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TOPIC HIGHLIGHT

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Patients with hematological malignancies and serological signs of prior resolved hepatitis B

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Abstract

Hepatitis B virus (HBV) infection affects a large part of the world population. Within the different virological HBV categories that have been identified, patients with occult HBV infection represent a peculiar group. These individuals harbor a replication competent virus, inhibited in its replicative function. Accordingly, cases of reactivations have been observed in immunosuppressed individuals who lose immunological control over the infection. Patients with hematological malignancies (HM) are treated with intense myelo- and immunosuppressive chemotherapy regimens which favor HBV reactivation. This event can have severe consequences, such as hepatitis flare, hepatic failure and even death. In addition, it can lead to delays or interruptions of curative treatments, resulting in a decreased disease free and overall survival. In this review, we will examine the event of HBV reactivation in patients with signs of resolved HBV infection undergoing treatment for HM and propose possible management strategies.

Key words: Occult hepatitis B; Hematological malignancies; Hepatitis B virus; Chemotherapy; Hepatitis B reactivation

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INTRODUCTION

Hepatitis B virus (HBV) infection affects a large part of the world population[1]. Its persistence can lead to chronic liver disease and the development of end stage liver disease. Different virological HBV categories have been identified (Table 1)[2]. The occult HBV infection category (OBI) represent a peculiar group who harbor replication competent HBV which is inhibited in its replicative function[3]. Accordingly, cases of HBV reactivation in OBI

have been observed in individuals losing immunological control over the infection[4,5].

Patients with hematological malignancies (HM) are treated with intense myelo- and immunosuppressive chemotherapy (CHT) regimens. Furthermore, even untreated patients with HM often have, *per se,* an immunocompromised state. Among HM, lymphoma patients have a particularly increased risk of developing HBV related complications[5]. These patients have been consistently reported to have a higher rate of HBV infection than the normal population[6-8]. Reactivation in HM patients can have severe consequences, such as hepatitis flare, hepatic failure and even death[4,9]. Reactivation in HM patients can also lead to delays or interruption of curative CHT, resulting in a decreased disease free and overall survival[10].

In this review, we will examine the event of HBV reactivation as the result of CHT in patients with HM and OBI.

SEARCH STRATEGY, STUDY SELECTION CRITERIA AND DATA EXTRACTION

A computerized literature search of MEDLINE was performed using different combinations of the following terms: hepatitis B surface antigen (HBsAg) negative, reactivation, lymphoma, hematology, hepatitis B core antigen antibodies (anti-HBc) and occult carrier, considering English-written literature only. To identify additional studies, the bibliographies of the identified papers were searched for further relevant articles. Since our aim was to retrieve information on the effects of HBV infection reactivation in patients undergoing CHT, studies on patients undergoing hematopoietic stem cell transplantation were excluded since these have higher incidence of reactivation[2,4] and were deemed to potentially affect the homogeneity our results. As stem cell transplantation followed CHT in some studies, these were included. Studies were also excluded if only published in abstract form and if it was not possible to extract the exact number of anti-HBc. Case reports were considered only if they added relevant information.

CONCEPT OF OCCULT HEPATITIS B INFECTION: DEFINITIONS

The occurrence of HBV reactivation in patients with signs of resolved infection, in particular of anti-HBc-positive patients, relies on the existence of OBI, one of the HBV virological categories (Table 1)[2]. Patients with OBI are supposed to harbor HBV covalently-closed-circular DNA in the nuclei of their hepatocytes[11] after the resolution of acute infection. This category has recently been defined as the fifth phase of the dynamic process characterizing the natural history of chronic hepatitis B[12]. Most OBI individuals are infected with replication-competent viruses, whose replication and gene expression are strongly inhibited[3]. The exact mechanisms of inhibition have not yet been determined but long lasting specific host T-cell immune surveillance against HBV epitopes and epigenetic factors are presumably the major causes of long-term viral suppression[3,13].

Various definitions of OBI emerged during the years, causing difficulties in diagnostic characterization. The consequent need for clear cut criteria led to an international workshop held by the European Association for the Study of the Liver in Taormina. A number of statements were produced, paving the way to a better characterized and shared definition of OBI.

