Review

Research advances in reactivation of hepatitis virus after chemotherapy for non-Hodgkin's lymphoma-combined hepatitis B virus infection

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Abstract

Infection rate of hepatitis B virus (HBV) in our country remains high. Many patients showed combined HBV infection; the most common blood system disease is non-Hodgkin's lymphoma (NHL)-combined HBV infection. Drugs used in treating lymphoma may induce different degrees of HBV reactivation. Such condition may lead to hepatic failure or death. Currently, scholars pay increasing attention to reactivation of HBV by rituximab and/or chemotherapy for NHL-combined HBV patients. This study summarizes research advances in this topic, with a view of providing background information for further research.

Hepatitis B virus (HBV) is a prevalent organism in our country. Many patients may feature combined HBV infection. Among HBV-infected patients, those with non-Hodgkin's lymphoma (NHL)-combined HBV must be acknowledged. With continuous development of treatment drugs for lymphoma, most scholars focus on reactivation of HBV in NHL-combined HBV patients after receiving Mabthera (rituximab) and/or chemotherapy. In this study, we summarize research advances in relevant predisposing factors, mechanism of occurrence, and treatment and prevention of HBV infection.

Status of patients with NHL-combined HBV infection

HBV infection is distributed worldwide, mostly in Asia, Africa, Latin America, and other developing countries. In China, HBV infection is also prevalent. According to results of our epidemiological survey, HBV surface antigen-positive rate in Chinese population approximates 9.09%^[1].

HBV and lymphoid tissues are ecotropic. As lymphoma patients often feature low-level immune functions, they are more prone to HBV infection than the general population or patients with other tumors.

Currently, three hypotheses are mainly provided

regarding the correlation between HBV infection and NHL^[2]: (1) direct immunosuppressive effects of lymphoma may lead to increased risk of HBV infection and reactivation; (2) HBV carriers may activate lymphoma pathogenicity gene; and (3) another unknown virus may be present, and its propagation mode, which is similar to that of HBV, may lead to activation of lymphoma pathogenicity gene.

Epidemiological statistics showed that HBV surface antigen-positive rate of NHL patients reaches 24%–77%^[3]. Case-control study of Kim *et al.*^[4] showed that among 222 newly diagnosed NHL patients, HBV surface antigen-positive rate totaled 12.6%, whereas rates in concurrently controlled 439 cases of nonblood system tumors and 444 cases of nontumor patients reached 7.3% and 4.7%, respectively. Therefore, NHL and HBV present statistically significant correlation. In recent years, epidemiological statistics showed that incidence of NHL increases at a rate of 4% each year^[2]. Thus, increasing attention centered on populations with NHL-combined HBV infection.

Status of NHL chemotherapy

Cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) are regarded the standard regimens for NHL patients, with overall response rate of 80%–90%, complete

remission rate of 45%–55%, and five-year survival rate of 30%–40% [5]. Invention of rituximab (product name: Mabthera) provided a new option for NHL treatment.

As the first monoclonal antibody applied in NHL clinical treatment, rituximab displays advantages, including high monotherapy efficiency, good safety, no dose-limiting toxicity, and bone marrow hematopoietic stem cell toxicity. Rituximab can also be used in combination with chemotherapeutic drugs to enhance sensibility of tumor cells to chemotherapeutic drugs.

Recently, multiple large-scale clinical tests were conducted to assess therapeutic effects of rituximab and CHOP (R-CHOP) as the first-line regimen for NHL. MinT test [6] was used to assess therapeutic effects of rituximab combined with CHOP-like chemotherapy or single CHOP-like chemotherapy among 824 young patients of diffuse large B-cell lymphoma with improved prognosis. Results showed that within a median follow-up period of 34 months, three-year event-free survival rate (EFS) (79% and 59%, respectively, in rituximab combined with CHOP-like chemotherapy group and chemotherapy group, $P < 0.0001$) and overall survival rate (OS) (93% and 84%, respectively, in rituximab combined with CHOP-like chemotherapy group and chemotherapy group, $P = 0.0001$) of patients who received rituximab with chemotherapy were all superior to those of single-chemotherapy group. The French Study Group of the Adult Lymphoma test [7] conducted a seven-year follow-up for untreated elderly NHL patients treated with R-CHOP and CHOP regimens. Results showed that EFS rate (42% and 25% in R-CHOP group and CHOP group, respectively; $P = 0.0002$), progression-free survival rate (52% and 29% in R-CHOP and CHOP groups, respectively; $P < 0.0001$), disease-free survival rate (66% and 42%, in R-CHOP and CHOP groups, respectively; $P < 0.0001$), and OS rates (53% and 36% in R-CHOP and CHOP groups, respectively; $P = 0.0004$) of R-CHOP group were superior to those of the CHOP group. These large-scale clinical tests showed that R-CHOP exhibits remarkable advantages than CHOP. As a result, R-CHOP regimen became widely used in clinical practice.

