

Review

Hematological malignancies and HBV reactivation:

Suggestions for clinical management

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Abstract: It is well known that the event of hepatitis B virus reactivation can occur among patients undergoing treatment for hematological malignancies.

In this paper we will present the available data regarding the risk of hepatitis B virus reactivation in this special population of immunosuppressed patients and explore the relevance of an accurate prevention and management of this condition. A computerized literature search was performed using appropriate terms arrangement, including English-written literature only or additional relevant articles.

The evaluation of hepatitis B reactivation risk is a multidimensional process, which includes conducting an accurate clinical and physical history, considering the virological categories, the knowledge of the medication chosen to treat these hematological malignancies and the induced grade of immunosuppression. Adopting adequate preventive strategies and surveillance according to the current international recommendations is crucial to prevent HBVr and its dire clinical consequences (hepatitis, liver failure, interruption of lifesaving anti-neoplastic treatments).

Universal HBV screening of patients scheduled to undergo treatment for hematological malignancies should be the chosen policy, and clinicians should be aware of the inherent risk of viral reactivation among the different virological categories and the classes of immunosuppressive drugs.

Keywords: HBV reactivation, lymphoma, hematology, immunosuppressive therapy, prophylaxis, hepatitis B virus, occult/active/inactive carrier

1. Introduction

Brief historical perspective on Hepatitis B reactivation among patients with hematological malignancies treated with chemotherapy

The event of hepatitis B virus (HBV) reactivation (HBVr) has long been known to occur among patients undergoing treatment for hematological malignancies (HM). The first descriptions regarding the modifications of Hepatitis B surface antigen (HBsAg) and antibody (anti-HBs) occurring in patients with myelo- and lymphoproliferative disorders undergoing chemotherapy were first published during the mid seventies [1,2]. In the same year, the dire clinical consequences of HBVr and possible approaches to treatment with the then available resources were described [2]. During the following years, other observations followed concerning the clinical and virological events developing in patients with serological signs of current or previous contact with HBV undergoing either treatment for HM [3,4,5,6,7,8,9,10,11,12,13,14,15]. Even if large data set of retrospective observations had already been produced [16], it had to be waited until 1991 to have the first prospective data on the issue of HBVr among patients undergoing cytotoxic treatments [17]. Lamivudine (LAM) was one of the first reliable antiviral nucleosidic analogue resource to fight back HBV replication which became available during the mid 90' [18,19], and at the end of that decade it was

selected to manage chemotherapy induced reactivation [20]. The seminal work by Lau paved the way to the systematic prophylactic approach with LAM to prevent of HBVr [21]. This paper was then followed by others, testing antivirals of increasing potency to prevent HBVr in both HBsAg carriers [22,23,24] and in patients with signs of previous contact with the hepatitis B virus (potential occult carriers) [25,26]. In later prospective trials, entecavir (ETV) established itself as the treatment of choice to prevent HBVr in HBsAg positive lymphoma patients as compared to LAM [27]. Also, acknowledging the role of new and specific antineoplastic agents such as the anti-CD 20 Rituximab (RAb) as relevant risk factors in inducing HBVr, represented a considerable step forward in the fine tuning of preventing strategies [28]. HBVr is relevant in the treatment of these patients since it has the potential to negatively impact on clinical outcomes, by interfering with the chance of cure and hampering treatment completion [29,30]. In addition it has recently been suggested that HBsAg- and anti hepatitis B core antigen antibody- (anti-HBc) positive status in itself, even in the absence of HBVr, might interfere with the reach of overall and progression free survival in patients with HM [31]. HBVr among special populations has thus become along the years a relevant issue, addressed in both general HBV guidelines [32,33], and in position papers dedicated to the management of this condition in specific group of immunosuppressed patients [34,35 ,36,37,38]. In this paper we will focus and critically present and discuss the available data regarding HBVr among patients with HM. To collect the most relevant and updated information on this issue, we performed a computerized literature search in MEDLINE using appropriate terms arrangement, including English-written literature only but also selecting additional relevant related articles. The result of the search will be critically presented to provide a practical approach to the clinical management of HBVr among this special population.

