-3]. Reports, however, indicate that it may be associated with such complications as several serious viral infections and work is currently underway to understand and deal with this problem[4-7]. One such complication is the reactivation of hepatitis B virus (HBV), an important problem that was sometimes observed with chemotherapy treatments even before the introduction of rituximab[8-12]. The deleterious effects of HBV reactivation in rituximab-containing chemotherapy regimens have been reported and the effect of lamivudine treatment in the prevention of HBV reactivation is also well documented[13-17]. Several issues remain, including the optimal timing and the treatment length of preventive lamivudine and the follow-up range of patients who are

responsive to this treatment. Once reactivated, HBV may lead to death due to hepatitis in some patients[18-22]. Even in cases where hepatitis has been overcome, HBV reactivation can disrupt the optimal treatment schedule for lymphomas and lead to relapse and shortened survival. In this review, we discuss factors in preventive lamivudine treatment, including to whom lamivudine should be given and for how long, based on case studies and reports that span from rituximab's debut on the Japanese market in 2002 to June 2013.

HBV REACTIVATION FOLLOWING RITUXIMAB TREATMENT

Upon HBV infection, HBV-DNA synthesis is initially suppressed by cytokine production by NK and other cells. A subsequent cytotoxic T cell (CTL) reaction occurs due to the CD8-positive T lymphocyte. Because hepatitis is triggered by CTLs, a time lag probably exists between HBV infection and hepatitis's manifestation[23,24]. Hepatitis that stems from HBV reactivation is thought to progress in a smaller time period than the initial infection because the virus is induced when immunosuppression is engaged under conditions where CTLs are being induced and HBV has been reactivated and has replicated. This system, which leads to accelerated hepatitis progression, might be linked to the number of deaths that occurred despite the administration of such drugs as lamivudine upon HBV reactivation when using chemotherapy or immunosuppressive agents.

We previously reported the occurrence of HBV reactivation following rituximab therapy as well as rituximab-combined chemotherapy treatments. Despite some variations, the prevalence of HBV reactivation is estimated at between 20%-55%[25-28]. However, there are reports of a 3% prevalence rate in HBsAg-negative cases[29]. Reactivation is often associated with the chemotherapy given for lymphomas and is probably influenced by steroids[26,30]. Upon the introduction of rituximab, it was initially debated whether rituximab alone or combined with chemotherapy could induce HBV reactivation and our subsequent study, as well as work by Yang *et al*[22], reported HBV reactivation after rituximab alone, suggesting that rituximab itself, without chemotherapy, can induce HBV reactivation[14,22]. Although rituximab is more likely to induce HBV reactivation in combination with chemo- or steroid-therapies, since it alone can induce HBV reactivation, caution must be exercised in its use[14]. Debate continues over whether the addition of rituximab to chemotherapy increases the risk of HBV reactivation. Our results involving a survey at a hematology institute in Hokkaido showed that reactivation only developed when rituximab was used. This result is consistent with another study by Yeo *et al*[31] that suggested that rituximab increases the chance of HBV reactivation more than chemotherapy alone[14,31]. Rituximab is more likely to induce HBV reactivation in combination with chemo- or steroid- therapies, since it alone increases the chance of HBV reactivation.

Risk factors for HBV reactivation

Reports have identified the risk factors for HBV reactivation and they include being male, a lack of anti-HBs antibodies, HBV-DNA level, presence of lymphomas, anthracycline/steroid use, second/third line anticancer treatment and youth. These risk factors were reviewed by Yeo *et al*[32], who concluded that being male, young and liver function prior to chemotherapy are associated with risk factors. When rituximab is used, the identified risk factors for HBV reactivation include being male, a lack of anti-HBs antibodies and using rituximab[28,31,32]. Huang *et al*[33] recently reported that the lack of entecavir administration is the most important factor of HBV reactivation in rituximab-associated therapy. This report concluded that the most important treatment to prevent HBV reactivation was the preventive prophylactic administration of preventive nucleoside analog therapy, not only for HBe antigen-, HBs antigen- and anti-HBc-positive cases but also for anti-HBs-positive cases. A lack of prophylactic nucleoside analog therapy is the most important risk factor of HBV reactivation.

