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Mini Review

Hepatitis B Virus Reactivation in Patients with Hematological Malignancies Receiving Novel Anticancer Drugs: Less Worry More Calm

Zheng Yan, Shuna Yao, Yanyan Liu*, Zhihua Yao*

Department of Internal Medicine, Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Zhengzhou, Henan, China

ABSTRACT

Hepatitis B Virus Reactivation (HBV-R) is a potentially fatal complication in HBV-infected patients with hematological malignancies receiving immunosuppressive anticancer drugs. The risk of HBV-R has been well evaluated in the rituximab era. In recent years, an increasing number of novel anticancer drugs have been approved or under investigation for the treatment of hematological malignancies. However, cumulative data on HBV-R in patients treated with these novel drugs are very scarce. This mini-review aims to summarize recently published data concerning HBV-R in patients with hematological malignancies receiving novel drugs. Data accumulated to date show that HBV-R is highly preventable and manageable in this population.

Keywords: Hepatitis B virus; Reactivation; Hematological malignancy; Novel anticancer drug; Lymphoma; Incidence

INTRODUCTION

Although Hepatitis B Virus (HBV) vaccines and anti-HBV drugs are readily available today, HBV remains a global health problem, especially in epidemic areas [1]. HBV infection is a challenge in managing cancer patients, especially those with blood cancers. Although all HBV-infected cancer patients are at risk for Hepatitis B Virus Reactivation (HBV-R) during anticancer treatment, patients with hematological malignancies deserve special attention because immunosuppressive anticancer therapy increases their risk of HBV-R. In the era of rituximab, it was recommended that all patients be screened for HBV infection before starting immune chemotherapy. For patients with chronic HBV infection, Prophylactic Antiviral Therapy (PAT) should be started before anticancer therapy regardless of serum HBV DNA levels; for patients with past HBV infection, both HBV DNA monitoring and PAT are options [2].

In recent years, an increasing number of novel anticancer agents beyond anti-CD20 antibodies have been approved or are being investigated for the treatment of hematological malignancies. Most of these drugs have immunosuppressive effects. However, there are few data on HBV-R in patients treated with these novel drugs to date. The reason is that most clinical trials of these novel drugs excluded HBV-infected patients due to concerns about the potential risk of HBV-R. In practice, novel anticancer drugs are frequently delayed or avoided when treating HBV-infected patients with hematological malignancies, which may compromise clinical outcomes.

Recently, we evaluated HBV-R risk in patients with hematological malignancies receiving novel anticancer drugs beyond anti-CD20 antibodies in a relatively large cohort from a tertiary cancer hospital in China [3]. Our data showed that HBV-R mainly occurred in patients with past HBV infection who did not receive PAT. To get a better understanding of the risk of HBV-R in this patient population, we further addressed this issue in this review.

Correspondence to: Yanyan Liu, Department of Internal Medicine, Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Zhengzhou, Henan, China, E-mail: yyliu@zzu.edu.cn

Zhihua Yao, Department of Internal Medicine, Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Zhengzhou, Henan, China, E-mail: zlyyyaozhihua1260@zzu.edu.cn

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LITERATURE REVIEW

Definition of HBV-R and strategies for preventing HBV-R in the rituximab era

HBV infection can be classified into chronic infection and past infection according to the status of HBV markers. Chronic HBV infection is defined as persistent Hepatitis B Virus Surface Antigen (HBsAg) positivity for more than 6 months, while past HBV infection is defined as HBsAg negative but HBV core antibody (HBcAb) positive, regardless of HBsAb status. Different guidelines may define HBV-R differently, but the general principles are similar. According to the recommendations of the American Society of Clinical Oncology (ASCO), HBV-R is defined as an increase in serum viral load compared to baseline in patients with chronic HBV infection (10,000 IU/mL if baseline DNA is unavailable; 1,000 IU/mL if baseline DNA is undetectable; or 100-fold increase if baseline DNA is detectable), and for patients with past HBV infection, it is defined as the development of detectable serum HBV DNA or reappearance of HBsAg [4].

About half of patients with hematological malignancies and chronic HBV infection experienced HBV-R after chemotherapy [5,6]. It has become a consensus since the early 2000s that hematological malignancy patients with chronic HBV infection should receive PAT before initiating immunosuppressive anticancer therapy [7]. Patients with past HBV infection may also develop HBV-R, although the incidence is relatively low. In prospective studies of patients with past HBV infection receiving anti-CD20 antibodies, the incidence of HBV-R was 10.7%-17.9% in patients without PAT and 0%-2.4% in patients with PAT [8-10]. There are two strategies for patients with past HBV infection: PAT or periodic HBV DNA monitoring followed by on-demand antiviral therapy. Preferred recommendations vary between guidelines.