Regarding the general consideration on HBV epidemiology, data on reactivation mechanisms, technical definitions of virological and clinical events in the special population of immunosuppressed patients, reactivation rates, virological and risk of reactivation classes, please refer to the previous sections of this special issue on epidemiology and to the following references [33,34,35,37].

2. Considerations on the issue of HBVr among patients treated for hematological malignancies

Even if the issue of HBVr in hematology has seemingly received increasing attention, we however witness every year the publication of case report regarding missed diagnosis and their serious clinical implications. Thus, it seems that in spite of the fact that the current literature on HBVr is becoming gradually more solid and prospective data available, awareness of the problem still seems to be not strong enough to become part of common good clinical practice. A recent paper also including patients with hematological malignancies, showed that substantial portions of HBV (and HCV) infections present at the time of cancer diagnosis were unknown to patients, and that many had no known risk factors for infection, suggesting that risk-based models for screening, proposed by some [38], may be insufficient [39]. It is true that the data obtained in a surveillance targeting specialist treating patients with lymphoma show that these have a higher level of awareness concerning HBV reactivation under immunosuppression, fitting with the reported observation that a predominantly hematological practice is significantly associated with an increased likelihood of screening for HBV [40]. Accordingly, these professionals seem to adopt in a high percentage the strategy of universal screening (>90%) [41].

Nevertheless, given the limited knowledge of HBV prevalence among HM, especially among western world patients, adding that data are mostly coming from the treatment of lymphomas [42,43], even the approach of universal screening might be insufficient. In short, a screening procedure should be aimed to a selected population at higher risk of developing a disease condition, thus being based on the prevalence of that condition in the population or in a selected group. Given the paucity of prevalence data among HM other than lymphoma, considering that these are mostly coming from far east populations, a preferable approach could be represented by the strategy of testing. This has been discussed during the recent conference on the management of HBV positive immunocompromised, held in Turin under the auspices of the Italian Association for the study of the liver [37] in December 2017. As opposite to screening, testing instead applies to the single individual, and it is based on the intrinsic probability that a certain drug (i.e. rituximab, RAb) has to induce reactivation (Tommaso Stroffolini, personal communication). Thus, we believe that universal

HBV testing should be policy of choice when managing patients scheduled to undergo treatment for HM, even if these strategies should be supported by cost-effectiveness studies.

3. Factors predisposing to HBVr among patients with serological signs of either current or previous, resolved hepatitis B infection affected by HM and undergoing immunosuppressive treatments

HBsAg-positive patients undergoing treatment for HM run a relevant risk of HBVr (24-88%, median 50%), and reactivation is increased by the use of immunochemotherapy, with most of the data coming from the RAb combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy [28,44,45]. Also patients with serological signs of past resolved exposure to HBV receiving either immunochemotherapy (the main group being HBsAg negative/anti-HBc positive patients, also categorized as potential HBV occult carriers), are exposed to a substantial risk of reactivation (>10%; median 16.9%; range 13.1-21.9) [24,25,45,46,47,48,49].

Among these virological categories, several risk factors predisposing to HBVr have been identified. HBVDNA concentration does correlate with HBVr risk. HBsAg positive subjects with high baseline levels of HBVDNA before starting immunosuppression are the most prone to develop HBV as compared to those with low/undetectable viral DNA [50,51,52]. In particular, risk of HBV reactivation is 5- to 8-fold higher among HBsAg positive patients [53], and highest in hepatitis B e antigen- (HBeAg-) positive individuals [50]. The lowest risk is present among those with signs of previous resolved contact with the HBV, such as isolated anti-HBc without detectable HBVDNA and HBsAg [54]. Older age and male sex have also been suggested as potential risk factors for HBVr in this special population [30].