HBs antigen-positive, anti-HBc-positive and HBV-DNA-positive cases

HBV reactivation has been reported in HBs antigen-positive patients after chemotherapy and rituximab plus chemotherapy[8,17,22,34,35]. In these patients, caution is advised to prevent HBV reactivation, with or without rituximab. Such preventive nucleoside analog approaches as lamivudine or entecavir administration are currently recommended and a combination of lamivudine and chemotherapy has been suggested[36-40]. These reports indicate that HBV reactivation during chemotherapy is markedly suppressed in groups given preventive nucleoside analog administration and that chemotherapy can proceed as scheduled. There are few systematic studies on the concomitant usage of lamivudine and rituximab; however, some, including He *et al*[41], suggest the efficacy of preventive lamivudine[41-44]. Recently, Huang *et al*[33] also reported the efficacy of the preventive administration of entecavir. Studies using lamivudine to treat HBV hepatitis have reported an annual increase of approximately 15%-20% in HBV lamivudine resistance[45,46], indicating the problem of the emergence of drug-resistant HBV strains during preventive lamivudine administration. Pelizzari *et al*[47], however, showed that for lamivudine treatment during chemotherapy for hematological malignancies, the frequency of drug resistance may be lower than what was seen in hepatitis B treatment, suggesting that long-term lamivudine treatment might be possible. But the study's observation period was short and the number of cases was limited. Perhaps resistance was also difficult to acquire because the nucleoside analogs were administered for cases initially negative for HBV-DNA.

Picardi *et al*[48] reported a high prevalence of HBV genomic mutations after fludarabine-based chemotherapy, arguing that strong immunosuppression might induce HBV resistance to lamivudine. Similar reports

exist with combined rituximab chemotherapy, suggesting that adding steroids or fludarabine to rituximab may result in a high frequency of drug resistance[49]. We believe that the relationship of immunosuppression and HBV genomic mutations requires further study because it remains undetermined whether long-term preventive lamivudine treatment combined with strong immunosuppression treatment is possible. Perhaps preventive methods concerning HBV-DNA levels among HBsAg-positive cases will change. In each guideline, for cases that require a year or more of long-term administration of nucleoside analogs against HBV-DNA, switching to entecavir is recommended. This is because in patients with high HBV-DNA levels, using entecavir is desirable based on its relationship to YMDD mutations[50-52]. In referring to the guideline treatments against the chronic hepatitis of HBsAg, entecavir use is desirable when HBV-DNA exceeds 20000 IU/mL and lamivudine use is adequate if HBV-DNA falls under 20000 IU/mL. In addition, in HBV-DNA-positive cases, we must examine the YMDD mutations beforehand. If they are detected, using tenofovir or the combined use of two nucleoside analogs might become necessary[50-52]. (1) The prevention of nucleoside analog approaches was necessary in HBs antigen-positive, anti-HBc-positive and HBV-DNA-positive cases; (2) HBV genomic mutations were observed in the regimens that used fludarabine but it remains unclear whether strong immunosuppression caused the HBV genomic mutations; (3) YMDD mutations are desirable to select the prophylactic administration of nucleoside analogs; and (4) Entecavir use is desirable when HBV-DNA exceeds 20000 IU/mL and lamivudine use is adequate if HBV-DNA falls below 20000 IU/mL.