Reactivation of HBV

Reactivation of HBV is based on detection of valence of HBV surface antigen and HBV surface antibody. Two independent clinical hypotheses during immunosuppressive therapy are

proposed: (1) increased valence of HBV surface antigen in HBV surface antigen-positive patients; and (2) HBV surface antigen-negative and/or HBV surface antibody-positive patients feature surface antibody loss accompanied by reproduction of HBV surface antigen (serotype conversion). With progression of HBV–DNA quantitative analysis, HBV reactivation can be tracked through correlation between HBV–DNA levels and hepatitis and chemotherapy time.

Currently, HBV reactivation is defined as HBV replication during cytotoxic or immunosuppressive therapy or closely thereafter in chronic HBV patients combined tumor [HBV–DNA is elevated over 10 times, or its absolute value $> 10^9$ copies/mL, with low detection limit of branched DNA method as 7.0×10^5 copies/mL, whereas polymerase chain reaction (PCR) detects 300 copies/mL], excluding other infections [8]. After chemotherapy, HBV reactivation may cause continuous necrosis of liver cells and progressive decrease in liver functions, eventually leading to hepatic damage with varied severity. In less severe cases, HBV reactivation may induce hepatitis symptoms, such as elevated liver enzymes or jaundice; in severe cases, this condition may lead to fulminant hepatic failure or death [8].

Reactivation of HBV generally occurs in HBV surface antigen-positive patients. HBV reactivation may also occur in HBV surface antigen-negative patients, HBV antibody and HBV surface antigen-negative patients, and HBV core antibody-positive patients.

In general, two routes exist for HBV reactivation [9,10]: (1) cytotoxic drugs and immunosuppressive agents inhibit immunologic mechanism that controls HBV replication, thereby leading to massive replication of HBV; (2) after controlling patients' condition, immune function gradually recovers, thereby causing damage to immune-mediated infected liver cells. With two different routes, HBV reactivation can be divided into two stages [9,11]. The first stage occurs during intensive chemotherapy with cytotoxic drugs and immunosuppressive agents and is characterized by replication and increase in HBV and mainly manifested as increase in serum HBV–DNA, HBV antigen and HBV–DNA polymerase, and HBV-infected normal liver cells; the second stage relates to recovery of immune function after discontinuation of medication, clinically manifested as symptoms of hepatitis-like elevated liver enzyme and jaundice, and may lead to hepatic failure or death in severe cases [12].

Reactivation of HBV after Mabthera and/or chemotherapy of NHL patients

As mentioned, among NHL patients, several HBV-infected patients may present HBV reactivation after receiving chemotherapy. In surface antigen-positive patients with lymphoma, incidence of HBV reactivation after chemotherapy reaches 20%–55%; this value is two to three times higher than that of other tumors [13]. Therefore, HBV reactivation is currently considered as one of the possible complications after chemotherapy of tumor patients, especially of NHL patients with chronic HBV infection. Factors that possibly induce HBV reactivation are as follows.