According to the presently accepted definition, patients with OBI are serologically HBsAg negative individuals with detectable HBVDNA in the liver. Their serum HBVDNA is undetectable or very low (usually < 200 IU/mL). HBV serum markers profile (antigen and antibodies) allows further division of this category into seropositive-OBI, i.e., anti-HBc ± anti-hepatitis B surface antigen antibodies (anti-HBs) positive individuals, and seronegative-OBI (anti-HBc and anti-HBs negative). Seropositive OBI can be the result of either acute hepatitis B resolution or of HBsAg negativization years after chronic HBV infection[11]. Seronegative OBI might have progressively lost the hepatitis B specific antibodies. Another possibility, mutuated from the study of hepadnavirus infecting Woodchuck, is that these individuals may have been negative for hepatitis B specific antibody from the beginning of the infection[11]. It is not entirely clear if these two categories have a different clinical outcome in case of reactivation[3]. However, it has been observed that anti-HBc positive patients show a T-cell response typical of protective memory, suggesting that this condition represents a resolved infection with immune-mediated virus control[13].

Another category deserving mention is that of "false" OBI. These patients have serum HBVDNA levels comparable to those present in overt HBV infection but with a mutated HBsAg (escape mutants) not detectable by some commercially available detection assays, and thus "falsely" HBsAg-negative. Multivalent anti-HBs antibody assays are strongly recommended for the detection of these variants[3].

From a diagnostic standpoint, the Taormina meeting stated that the gold standard for identifying occult HBV infection is the analysis of liver DNA extracts by a sensitive polymerase chain reaction (PCR) procedure. However, since hepatic biopsy is not routinely feasible and robust standardized assays for HBV detection in the liver are not available, it was concluded that PCR analysis of HBVDNA in the serum is the method of choice for routine identification of OBI cases[11]. It was also strongly recommended that highly sensitive and specific "nested" or "real time" PCR techniques with oligonucleotide primers specific for different HBV genomic regions and complementary to highly conserved nucleotide sequences be carried out[11]. Commercially available real time, PCR-based assays for serum (or plasma) HBVDNA are sufficiently sensitive to detect many (but not all) OBI cases[3].

Table 1 Main characteristics of hepatitis B virological categories

Definition	Serum HBsAg	Serum transaminases	Serum antibody pattern	Serum HBVDNA (IU/mL)	Liver tissue HBVDNA
Active Carrier[1]	Positive	Persistently or intermittently increased	Anti-HBs negative Anti-HBc positive	> 2000	Positive
Inactive Carrier[2]	Positive	Persistently Normal[3]	Anti-HBs negative Anti-HBc positive	Negative or < 20 000[4]	Positive
Anti-HBc positive[5]	Negative	Persistently Normal[3]	Anti-HBs positive/negative Anti-HBc positive	Negative (> 90%)	Positive

[1]> 90% have relevant liver damage; [2]> 90% do not have relevant liver damage; [3]In the absence of other causes of liver damage; [4]Currently some experts suggest a cut off of < 2000 IU/mL; [5]Without liver damage in the absence of other causes of chronic hepatitis and/or with a previous history of chronic hepatitis B. HBsAg: Hepatitis B surface antigen; Anti-HBc: Antibody to hepatitis B core antigen; Anti-HBs: Antibody to hepatitis B surface antigen; HBVDNA: Hepatitis B virus deoxyribonucleic acid. From Marzano *et al*[2], adapted.

Detection of OBI by PCR techniques has also been performed on peripheral blood mononuclear cells in patients with chronic lymphocytic leukemia[14].

The Taormina meeting also stated that the presence of anti-HBc alone should be considered an imperfect surrogate to identify seropositive OBI when highly sensitive HBVDNA testing is not feasible[11]. However, since carrying out liver biopsy is complicated, the presence of detectable viremia in the serum is rare (even with sensitive techniques) and the detection of anti-HBc ± anti-HBs in OBI is frequent[15], there is a general agreement to consider all the anti-HBc positive subjects as potential occult carriers (pOBI)[2,16]. However, it should be kept in mind that 7%-20% of OBI is completely negative for all the serum markers of HBV infection[15,17].

OCCULT INFECTION REACTIVATION: MECHANISMS, EFFECTS AND DEFINITIONS

OBI individuals can resume their replicative activity in the case of immunosuppression produced by either the disease process itself or as the result of cytotoxic and severely immunosuppressive CHT. Suppression of a normal immunological response to HBV leads to enhanced viral replication and widespread infection of hepatocytes[9]. On discontinuation of immunosuppressive treatment, immunocompetence is gradually restored, leading to an immune clearance-like response, resulting in widespread cytotoxic T cell-mediated lysis of infected hepatocytes with consequent severe liver injury. The clinical manifestations of reactivation can range from asymptomatic self-limiting anicteric hepatitis to the development of severe hepatitis, hepatic failure and even leading to death as the result of progressive, decompensated hepatitis[4,9,18]. The resumption of active viral replication in OBI results in the re-emergence of HBsAg (usually associated with a decline of anti-HBs, when present), an event referred to as either reverse seroconversion or seroreversion[4,19].