Anti-HBc-positive, anti-HBs-negative and HBsAg-negative cases

Anti-HBc-positive cases indicate the occurrence of a prior HBV infection. Some cases fall into the window period or they are anti-HBs and HBs antigen-negative, but anti-HBc and HBV-DNA positives (occult HBV infection)[53] require caution when using chemotherapy with rituximab and anti-cancer agents[29]. Additionally, there are reports of HBV reactivation following chemotherapy in anti-HBs-positive and anti-HBc-positive patients[16,25,30]. Furthermore, Hui *et al*[29] reported hepatitis that originated from HBV reactivation in anti-HBc-positive and anti-HBs-negative cases, even when HBV-DNA is negative. This shows that in anti-HBc-positive cases, hepatitis can develop from HBV reactivation regardless of the HBV-DNA status. The guidelines recommend strict observation of HBV-DNA levels for these groups, since hepatitis due to HBV reactivation is infrequent and the treatment costs of HBV prevention are high[50-53]. Although HBV reactivation in these patients is infrequent, it may lead to prolonged use of chemotherapy, less chemotherapeutic efficacy against lymphoma, and even death from HBV hepatitis. In particular, the lethality rate is 30%-38% in cases where hepatitis occurs from HBV reactivation[29,54]. When considering cost, however, it is desirable to identify a subgroup of patients within the anti-HBc-positive group that is especially prone to HBV reactivation. Previous analysis showed that the only risk factor of HBV reactivation was without the prevention of a HBV reactivation drug[33]. Therefore, preventive nucleoside analog in all anti-HBc-positive patients is recommended; (1) In anti-HBc-positive, anti-HBs-negative and HBsAg-negative cases, one idea is the strict observation of HBV-DNA levels since hepatitis due to HBV reactivation is infrequent; (2) In these patients, HBV reactivation is infrequent and the lethality rate is 30%-38% in cases where hepatitis occurs from HBV reactivation; and (3) Although HBV reactivation in these patients is infrequent, it is desirable to use a preventive nucleoside analog in all anti-HBc-positive patients because of the lethality rate or HBV reactivation.

Anti-HBs-positive, anti-HBc-positive and HBsAg-negative cases

Hepatitis from HBV reactivation has been reported in anti-HBs-positive, anti-HBc-positive and HBsAg-negative cases[16,25,29,30]. Few reports exist of HBV reactivation following rituximab treatment in patients positive for anti-HBs alone, but reactivation may occur, and these patients require careful observation[17,29,55]. Perhaps in these cases, antibody production may have declined with age, only anti-HBs remain and the specific details are unknown. However, since perhaps even anti-HBs-positive cases are due to HBV reactivation, caution is warranted. We previously studied the changes in anti-HBs titers during rituximab chemotherapy[13,20,21]. In these cases, perhaps because the initial antibody titer was relatively low, we observed a linear decrease in the titer in correlation with the amount of rituximab. We also reported a patient in whom anti-HBs and anti-HBc titers decreased, while HBV-DNA increased and HBV reactivation occurred[20,21]. These results show a correlation between anti-HBs antibodies and HBV reactivation and suggest that monitoring their titers can provide important clues about HBV reactivation. Additionally, Onozawa *et al*[56] reported that hepatitis from HBV reactivation occurs from a decline in HBs antibody titer levels during bone marrow transplantation. Since HBs antibody is a humoral immune response that monitors HBV, a change in the HBs antibody titer could predict hepatitis that occurs from HBV reactivation. In this report, we continued to analyze the titer in an anti-HBs-positive patient who was treated with rituximab alone or rituximab plus chemotherapy between January 2002 and July 2013. The 35 subjects (18 males and 17 females) ranged from 42 to 87 years of age (Table 1) and included 17 cases of diffuse large B-cell lymphoma and nine cases of follicular lymphoma. In almost all the patients, the initial treatment consisted of two to six rounds of CHOP (cyclophosphamide, 750 mg/m^2, vincristine, 1.4 mg/m^2, adriamycine, 50 mg/m^2 on day 1, and prednisolone, 60 mg/m^2 on days 1-5) that was mainly combined with rituximab

Table 1 Analyzed patients were 18 males and 17 females, with 17 cases of diffuse large B-cell lymphoma and nine cases of follicular lymphoma

Characteristics of anti-HBs Ab positive patients	
Age (yr)	67 (42-87)
Males/Females	18/17
Disease	
DLB	17
FL	9
MCL	1
MALT	3
Burkitt lymphoma	1
EBV associated LPD	1
WM	1
CLL	2
Stage	
Ⅰ	3
Ⅱ	3
Ⅲ	7
Ⅳ	21
Chemotherapy	
R-CHOP	10
R-THP-COP	20
R+VP16	1
R+MVP	1
R+TEOP	1
R+bendamustine	1
R	2
R-Course	10 (1-30)

In these patients, 21 were clinical stage Ⅳ. In 30 patients, the initial treatment consisted of 2 to 6 rounds of CHOP mainly combined with rituximab or THP-COP. DLB: Diffuse large B cell lymphoma; FL: Follicular lymphoma; MCL: Mantle cell lymphoma; MALT: Mucosa-associated lymphoid tissue; EBV: Epstein-Barr virus; LPD: Lymphoproliferative diseases; WM: Waldenstrom macroglobulinemia; CLL: Chronic lymphocytic leukemia.

