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LETTER TO THE EDITOR

Prevention of hepatitis B reactivation in patients with hematologic malignancies treated with novel systemic therapies: Who and Why?

Matteo Tonnini, Clara Solera Horna, Luca Ielasi

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Abstract

The risk of reactivation in patients with chronic or past/resolved hepatitis B virus (HBV) infection receiving chemotherapy or immunosuppressive drugs is a well-known possibility. The indication of antiviral prophylaxis with nucleo(t)side analogue is given according to the risk of HBV reactivation of the prescribed therapy. Though the advent of new drugs is occurring in all the field of medicine, in the setting of hematologic malignancies the last few years have been characterized by several drug classes and innovative cellular treatment. As novel therapies, there are few data about the rate of HBV reactivation and the decision of starting or not an antiviral prophylaxis could be challenging. Moreover, patients are often treated with a combination of different drugs, so evaluating the actual role of these new therapies in increasing the risk of HBV reactivation is difficult. First results are now available, but further studies are still needed. Patients with chronic HBV infection [hepatitis B surface antigen (HBsAg) positive] are reasonably all treated. Past/resolved HBV patients (HBsAg negative) are the actual area of uncertainty where it could be difficult choosing between prophylaxis and pre-emptive strategy.

Key Words: Hepatitis B reactivation; Hepatitis B virus; Antiviral prophylaxis; Hematologic malignancies; Chimeric antigens receptor-T cell therapy; Immune checkpoint inhibitors

Core Tip: In the last few years, the advent of several new therapies has characterized the therapeutic scenario of hematologic malignancies. There is now the open issue of assessing the risk of hepatitis B virus reactivation in these patients in order to decide which patients should undergo antiviral prophylaxis.

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TO THE EDITOR

We read with interest the article recently published by Mak *et al*[1] reviewing prevention and management of hepatitis B virus (HBV) reactivation in the setting of hematologic malignancies in the era of new targeted therapies. They well differentiated two entities as HBV reactivation: Exacerbation of hepatitis B surface antigen (HBsAg) positive chronic hepatitis B (CHB) or reactivation of past/resolved HBV infection (HBsAg negative and hepatitis B core antibody positive).

They subsequently analyzed the risk of reactivation and therefore the need for antiviral prophylaxis associated with monoclonal antibodies and the novel targeted therapies in the hematological setting for both CHB and past/resolved HBV infection. For HBsAg positive patients there is a consensus, as also described in the review of Mustafayev and Torres[2] that patients treated with drugs which have a moderate (1%-10%) to high risk (> 10%) of reactivation, such as B-cell depleting drugs, immune checkpoint inhibitors (ICIs) and targeted therapies, should be given an antiviral prophylaxis as soon as the treatment has started[1].

The recent guidelines of Asian-Pacific Association for the study of the liver also recommend starting antiviral prophylaxis in HBsAg positive patients who need to undergo an immunosuppressive treatment due to a moderate-high risk of HBV reactivation[3]. An exception is made for patients receiving traditional immunosuppressants (*e.g.*, azathioprine and methotrexate), which is also confirmed by Shi and Zheng[4].

On the other hand, for resolved HBV infection the risk of reactivation associated with these new drugs is still a matter of debate. The current review by Mak *et al*[1], as well as the one by Mustafayev and Torres[2], agree on a moderate/high risk of HBV reactivation and therefore a need of antiviral prophylaxis for patients undergoing a B cell-depleting regimen, an allogenic stem cell transplantation or an anthracyclines based chemotherapy, but a certain degree of uncertainty remains for chimeric antigens receptor (CAR)-T cell therapies and ICIs.

The issue of HBV reactivation for patients receiving CAR-T cell therapy remains unexplored and further investigations are needed, though an antiviral prophylaxis for resolved HBV seems reasonable. A recent meta-analysis of Papatheodoridis *et al*[5] showed an HBV reactivation rate of 4% in 112 patients undergoing CAR-T cell therapy and not receiving nucleo(t)side analogue (NA). Despite very limited data, they suggest starting antiviral prophylaxis in this group of patients[5].

Regarding ICIs, the risk of HBV reactivation and therefore the need of an antiviral prophylaxis is differentiated between chronic and past/resolved HBV infection. In HBsAg positive patients the meta-analysis of Papatheodoridis *et al* [5] showed a pooled rate of reactivation in patients not receiving NA prophylaxis of 6%-11%, confirming these patients as at moderate/high risk of HBV reactivation. Instead, HBsAg negative not receiving NA prophylaxis have a pooled rate of reactivation of 0.2%, so a pre-emptive strategy is suggested[5]. A more recent meta-analysis of Ding *et al*[6], focused on HBV reactivation in patients undergoing ICIs, showed similar results and proposed the same recommendations of antiviral prophylaxis for CHB patients and pre-emptive strategy for past/resolved HBV patients. The actual mechanism of HBV reactivation induced by ICIs is still unclear. On the other hand, there are several ongoing clinical trials on the potential role of ICIs as a curative treatment for CHB based on their activity in regain the original immunosurveillance capacity of exhausted CD8+ T cells[7].

Regarding the preferred antiviral prophylaxis regimen, as recommended by the main HBV management guidelines, all the available nucleot(s)ide analogue are possible options for past/resolved HBV infection[8,9]. In this setting of patients with not detectable HBV-DNA, even a low barrier to HBV resistance agent, such as lamivudine, may be used safely and it is cost-effective. Patients with CHB or HBsAg negative with detectable HBV-DNA should instead be treated with agents with high barrier to HBV resistance such as entecavir, tenofovir disoproxil-fumarate and tenofovir alafenamide.

In conclusion, the review of Mak *et al*[1] well resumed the risk of HBV reactivation in patients with hematologic malignancies undergoing novel therapies. In the cited studies, the populations are very heterogeneous dealing with patients with both solid and hematologic tumors, the latter representing generally a smaller part of the sample size. Authors' conclusions are reasonably suitable in these group of patients, but solid results are still lacking.

FOOTNOTES

Author contributions: Tonnini M, Solera Horna C and Ielasi L conceived the manuscript; Tonnini M reviewed the literature and wrote the original draft; Tonnini M and Ielasi L reviewed and edited the manuscript; Solera Horna C supervised; and all authors read and agreed to the published version of the manuscript.

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