Different and inconsistent definitions of HBV reactivation have been proposed and used over the years for patients with HM, especially for pOBI individuals. Initial studies based the diagnosis of reactivation on the occurrence of hepatitis, using it as a surrogate endpoint to describe HBV reactivation, thus underestimating its incidence[20]. In addition to seroreversion, seroconversion from envelope antigen (HBe) antibody positive to HBe-positive or reappearance of anti-HBc of the IgM class has also been considered as strong evidence for reactivation[21].

With the availability of DNA testing, it was possible to track the temporal relationship between HBVDNA increase, occurrence of hepatitis and CHT administration[4]. This allowed definition of reactivation as the occurrence of hepatitis (serum alanine aminotransferase, sALT, > 3 × normal value) during or after chemotherapy, accompanied either by an increase in HBVDNA levels of > 10-fold compared to pre-reactivation, or an absolute increase of HBVDNA serum level exceeding 2×10^8 cp/mL, or more commonly 2×10^5 IU/mL[22], during chemotherapy[4].

Molecular biology testing also showed that when signs and symptoms of hepatitis ensue, HBVDNA levels can actually decrease[23].

In the effort to produce a more comprehensive definition, some authors merged previous descriptions, frequently adopting different cut-offs for sALT increase to classify hepatitis and HBVDNA tests with different detection limits[24-29], further hampering standardization. Different terms were also used to define reactivation in the presence of seroreversion, HBVDNA increase and hepatitis development, such as *de novo* hepatitis[30,31]. Some authors adapted, with slight variations, definitions derived from previous studies conducted on HBsAg positive patients[32,33]. Interestingly, in the 2009 practising guidelines from the American Association for the Study of the Liver, in order to define HBV reactivation, the reappearance of active necroinflammatory liver disease in a person known to have resolved hepatitis B was also required[34]. This requirement added another alternative definition to an already long list. Recently, the possibility of using only HBVDNA monitoring to make an early diagnosis of HBV reactivation was proposed[35]. In this prospective study, detection of HBVDNA levels > 12 IU/mL was the only needed requirement to make the diagnosis, while seroreversion and occurrence of hepatitis were not necessary.

The above mentioned evidence indicates that the definition of HBV reactivation in pOBI is, at best, not

standardized. In 2007, the Italian Association for the Study of the Liver published specific guidelines for hepatitis B in immunocompromised patients. The aim was to standardize clinical and virological definitions and to approach the management of patients, also considering the availability of new powerful antiviral drugs. Virological HBV categories and events were clearly defined. In the category of immunosuppressed pOBI, seroreversion and a HBVDNA increase of at least one log (as compared to its nadir and reconfirmed in two consecutive serum tests during monitoring) were defined as significant virological events. Clinically, reactivation of hepatitis B was defined by the presence of a significant viremia and sALT levels above the upper normal value. Since, even if rarely, some pOBI can have advanced liver disease[2,12], baseline assessment of underlying liver disease status was considered fundamental to complete the diagnostic work up.

PREVALENCE OF HBV INFECTION OR SIGNS OF ITS PRIOR RESOLUTION IN HM

The available data on HBV prevalence in patients with HM has been mainly derived from non Hodgkin's lymphoma (NHL) populations[7]. In a recent meta-analysis, a high prevalence of HBV infection has been demonstrated in lymphoma patients, with a 72% higher chance of encountering it in this group compared to controls (odds ratio: 2.56, 95% CI: 2.24-2.92)[7]. We retrieved data on the prevalence of serological stigmata of prior resolved hepatitis B infection in patients with HM, predominantly lymphomas. In this population, median anti-HBc antibodies prevalence is high: 18.8% in Italy (range 6.3%-56%)[8,14,36-42]; 44.2% in China (17%-62.3%)[30,33,43-45]; and 24.3% in Japan (range 13.7%-37.8%)[25,35,46]. These percentages of pOBI are higher than those reported for HBsAg positivity in similar populations from the same countries, respectively a 4.4%-8.5% range for Italy[8,40], a median 24.5% for China (range: 21%-27%)[20,45,47,48] and 4.1% for Japan (range: 2%-12.6%)[25,46,49,50]. Thus, the prevalence of patients at potential risk for HBV reactivation seems to be higher than that derived only from data regarding HBsAg-positive patients.