Hematological malignancies are also at a higher risk for HBVr as compared to other diseases treated with immunosuppressant drugs [55], and different HM might display different risk for HBVr [54]; nevertheless, there are no studies available comparing similar therapeutic regimens in different hematological settings [30]. Most data among patients with HM came from lymphoma studies, with diffuse large B cell lymphoma seeming to display the highest HBVr risk [56]. It should be considered that it is not clear if this observation reflects an intrinsic propensity of this disease to favor HBVr or a mere effect of the medications used to treat these conditions. A long postulated relationship between HBV infection and non Hodgkin lymphoma development is well known [57], but a clear connection between this suggestion and HBVr has not been found.

Multiple myeloma patients are also at risk of HBVr. In the advanced stages of this disease, a more critical immune dysregulation occurs and might predispose to HBVr [58], with rates of around 5% reported [59]. A substantial risk of viral reactivation has also been described among HBsAg patients treated for acute myeloid leukemia, with HBV-related hepatitis occurring in 8.3 per 100 person-years, and HBVr rates as high as 28% [60]. As far as patients with serological signs of previous resolved contact with HBV are concerned, a recent review reported a risk of HBVr ranging from 2 to 20% among adult T-cell leukaemia-lymphoma, chronic lymphocytic leukaemia and multiple myeloma [43].

Anti hepatitis B surface (anti-HBs) antibody positive status in patients with serological signs of previous resolved contact with HBV (potential occult HBV carriers). Data from prospective studies conducted in this population, consistently report that the presence of a significant concentration anti-HBs antibodies identifies a group at a lower risk to develop HBVr [48,61]. Nevertheless, the strategy to perform serial anti-HBs level testing to predict HBVr has not been shown to be either practical or useful [48]. Several authors suggested a differential approach based on the presence/concentration of anti-HBs antibodies to apply either prophylaxis or preemptive therapy for these two subgroups of HBsAg negative/anti-HBc positive patients, especially addressing this issue among those undergoing treatment with anti-CD20 drugs [48,56,61]. In a metaanalysis involving 1672 hematological patients not undergoing antiviral prophylaxis, HBVr risk was shown to be 14% (95% CI: 9.4–19%) in HBsAg negative/anti-HBc positive as compared to the 5.0% (95% CI: 3.0–7.0%) observed among those also anti-HBs positive [62]. It was thus suggested that HBsAg negative/anti-HBc positive patients without anti-HBs should receive antiviral prophylaxis and that anti-HBs testing can help stratify reactivation risk. However, these data also indicate that reactivation risk it is not eliminated by the presence of anti-HBs; in fact, when RAb-based treatments were used, a residual reactivation risk (5 %) remained among anti-HBs positive. Given this latter observation, it was suggested

that patients undergoing RAb-based treatments (and possibly the same strategy should be run for other anti-CD 20/immunotherapy based protocols), should undergo antiviral prophylaxis regardless of anti-HBs status. Also quantification of HBV core antibodies might also help to predict HBVr in the group of HBsAg-negative/anti-HBc (\pm anti-HBs) patients undergoing lymphoma treatment [63]. Nevertheless, results regarding this test are still preliminary and more data are needed to add this tool to the manging palette of these complex and demanding patients. However, even if the management of HBsAg negative/anti-HBc positive patients not receiving anti-CD-20 based chemotherapy regimens remains uncertain [62], in these latter cases anti-HBs titer might provide a criteria to choose a preemptive management approach over pophylaxis. From a practical stand point, considering the lack of studies using anti-HBs titers to guide whether or not to start prophylaxis even in anti CD-20 treated patients, we contend that there is still insufficient evidence to support the use antiviral prophylaxis based on the presence or specific cutoff concentrations titers of anti-HBs when anti-HBc is present [34,35].