DISCUSSION

HBV-R in HBV-infected patients receiving novel anticancer drugs

In recent years, numerous novel drugs for the treatment of blood cancers have been approved or are under intensive investigation. Immunotherapies, mono- or multi-targeted antibodies, CAR-Ts, and antibody-drug conjugates targeting various antigens on blood cancer cells and/or other immune cells, including but not limited to CD19, CD20, CD21, CD30, CD38, CD52, CD79, CD138, BCMA, and GPRC5D, are emerging rapidly, most of which are immunosuppressive, especially those targeting B cells that can lead to long-lasting B-cell depletion [11,12]. Small molecule drugs, such as (Bruton Tyrosine Kinase) BTK inhibitors, (Janus kinase) JAK inhibitors, and PI3K inhibitors, also have varying degrees of immunosuppression. Theoretically, HBV-infected patients receiving these drugs are at risk of HBV-R.

In a recent report, we evaluated the risk of HBV-R in patients with hematological malignancies receiving novel anticancer drugs in a relatively large cohort [3]. The novel drugs used included monoclonal antibodies (excluding anti-CD20 antibodies and immune checkpoint inhibitors), bispecific antibodies, antibody-drug conjugates, CAR-Ts, and small molecule drugs. No HBV-R was observed in 112 patients (47 with chronic HBV infection and 65 with past HBV infection) who received PAT, whereas HBV-R was observed in 3 of 146 cases who did not receive PAT. Despite the limited number of patients evaluated, our data show that the risk of developing HBV-R is quite low in patients receiving PAT, regardless of chronic or past HBV infection, elevated or undetectable serum HBV DNA, and administration of novel drugs alone or in combination with other anticancer drugs.

After publication of our findings, Chiu, et al. reported HBV-R in 3 of 29 patients treated with BTK inhibitors [13]. Including our report and 10 studies published by other authors, a total of 494 HBV-infected patients with hematological malignancies receiving novel anticancer drugs were evaluated for HBV-R.3, 13 The pooled incidence of HBV-R in all patients at risk was 2.8% (14/494, 95% CI:1.7-4.7). Of the 14 patients with HBV-R, only 1 (1/14, 7.1%) received PAT. The incidence of HBV-R was 0.6% (1/156, 95% CI: 0-3.5) in patients with PAT compared with 3.4% (13/383, 95% CI: 2.0-5.7) in patients without PAT. HBV-R-related death occurred in 0.4% (2/494, 95% CI: 0.1-1.5) of all patients at risk for HBV-R and 14.3% (2/14) of those experiencing HBV-R. No HBV-R was observed in 78 patients with past HBV infection and PAT, while the incidence of HBV-R in patients with past HBV infection and no PAT was 3.6% (12/334, 95% CI: 2.1-6.2).

Together with known case reports, a total of 37 patients developed HBV-R after receiving novel anticancer drugs, and 89.2% (33/37) of them did not receive PAT prior to HBV-R, again indicating that most HBV-R is preventable [3,13]. Four (10.8%) patients (3 receiving CAR-T therapy and 1 receiving anti-CCR4 therapy) developed HBV-R on continuous PAT, and two of them died of HBV-R. Among 5 patients with chronic HBV infection and HBV-R, 4 received CAR-T therapy. Therefore, patients treated with CAR-T therapy appear to be at higher risk for HBV-R.

HBV-R in patients with isolated positive HBsAb

Patients who are isolated positive for HBsAb are conventionally not considered at risk for HBV-R [14]. However, we observed HBV-R in 3 of 279 (1.1%, 95% CI: 0.3-3.1) isolated HBsAg-positive patients in our cohort [3]. These patients may have HBcAb false negatives at baseline, but the more important and non-negligible concern is that HBsAb titers will decline over time and may lose protection, thus HBV-R or de novo infection may occur. A previous study demonstrated that HBsAb titers below 100 IU/L are insufficiently protective in lymphoma patients undergoing immune chemotherapy [15]. Therefore, regular HBV monitoring is also of value in patients with isolated positive HBsAb.

Recommendations for HBV-infected patients receiving novel anticancer drugs

As showed in our study, the incidence of HBV-R was only 0.6% in patients with PAT, and the majority of HBV-R patients (92.9%) did not receive PAT, all of which clearly indicate that HBV-R is highly preventable [3]. The risk of HBV-R may be much lower when the costs and harms of the cancer itself are taken into account. Therefore, as long as the liver function is normal, the use of novel anticancer drugs should not be intentionally avoided in the management of HBV-infected patients, regardless of infection status and HBV DNA levels. Nevertheless, currently for patients receiving (Chimeric Antigen Receptor) CAR-T therapy, undetectable serum HBV DNA should be achieved prior to CAR-T cell infusion.