or THP-COP (cyclophosphamide, 500 mg/m^2, vincristine, 1.0 mg/m^2, and pinorubine, 30 mg/m^2 on day 1, and prednisolone, 30 mg/m^2 on days 1-5). The clinical course of the anti-HBs antibody is shown in Figure 1. In five of 35 cases, the antibody titer slightly increased, and in three cases, it declined. In nine of 45 cases, the antibody titer was the same, and in 21 of 35, it declined after rituximab and chemotherapy. In six of nine cases with anti-HBs titers > 1000 mIU/mL at the time of the initial treatment, the titer did not fall below 1000 mIU/mL. However, in one particular case, the initial titer was > 1000 mIU/mL, and the anti-HBs titer fell to 71.1 mIU/mL after three rounds of treatment. This demonstrates that even in patients with initial anti-HBs titers > 1000 mIU/mL, HBV reactivation can nonetheless occur, indicating that caution must be exercised. Among these 35 patients, the antibody titers in ten were the same or elevated compared with the titer before the treatment. In 24 patients whose anti-HBs titer levels finally decreased, 16 patients had initial titers < 300 mIU/mL (16/18 patients of < 300 mIU/mL), and 11 had initial titers < 100 mIU/mL (11/12 patients of < 100 mIU/mL), demonstrating the need for preventive nucleoside analog administration. Six patients with anti-HBs titers > 1000 mIU/mL did not show a titer decrease. Although these cases are not completely accurate since we cannot measure titers above 1000 mIU/mL, in these patients, the titers probably did not drop below 1000 mIU/mL. Pei *et al*[57] reported anti-HBs antibody titers after rituximab therapy and concluded that the risks of HBV reactivation are the reduction of anti-HBs titers, especially low pretreatment anti-HBs titers and the loss of anti-HBs. These results on titer changes might provide an index for preventive lamivudine or entecavir administration in patients who are only anti-HBs-positive. Consistent with our results, Westhoff *et al*[16] reported HBV reactivation in a patient with an anti-HBs titer of approximately 868 mIU/mL, demonstrating the possibility of HB ion may occur. Even when anti-HBs-positive cases are due to HBV reactivation, caution is warranted; (2) Anti-HBs titer decreased in correlation with the amount of rituximab. Anti-HBs and anti-HBc titers decreased, while HBV-DNA increased and HBV reactivation occurred. The reduction of anti-HBs titers, especially low pretreatment anti-HBs titers, and the loss of anti-HBs are risk of HBV reactivation; (3) For anti-HBs titers > 1000 mIU/mL at the time of initial treatment, the titers of most patients did not fall below 1000 mIU/mL. In almost all cases where the initial anti-HBs titer was < 300, titers decreased; and (4) Monitoring HBV-DNA and anti-HBs titers is useful to prevent HBV reactivation.

Nucleoside analog treatment for the prevention of HBV reactivation

As mentioned above, HBe and HBs antigen-positive patients can be treated with preventive nucleoside analogs. In HBs antigen-negative and anti-HBc-positive patients, the frequency of HBV reactivation is not high; however, since it can result in death from hepatitis, preventive nucleoside analog should be considered for them as well. We previously reported the relatively high frequency of HBV reactivation in anti-HBc-positive and HBsAg-negative patients with rituximab and bendamustine treatment[58]. These results also support the preventive nucleoside analog for HBV reactivation in the new agents that have cytotoxic and immunosuppressive reactions.

On the other hand, in HBs antigen-negative and anti-HBs-positive patients, preventive nucleoside analog treatment may be considered when the anti-HBs titer is < 300 mIU/mL, especially when the titers are < 100 mIU/mL. In cases where the titer is between 300 and 1000 mIU/mL or higher, the titer levels should be closely examined, and when the titer drops below 300 mIU/mL, HBV-DNA monitoring or preventive nucleoside analog treatment should be performed. Periodic examination of HBV-DNA is also recommended to predict HBV reactivation[59,60]. The emergence of antibodies may also be slow in cases where a mutation occurred and thus HBV-DNA monitoring is essential[59]. However, in patients where only HBV-DNA monitoring was performed, the frequency of HBV reactivation was higher than those who were treated with preventive lamivudine, demonstrating the importance of identifying a subgroup of patients for which preventive lamivudine is recommended[37]. In evaluating methods to predict