REACTIVATION AND RISK FACTORS

The median reported incidence of HBV reactivation in pOBI patients treated for HM is 4.5% (range: 0.72%-50%)[20,25,30,33,35-37,40,42,44-46,51,52]. The reported rate of mortality as a consequence of reactivation is variable, with 64% of studies examined not describing any mortality[25,35-37,40,42,44,46,52], while the remaining 36% report a median value of 50% (range 14.3%-100%)[20,30,33,45,51]. However, it should be considered that mortality in immunocompetent patients developing acute hepatitis B is rare, for instance, 0.4% in Italy[53]. Accordingly, efforts have been made to identify risk factors increasing the chance of HBV reactivation in HM pOBI patients undergoing CHT.

Absence of anti-HBs in pOBI has been suggested as a potential risk factor for reactivation[33,40,46] but reactivations do also occur in patients without it[20,35,37,38,44,51]. Similar observations have been obtained in the liver transplant setting, in which anti-HBs positive status of donor reduces the risk of HBV reactivation in recipients[54]. Also, in the transfusional medicine setting, the presence of anti-HBs is considered to prevent transmission of HBV infection in the case of pOBI donors[3]. Antibody titer may play a role in preventing infection transmission[55]. Furthermore, no cases of HBV transmission were reported from the Japanese Red Cross in recipients who were given HBVDNA-positive components containing anti-HBs, whereas infections were detected among those receiving components in which anti-HBs were not present[56].

The rate of HBV reactivation is also influenced by the specific immunosuppressive action of the drugs used, alone or in combined schedules, to treat HM. HM patients with OBI receiving CHT regimens containing glucocorticoids and anthracyclines are considered at risk for HBV reactivation[29]. Fludarabine, alone or used with other drugs, has also been associated with HBV reactivation[36], while anthracyclines have been shown *in vitro* to stimulate HBVDNA secretion[29]. In addition, HBV has been shown to contain a glucocorticoid-responsive element that may enhance viral replication favoring diffusion and the possible emergence of resistant strains[57]. Consequently, glucocorticoid-free CHT has been used to reduce the risk of reactivation. However, as derived from studies on HBsAg-positive HM patients, even if these regimens obtain a significant decrease in the rate of HBV reactivation, patients in the glucocorticoid-free arm had a significantly lower rate of HM complete remission and a shorter overall survival, presumably owing to suboptimal therapy[58].

The anti-CD20 monoclonal antibody Rituximab was the first drug of this class to be approved by the Food and Drugs Administration (FDA) in 1997 for the treatment of a human neoplasia, CD20-positive B-cell NHL. It was introduced for its characteristics of high selectivity of action against B cells and consequently for its ability to limit systemic toxic side effects. At the beginning of the new millennium, however, case reports started to emerge describing reactivation of HBV in HBsAg-negative patients[59], some even leading to the death of the patient[60]. In 2004, the FDA and the manufacturers of the drug issued a "Dear Healthcare Professional" letter regarding Rituximab-associated HBV reactivations in HM patients[61]. Some papers were published reporting data on this issue and these were recently aggregated and analyzed by meta-analytical methods[62]. When case series dealing with pOBI were analyzed[25,30,33,42], treatment with Rituximab was confirmed as a relevant risk factor for HBV reactivation in HM patients, with an odds ratio of 5.73 (95% CI: 2.01-16.33, $P = 0.0009$). The monoclonal anti-CD 52 antibody Alemtuzumab has also been involved in HBV reactivation in pOBI[63].

Male sex has also been reported as another potential risk factor for HBV reactivation[33,35] but this was not clearly demonstrated in all studies[25,26,42]. Both old and young ages have also been inconsistently indicated as a potential risk factor[35,64].

Interestingly, in the study by Yeo, HM related variables, such as stage of disease, severity of illness, involvement of extranodal sites and bone marrow and the presence of lymphoma-associated "B" symptoms, were not associated with HBV reactivation[33].

Lastly, virological characteristics have been suggested to have a potential role in influencing the outcome of reactivation in HM patients. According to Sugauchi, patients harbouring the Bj genotype in association with a mutation contributing to high viral replication could be more prone to develop a fulminant outcome[52]. However, more data are needed to better define the relevance of this particular aspect.

MANAGEMENT

Given the risk associated with HBV reactivation of pOBI patients with HM, strategies have been developed to handle this event. Two main managing trends exist: to detect reactivation and start antiviral treatment or to apply prophylaxis in at risk patients.

Early detection of seroreversion or of HBVDNA in pOBI allows for institution of targeted prophylaxis (TP), i.e., administration of antiviral medications to suppress HBV replication in the absence of hepatitis reactivation. On the contrary, in those cases in which hepatitis has emerged as the result of HBV reactivation, its management is defined as therapy[2].

Instead, true prophylaxis (in this case defined as universal prophylaxis (UP) to distinguish it from TP) entails the pre-emptive administration of antiviral medications to the entire population at risk of reactivation[2].