Virological factors

Currently, speculations indicate that presence of HBV antigen is related to HBV reactivation. However, studies also showed that HBV antigen-negative patients may also face increasing risk of reactivation because of variations in HBV pre-C zone and basic core promoter. Early studies indicated that viral load before chemotherapy is irrelevant to HBV reactivation post-chemotherapy. With application of methods including PCR, new insights into this conclusion became available. Study by Zhong *et al.* [14] showed that high-serum HBV–DNA load ($>3 \times 10^5$ copies/mL) before chemotherapy increases possibility of HBV reactivation. Currently, some conclusions were formed concerning covalently closed circular DNA of HBV (HBV cccDNA), i.e., HBV cccDNA is an existing form of HBV in humans. As an original copy template of HBV, HBV cccDNA plays a significant role in HBV replication and establishment of infection status. As long as HBV cccDNA exists in liver cells, HBV replication continues. Currently, most used antiviral drugs can only inhibit HBV cccDNA. With its long half-life (33–70 days [15]), HBV is not easily eliminated. Thus, once medication is discontinued or comes the outer simulations, disease relapse occurs [16]. Hui *et al.* [17] raised that high levels of cccDNA in the liver may be used to predict HBV reactivation in HBV surface antigen-positive patients after chemotherapy.

Antineoplastic drugs

Two types of available antineoplastic drugs may induce HBV reactivation: traditional cytotoxic drugs and biological agents related to anti-B-cell and anti-T-cell monoclonal antibody treatment.

Among traditional cytotoxic drugs, corticosteroids and

anthracycline drugs present the closest correlation with HBV reactivation [18]. Corticosteroids and glucocorticoids easily lead to HBV reactivation, possibly because they can directly promote HBV replication by acting on corticosteroid response element of HBV genome. These drugs can inhibit normal lymphocyte function and immune function by inducing DNA degradation, inhibiting substance metabolism, and inducing apoptosis in lymphocytes, thereby leading to HBV reactivation. Anthracycline drugs stimulate HepG2.2.15 cells to secrete HBV–DNA in a dose-related manner. This phenomenon increases incidence of HBV reactivation when patients diagnosed with HBV use anthracycline drugs. NHL patients most commonly use corticosteroids and anthracycline drugs as chemotherapeutic drugs. These compounds are also used in combination in most cases. Thus, during chemotherapy, NHL patients exhibit much higher incidence of HBV reactivation than those with other diseases.

As for anti-B-cell and anti-T-cell monoclonal antibodies, anti-CD20 monoclonal antibody (rituximab) is the most commonly used drug with definite curative effects; it also serves as the first-line drug treatment for CD20-positive diffuse large B-cell lymphoma. CD20 is expressed on surfaces of all pre-B cells and mature B cells. Rituximab binds to CD20 antigen on B lymphocytes through complement-dependent cytotoxicity and antibody-dependent cell-mediated cytotoxicity. Rituximab inhibits proliferation of B lymphocytes and induces their dissolution and apoptosis. These actions may directly lead to a decrease in the number of plasmocytes differentiating from B lymphocytes, followed by a decrease in generation of antibodies. This phenomenon helps create favorable conditions for HBV reactivation after chemotherapy. Dai *et al.* [19] provided six courses of R-CHOP chemotherapy to four patients with HBV surface antigen-positive diffuse large B-cell lymphoma. These researchers also used lamivudine for antiviral therapy during chemotherapy, conducted follow-up visits for 14 months, and discontinued lamivudine treatment after six-month chemotherapy. Results showed that within one month after medication was stopped, four patients showed different degrees of HBV reactivation (abnormal increase in glutamic–pyruvic transaminase and HBV–DNA), indicating that rituximab combined with chemotherapy can induce HBV reactivation. Tsutsumi *et al.* [20] analyzed five diffuse large B-cell lymphoma patients receiving rituximab treatment and observed that all patients presented different degrees of

decrease in valence of HBV surface antibody and increased levels of glutamic-pyruvic transaminase. One HBV surface antigen-positive patient and who did not receive antiviral therapy manifested liver failure and died because of serious liver function damage. Tsutsumi *et al.* [20] analyzed research results in recent years and discovered that not only the HBV surface antigen-positive or HBV_e antigen-positive patients with replication of HBV-DNA showed different degrees of HBV reactivation after receiving rituximab treatment but also those who were HBV surface antibody-positive, HBV_e antigen-positive, and HBV_c antigen-positive and received HBV reactivation treatment. Law *et al.* [21] obtained results that agreed with those of Tsutsumi *et al.* [20]. Their study also showed that both single use of rituximab and its combined use with cytotoxic drugs induce reactivation of existing HBV. Although incidences between these two treatments were not statistically significant (the former results in 40% chance of HBV reactivation, and the latter approximates 38%), degree of severity of HBV reactivation induced by single use of rituximab was slightly lower than that induced by its combined use with cytotoxic drugs.