It is now well accepted that different classes of immunosuppressive drugs are associated to different risks of inducing HBVr. Several older drugs are notoriously known to directly act over specific promoter to induce HBV reactivation, such as corticosteroid [64] and antracyclines [65]. In general, drugs used in the treatment of HM are characterized by a severe immunosuppressive effect, as in the case of RAb, the anti-CD20 monoclonal antibody par excellence, a potent B-cells depleting agent [66], and well recognized to increase the chance of HBVr by more than fivefold [28]. The rate of HBVr inherent to these B-cell depleting agents is roughly 16.9% among patients with serological signs of previous resolved exposure to the hepatitis B virus (isolated antiHBc positive patients, potential HBV occult carriers), and the percentage of their seroreversion to HBsAg positive status ranges around 20%-40%. Characteristically, using this drug HBVr can develop as a delayed event, even up to 60 months after the cessation of immunosuppression, again underlining its relevant and prolonged influence on the recovery of immune competence [25,28,35]. Data from recent trials suggest that the newly available anti-CD-20 obinutuzumab induces HBVr rates not dissimilar from those occurring in RAb-treated patients [56]. Accordingly, also the other currently available anti CD-20 monoclonal antibody, ofatumumab is subject to similar precautions of use [67]. Other monoclonal antibodies also share HBVr risk such as the anti-CD 52 alemtuzumab, (refractory chronic lymphocytic leukemia), mogamulizumab (T-cell lymphoma), and brentuximab vedotin (refractory/ relapsed Hodgkin lymphoma)[30,68]. Several other newly introduced drugs, comprising biological and targeted medications, also used to treat HM, such as lenalidomide, bendamustine, imatinib, dasatinib, bortezomib, carfilzomib, romidepsin, temsirolimus, and phosphatidylinositol 3-kinase (PI3K) inhibitors, and BCL2 inhibitors, by acting with diverse mechanisms and on different pathways, are potentially able to interfere with the immune system and cases of HBVr have been reported. Thus, drug agencies warning reports regarding single drugs have been emanated and specific preventive strategies should be considered [30,69]. Also other newly introduced therapies for the treatment of HM are also at a potential risk of inducing HBVr, and even if specific reports of reactivation are not available, precaution suggest to consider preventive strategies [70]. Also the introduction of drugs fulfilling the definition of “biosimilar”, i.e. a biological medicine highly similar to another biological medicine (the so-called ‘reference medicine’) should be considered [71,72].

HBVr also correlates with the presence of complex quasi-species, detected by ultra deep sequencing techniques, characterized by the presence of HBsAg mutations in immune-active regions and additional N-linked glycosylation sites that might contribute to HBV escape by both neutralizing and diagnostic antibodies [73]. These mutants might then go undetected and HBVr go unnoticed by common monitoring strategies during and after immunosuppressive treatments. A specific immune-escape mutation has also been detected, whose presence significantly correlated with the use of RAb, suggesting that the grade of immunosuppression mediated by powerful drugs such as the anti CD-20 group, might progressively weaken the humoral response and favor the emergence of mutant species capable to evade antibodies [74].

4. Management of patients with HM and serological signs of current or previous, resolved contact with the HBV

These patients should follow differentiated management pathways according their risk of reactivation.