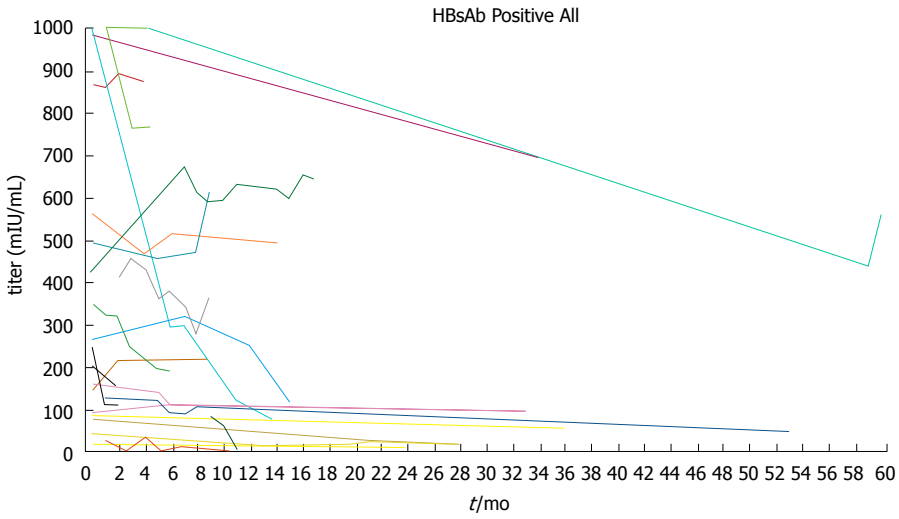

Figure 1 Antibody titer slightly increased and in three cases the titer declined. In nine cases, the antibody titer was the same and in 21 cases, it declined after rituximab and chemotherapy. In six of nine cases with anti-HBs titers > 1000 mIU/mL at the time of initial treatment, the titer did not fall below 1000 mIU/mL. In almost all cases where the initial anti-HBs titer was < 300 mIU/mL, the titer decreased. Of all cases where the initial anti-HBs titer was > 1000 mIU/mL, it dropped below 1000 mIU/mL in three of six patients.

HBV reactivation, HBV-DNA monitoring alone is insufficient and other pieces of information, such as shifts in the anti-HB titer levels (before and during the rituximab treatment), should be utilized to assist the early detection of HBV reactivation. Preventive nucleoside analog against HBV is currently recommended for 4-6 mo after chemotherapy completion[46,50,52,61]. However, reports of HBV reactivation 4 to 6 mo after chemotherapy[62-65] suggest that this number should be revised. The current 6 mo value probably reflects our knowledge about the changes in B-cell numbers[60,64,66-68]. The 2007 guidelines by Lok *et al*[50] are more specific than past guidelines and include a recommendation to extend the period of preventive lamivudine treatment, depending on HBV-DNA monitoring results. Some research reported a delayed onset of the HBV reactivation with rituximab therapy[69-71]. We also observed a case in which HBV reactivation was detected 4 years after chemotherapy and preventive lamivudine administration had been completed. The patient was a precore mutant case positive for HBe antibody, HBs antigen, and negative for HBe antigen. Due to declining blood cell counts, lamivudine therapy had been terminated and the patient was under observation for progression since entecavir had not yet been approved for HBV treatment in Japan. After initially administering lamivudine in 2002 and terminating it a month after completion of the treatment (2003), HBV-DNA was detected only sporadically in the patient. In 2003, HBs antibodies appeared with a natural progression and HBV-DNA disappeared in 2004. However, HBs antibody could not be detected, and from the latter half of 2004 to the beginning of 2006, detection was sporadic. From 2007, HBV-DNA was positive in every reading and in 2008, the individual died after being hospitalized for hepatitis from HBV reactivation. We believe that for anti-HBs-negative HBe or HBs antigen-positive patients, preventive lamivudine should be included when initiating treatment and continued indefinitely. On the other hand, anti-HBs-positive HBV-DNA became negative in this patient, suggesting that in anti-HBs-positive patients, nucleoside analog treatment should be continued until the anti-HBs titer returns to the pre-treatment level. We believe that 6 mo of preventive lamivudine treatment is too short; its length should be based on the recovery of the immune system, as judged by such criteria as anti-HBs levels. Long-term administration of such drugs as lamivudine or entecavir is problematic in terms of cost and cases that require long-term preventive administration must be clarified in the future by longitudinal surveys. In Japan, lamivudine is the only drug currently approved for preventive administration. Entecavir is also used to treat HBV infection; however, it is currently not allowed for preventive administration. For treatment regimens, 100 mg of lamivudine and 0.5 mg of entecavir are used. However, it is recommended that entecavir be increased to 1 mg to counter lamivudine resistance[50-52]. Telbivudine may also be used in the prophylaxis of HBV reactivation. Compared to lamivudine and telbivudine, entecavir is less likely to induce drug resistance in HBV, which has a treatment advantage and the preventive administration of HBV reactivation[65]. For this reason, entecavir administration is recommended for cases in which preventive administration against HBV will last 12 mo or more[50,52]. Additional effective drugs that combat HBV include 10 mg of adefovir, 600 mg of telbivudine, and 200 mg of tenofovir. With respect to lamivudine resistance, some recommend combining entecavir, adefovir or tenofovir with lamivudine[52], and others recommend switching[51]. However, it has also been reported that for lamivudine-resistant HBV strains, switching to adefovir alone quickly produces resistance. Thus, it may be desirable to use adefovir in conjunction with lamivudine[72]. Tenofovir is especially effective against lamivudine- and adefovir-resistant HBV and can be used to treat

