Different hepatitis B carrier categories need different management strategies in case of immunosuppressive chemotherapeutic regimens

We read Evens et al. [1] meta-analysis, which provides useful aggregated data about hepatitis B virus (HBV) reactivation in rituximab-treated oncohematology patients. However, some definitions and management strategies could be clarified using the specific Italian guidelines developed on this issue [2, 3].

In fact, the definition ‘hepatitis B surface antigen (HBsAg)-positive’ is not complete if the HBV DNA level is not reported, since it identifies different virological HBV categories and management.

HBsAg-positive patients with HBV DNA levels > 2000 IU/ml, defined active carriers, should be treated as immune competent patients, and nucleo(s)tide analogues (NA) with high potency and low resistance (entecavir, tenofovir or telbivudine) should be used to control the effects of immune suppression on viral replication while receiving chemotherapy.

HBsAg positive, HBV DNA negative or ≤ 2000 IU/ml individuals, defined inactive carriers, undergoing high-risk immune suppressive treatment should be prophylaxed with an NA preferably 2–4 weeks before starting immune suppressive treatment. Considering that baseline viremia in this group is usually undetectable and that resistance risk is low, a low cost NA (i.e. lamivudine, LAM) should be used. The preemptive approach has been proven superior to delayed treatment.

Curiously, in the paper by Pei et al. [4] a significantly protective effect of LAM is described, but in the discussion of the paper by Evens et al. [1], the same article is cited to underline LAM ineffectiveness in the prevention of HBV reactivation. In this study, HBV reactivated after LAM stopping, thus it can be argue that treatment duration, and not LAM per se, was inadequate to control viral replication. In fact, it has been suggested that antiviral treatment should be extended up to 12 months after immunochemotherapy [3]. Thus, the negative perspective regarding LAM use in prophylaxis of HBsAg positive should be carefully discussed and detailed presenting the positive evidences supporting its use in this setting [3].

Differentiating the management of active versus inactive carriers is crucial to start treatment with NA of adequate potency/resistance and to prevent ineffective replication control, development of viral resistances and breakthrough.

Occult hepatitis B carriers (OBI) are HBsAg- and HBV DNA-negative individuals, usually anti-HBc and/or anti-HBs positive [5], in which liver HBV DNA can be detected by specific PCR probes. These individuals harbor replication competent virus, inhibited in its replicative function by immunological/epigenetic mechanisms, and are at increased risk for HBV reactivation if treated with immunochemotherapy for oncohematological malignancies as monoclonal antibodies. Prophylaxis has been strongly suggested in this setting [2, 3]. Alternative strategies to manage OBI are monitoring for HBsAg reexpression or HBV DNA increase and consequential targeted prophylaxis before biochemical signs of hepatitis develop [2, 3].

The authors presented the effects of rituximab exposure by pooling a large group of patients from different HBV categories. Thus, even if acknowledging the intrinsic limits to all meta-analysis, the heterogeneity due to different virological HBV categories pooling and retrieval of data from different studies, since there are few large studies on this issue, the authors should be complimented for having provided useful
information to measure the risks of HBV reactivation in patients receiving rituximab.

Our comments should not be intended to be a mere academic remark but a tentative to accurately identify different HBV categories. Baseline HBV DNA testing is critical to obtain this result.

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**disclosure**

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**references**


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