Prevention and treatment of HBV reactivation

Previously, interferon was used for prevention and treatment of HBV reactivation. However, this treatment features weak direct antiviral effects and notable adverse reactions and poor compliance of patients. Interferon may enhance immunomodulatory damage in liver cells and lead to fatal hepatitis; thus, it is not widely used [18]. In recent years, scholars at home and abroad reported that the nucleoside analog lamivudine exhibited good therapeutic effect on HBV reactivation, and prophylactic use of drug before chemotherapy displayed better effects than using the drug after increase in HBV-DNA [22,23]. Hsu *et al.* [24] randomly divided 52 NHL/HBV carriers without treatment into two groups (prevention and treatment groups). Both groups received six courses of CHOP chemotherapy. The prevention group used lamivudine in combination with chemotherapy for prevention (oral treatment of 0.1 g lamivudine, once a day from the first day of chemotherapy to two months after the end). The treatment group received lamivudine only after presenting HBV reactivation (with administration route and dose similar to those of prevention group and continuous administration until recovery from

hepatitis). Patients were followed up for 12 months, and results showed that incidences of reactivation of HBV in prevention and treatment groups reached 11.5% and 56.0% ($P=0.0001$), respectively. In the prevention group, time from receiving chemotherapy to emergence of HBV was longer than that of treatment group ($P=0.018$). He *et al.* [25] included 29 NHL/HBV carriers in their study (28 received R-CHOP chemotherapy, and one received rituximab, fludarabine, mitoxantrone, and dexamethasone chemotherapy). All patients received lamivudine a week before the start of chemotherapy until two months after the end of treatment (oral administration of 0.1 g lamivudine, once a day). Patients were followed up for 16 months; four (13.8%) showed liver damage, but none showed increase in replication of HBV-DNA. Loomba *et al.* [26] summarized data and results of relevant tests in recent years and pointed out that lamivudine can effectively prevent HBV reactivation. After chemotherapy, lamivudine also significantly reduced incidence of HBV reactivation by 79% in patients with HBV surface antigen-positive tumor.

Currently, for HBV surface antigen-positive patients, the recognized regimen is administering lamivudine (0.1 g oral administration, once a day) as antiviral therapy a week before chemotherapy until four to six weeks after the end of treatment or the time determined as per patients' conditions [27,28]. The lately published *The Guideline of Prevention and Treatment for Chronic Hepatitis B* [29] corrects the duration of antiviral therapy. The guideline recommends that course of antiviral therapy should start at the beginning of immunosuppressive or chemotherapeutic therapy to at least 12 weeks after receiving such treatment. For HBV surface antigen-negative and other antibody-positive patients, studies should still clarify whether preventive antiviral therapy should be provided before using immunosuppressive agents or chemotherapy. When HBV reactivation occurs after chemotherapy, chemotherapy should be stopped immediately, and antiviral drugs, such as lamivudine, should be used consecutively for one-year treatment. During this period, liver function and viral indicators should be reexamined regularly.

Although lamivudine exhibits advantages on prevention and treatment of HBV reactivation, it features some limitations, such as drug resistance and virus variations at prolonged administration time and occurrence of withdrawal hepatitis after discontinuation of medication. This phenomenon drives scholars to develop safe and

effective drugs. To date, in comparison with lamivudine, lower incidences of drug resistance are observed when using adefovir and entecavir in treatment of chronic HBV infection. However, insufficient treatment data can describe effectivity of these drugs in preventing reactivation of HBV. Thus, in this regard, long-term follow-up studies are required for further assessment.

Conclusion

In NHL patients with combined HBV infection, HBV reactivation is one of the potential complications after rituximab and/or chemotherapy. Therefore, to reduce negative effects of HBV reactivation and to treat primary blood system diseases, patients must be treated with antiviral drugs during chemotherapy.

Declarations

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No.

Competing interests

The author declares that he has no competing interest.

Authors' contributions

SJ Ma made the literature analysis and wrote, discussed and revised the manuscript of this review.

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