In the absence of further evidence, guidelines established in the rituximab era can still be followed. Based on our understanding of HBV-R risk, we have developed more detailed recommendations for patients with hematological malignancies receiving novel drugs. Patients with chronic HBV infection, patients with past HBV infection and detectable serum HBV DNA, and patients receiving B-cell-depleting drugs regardless of infection status should receive PAT. The optimal duration of PAT is unclear. Premature discontinuation of PAT may result in delayed HBV-R, especially in patients receiving B-cell-depleting drugs. PAT should be maintained for at least 6 months, preferably 12 months after completion of anticancer treatment [7]. Extended antiviral treatment after 12 months may be advisable in patients with initially detectable HBV DNA. For patients with past HBV infection, undetectable HBV DNA, and receiving non-B-cell-depleting drugs, both PAT and HBV DNA monitoring are options. Behind the two choices is the balance between effectiveness and costs, and which strategy to choose depends on the cost-effectiveness analysis of each country. Recently, Fujita et al. conducted a cost-effectiveness analysis in Japan and found that HBV DNA monitoring is more cost-effective than PAT. The total cost of PAT with entecavir and HBV DNA monitoring was $4,129 and $2,969, respectively, so the authors recommended HBV DNA monitoring in patients with past HBV infection in Japan [16]. In China, the cost of PAT with entecavir is currently as low as $10 (72 RMB)/year. Given that most HBV-R occurred in patients with past HBV infection and no PAT, we recommend routine PAT for all patients at risk of HBV-R when receiving immunosuppressive anticancer drugs in China. Although the optimal frequency of HBV DNA monitoring is unknown, we recommend repeating every one to two months for patients not receiving PAT, with detectable HBV DNA, or receiving CAR-T therapy, and every three months for other patients at risk of HBV-R and for patients with isolated positive HBsAb.

Another way to prevent HBV-R is to promote vaccination. Patients who are negative for all HBV markers or positive for HBcAb only should receive at least two doses of the vaccine within a 3-4 weeks interval before starting anticancer treatment. The third dose can be given a few months after completion of anticancer treatment [7]. Given the observation that HBV-R occurred in isolated HBsAb-positive patients, an additional dose of vaccine may be considered for patients with baseline HBsAb titers <100 IU/L. The reliability of this method needs further evaluation.

Management of patients with HBV-R

Of the 37 patients known to have experienced HBV-R after treatment with novel anticancer drugs 30 were successfully treated with on-demand antiviral drugs [3,13]. The remaining 7 patients died of HBV-R, including 4 with past HBV infection and 3 with chronic HBV infection [3]. The median time from diagnosis of HBV-R to death was only 3 weeks, underscoring the importance of HBV-R prevention, prompt diagnosis, and appropriate treatment of HBV-R. For patients under HBV DNA monitoring, antiviral treatment should be started immediately when HBV-R is detected. Entecavir is preferred over other nucleoside analogs. For patients on continuous PAT, the management of HBV-R is a big challenge. Different HBV DNA mutants can lead to resistance to different nucleoside analogs, so genetic analysis can help guide the rescue treatment of patients with HBV-R on continuous PAT. However, not all viral breakthroughs can be explained by gene mutations. The mechanism of drug resistance in some patients is unknown. In our analysis, 4 patients experienced HBV-R on continuous PAT [3]. Although the cause of HBV-R in these patients was not investigated, two of them were successfully rescued by adding tenofovir to entecavir. In practice, if genetic analysis is not performed or the mechanism behind HBV-R cannot be identified, we recommend adefovir or tenofovir plus lamivudine combination therapy for patients who develop HBV-R on continuous PAT with entecavir, as this strategy rescued most patients with viral breakthrough during entecavir treatment [17]. Conversely, if a patient develops HBV-R on lamivudine or adefovir treatment, entecavir should be used for rescue. For HBV-R patients, in addition to antiviral treatment, aggressive supportive therapy and cessation of immunosuppressive and hepatotoxic drugs should also be considered. Further, patients should be closely monitored for liver enzymes, coagulation function, and viral load. Consultation with a hepatologist or referral to a liver center should be considered in selected patients.

CONCLUSION

A low incidence of HBV-R was observed after PAT in HBV-infected patients with hematological malignancies receiving novel anticancer drugs, although the accumulated data are limited. The vast majority of HBV-R episodes were preventable, and most cases experiencing HBV-R were manageable. Given the high mortality from hematological malignancies, we recommend that the use of novel anticancer drugs should not be intentionally avoided in the management of HBV-infected patients. On the other hand, we emphasize the importance of HBV prevention and monitoring. More data are needed to optimize the management of this patient population.

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