As previously discussed, the evaluation of HBVr risk is a multidimensional process, which includes conducting an accurate clinical and physical history, considering items such as vaccinal status, virological category, knowledge of medication chosen for the treatment of the underlying hematological disease and the grade of immunosuppression they both induce. Liver elastography is strongly recommended to define baseline liver status, since the outcome of HBVr will result in worst outcomes in patients with advanced liver fibrosis/ cirrhosis [37]. A liver stiffness below 6.0 kPa is considered to be a reliable surrogate indicator of a normal liver [75]. In case of active carriers (AC, HBsAg positive patients with chronic hepatitis according to the most recently proposed nomenclature [33]), these patients must undergo treatment with high potency and genetic barrier nucleos(t)ide analogues such as entecavir (ETV), tenofovir (TDF) or tenofovir alafenamide (TAF) as immunocompetent individuals [33,37]. Similarly, HBsAg positive chronic infection (CI, previously known as inactive carriers) with a high reactivation risk >10% according to the reactivation risk groups indicated in the literature [35] should also undergo prophylaxis with these highly effective drugs [30], which have been shown to be superior to LAM in this setting. By choosing potent and high genetic barrier medications over LAM we in fact better protecting these frail patients impacting over relevant clinical outcomes such as preventing the development of resistant mutants, and reducing interruption of lifesaving treatments [27]. On the contrary, available data suggest that the use of LAM has a favorable benefit profile to prevent HBVr among patients with resolved HBV infection (HBsAg negative/anti-HBc positive, potential occult HBV carriers) and either at high risk of reactivation ($\geq 10\%$) or/and with detectable HBVDNA at baseline (prophylaxis); this strategy should ideally be applied 2 to 4 weeks before immunochemotherapy initiation if time and clinical needs allow [34,46,47,72,76]. Recent studies conducted in Italy further support the application of this prophylactic strategy among patients with serological signs of resolved HBV infection at high risk of HBVr [77,78]. Use of more powerful antivirals in patients with resolved infection is questionable and still debated. Recent prospective data from China, even if with some acknowledge limitations, suggest in fact that this strategy might not be cost effective especially in those with low HBVr risk such as anti-HBs positive, and that a preemptive approach based on virological surveillance might prevent unnecessary prophylaxis in a large percentage of patients (96.8%) with resolved HBV infection [79]. Virological response to treatment should be tested as in immunocompetent in the case of both treated AC and prophylaxed, high risk CI subjects by monitoring HBVDNA and transaminases every 6 to 12 months. In case of virological breakthrough while on treatment with ETV, either TFV or TAF will be used as rescue strategies. In case of partial virological control, a multidrug combo (ETV+TFV/TAF) should be considered [37]. Among prophylaxed, high risk patients with serological signs of previous resolved infection with the HBV (potential occult HBV carriers) it is suggested to perform monitoring by testing HBsAg or HBVDNA. It is still not completely clear which test has the better performance in the clinical management of these patients, since even if HBVDNA testing is more sensitive in detecting significant replication resumption, but clinically less specific, more costly, less available and with a longer turnaround time than HBsAg testing [37]. Available data suggest that in case of a HBVr risk $\geq 10\%$, both inactive carriers and patients with signs of resolved HBV infection should undergo prophylaxis extension with the drug of choice for at least 18 months after anticancer treatment [37]. Instead, also according to the Italian position paper, patients with serological signs of resolved infection and HBsAg positive inactive carriers at a lower risk of HBVr (<10%), should be monitored for resumption of viral replication and managed by a pre-emptive strategy. In these cases, detection of either HBVDNA, appearance of HBsAg not present at baseline or, in the worst case scenario, of hepatitis occurrence, treatment with second generation antivirals without delays will be mandatory [37]. Also HBVDNA testing should be pursued in case of serum transaminases increase to test the rare, but possible, event of reactivation of mutated HBV surface antigens not detectable by all commercially available tests [73]. Timing and modality of monitoring strategies regulating the pre-emptive approach are mainly based on expert opinions, however we suggest to adhere to those proposed by the AIFS position paper. HBsAg and ALT testing in patients with signs of resolved HBV infection (potential occult HBV carriers) should be performed every three months, while in HBsAg-positive inactive carriers testing for HBVDNA should be performed every 3 to 6 months. Stopping prophylaxis should only be considered if clinical remission of the underlying HM has been reached, and if no further immunosuppressive strategy is planned. After stopping prophylaxis, monitoring of serum markers (HBsAg or HBV-DNA depending on the category) is however recommended in the six to 12 months to follow [23,28].

Conclusions

HBVr still constitute a threat in patients undergoing treatment for diseases with potentially curative but strongly immunosuppressive drugs [37]. In particular, it is our commitment as physicians to promote HBV testing before the initiation of such medications in patients with HM with the goal of manage those with serological signs of current or past contact with the HB virus, in order to prevent complications that could impair the success of anticancer treatments.

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