lamivudine-resistant HBV[45,60,73-75]. Also, using HBV vaccines is recommended for HBV-seronegative cases during the use of immunosuppressive or anti-cancer agents[52]. However, as mentioned above, just as anti-HBs decline and disappear when using rituximab, antibodies might not be produced after the pre-administration of a vaccine and the vaccine must be administered after completion of the treatment. On the other hand, cases may also exist in which hepatitis arising from HBV reactivation cannot be suppressed by a vaccine[55]. Perhaps HBV reactivation cannot be prevented solely by a vaccine. (1) Preventive nucleoside analog treatment may be considered when the anti-HBs titer is < 300 mIU/mL, especially when the titers are < 100 mIU/mL. For other cases, the titer levels should be closely examined, and when they drop below 300 mIU/mL, HBV-DNA monitoring or preventive nucleoside analog treatment should be performed. Periodical examination of HBV-DNA is also recommended to predict HBV reactivation; (2) Although preventive nucleoside analog against HBV is currently recommended for 4-6 mo after chemotherapy completion, delayed onset of the HBV reactivation was observed. The length of the treatment should be based on the recovery of the immune system, as judged by such criteria as anti-HBs levels; (3) Lamivudine and entecavir are used for the prevention of HBV reactivation in Japan. Telbivudine may also be used in the prophylactic administration of HBV reactivation. Compared to lamivudine and telbivudine, entecavir is less likely to induce drug resistance in HBV, which has a treatment advantage, and the preventive administration of HBV reactivation; and (4) Tenofovir is especially effective against lamivudine- and adefovir-resistant HBV and can be used to treat lamivudine-resistant HBV.

CONCLUSION

Chemotherapy-induced HBV reactivation is thought to be caused by HBV replication in hepatocytes due to immunosuppression by anti-cancer agents, followed by a decline in the immunosuppressive effect, triggering the immune system to attack HBV-infected hepatocytes[30]. Decreased antibody titer levels resulting from decreased numbers of B-cells may be one factor that causes rituximab-induced HBV proliferation. Additionally, rituximab can indirectly alter the T-cell population in the body and stimulate HBV replication, and during immune reconstitution, the targeting of HBV may be intensified[76]. As reported by Umemura *et al*[35], chemotherapy-induced HBV reactivation results in lower survival rates than acute HBV hepatitis and thus prevention of HBV reactivation is essential. However, the screening of HBV serology is not performed routinely (36.6%). Some HBV reactivation was developed by the lack of HBV screening[77]. We hope that in the future, HBV screening will be performed routinely so that we can better understand the effect of rituximab on the immune system as well as the mechanism of HBV reactivation for improved treatment of malignant lymphomas.

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