To detect reactivation, biochemical surveillance, aimed at the early detection of liver enzymes alterations, was the first approach used[45]. This strategy should be presently considered outdated if not unacceptable. Seroreversion and later HBVDNA determination were used to attribute the event to HBV reactivation[20,36]. This approach, at times with small modifications, has been widely adopted[25,26,30,33,37,44,46,51]. Hui detected reactivation applying this strategy, while HBVDNA testing allowed classifying all patients with reactivation as true OBI, since retrospectively all were positive to nested PCR at baseline[30]. Hepatic biopsy and real time PCR techniques allowed Persico and co-workers to identify occult infection in the liver, but not in the serum, of five out of 18 HBsAg-negative, anti-HBc-positive/anti-HBs-negative NHL patients[37]. Only these five patients developed reactivation after CHT. It was, however, underlined that this was not to be considered a routine approach to predict emergence of reactivation in clinical practice.

The approach of serological HBsAg surveillance and/or prospective sequential HBVDNA testing to detect HBV reactivation has been consistently adopted only recently[25,35,40,52], even although emergence of hepatitis as a criterion to detect reactivation has not been completely abandoned[46]. Interestingly, in two of these studies, TP was instituted even if only HBVDNA turned positive and when HBsAg seroreversion had not yet occurred[25,35]. Instead, in the study by Francisci, seroreversion in addition to HBV detection was needed to start TP[40]. However, it has been recently shown that some HM patients can intermittently be HBVDNA-positive without developing seroconversion or hepatitis[41]. In this study, serum HBVDNA testing was not shown to be satisfactory in forecasting seroreversion in pOBI, with a positive predictive value of only 25%, while it had a good negative predictive value in excluding reactivation (about 90%). Notably, in this retrospective series, it was shown that up to 10% of HBVDNA-negative patients might still develop seroreversion as the result of CHT[41]. Thus, the approach of starting TP only on the basis of novel HBVDNA positivity needs confirmation, since by this strategy some patients could receive unnecessary, costly and, presumably, long-term treatments[41].

The suggested timing of surveillance in order to detect seroreversion during treatment is also variable in the literature. Most authors agree in testing for HBsAg and/or HBVDNA at 1-3 mo intervals during and after CHT[25,35,40]. In the Niitsu and Francisci studies, a differential approach in surveillance was scheduled for anti-HBc positive patients depending on whether anti-HBs were present or not, given the different risk of reactivation already discussed in the previous section. In the Niitsu study, anti-HBc positive/anti-HBs negative patients underwent monthly HBVDNA testing. Instead, in those both anti-HBc and anti-HBs positive, HBVDNA was tested only if the anti-HBs titer decreased at levels below 200 IU/mL[35]. This differential approach has probably developed from the observation that in patients receiving stem cell transplantation, a drop in anti-HBs titer could identify patients at higher risk of seroreversion and thus are those more likely to benefit from antiviral prophylaxis[18]. It is, however, not applicable to anti-HBc positive/anti-HB negative patients and has not been tested in other patient populations[18]. In the Francisci study, anti-HBc positive/anti-HBs negative patients could be tested more frequently (every 1-3 mo) than those both anti-HBc and anti-HBs positive (every 3 mo)[40].

The timing of controls on treatment has been loosely settled but the time-frame at risk for HBV reactivation after CHT and the duration of surveillance after it has not been clearly defined. In existing reports, the proposed follow up after CHT to detect reactivation has been variable, ranging from few months to many years[26,30,33,35,40,42,44,46,51]. Despite no clear indications existing, since the onset of reactivation has been reported to be 4-36 mo after CHT initiation[64], it is reasonable to extend surveillance for HBV reactivation for up to at least 12 mo after treatment discontinuation[2], especially in patients receiving Rituximab or similar medications. Whether surveillance

is needed even after this period it is not known but considering that HM patients usually undergo long term follow up and that a percentage of OBI are negative for all serum markers, it has been suggested that all patients with HM malignancies should be periodically tested for ALT and HBsAg. These tests could also be performed in anti-HBc/anti-HBs patients[41], given the relatively low cost of this strategy.

Patients in whom HBV reactivation is managed by the TP strategy should be treated with antiviral medications. The nucleoside analogue lamivudine (LAM) was widely used in the past to manage hepatitis due to HBV reactivation, since for long time it was the only antiviral medication available. However, intervention with LAM when hepatitis has developed as the result of reactivation does not guarantee patient survival. As shown by Kusumoto, the incidence of fulminant hepatitis and the mortality rates among HBsAg-negative lymphoma patients with reactivation are higher than those observed in HBsAg-positive (40% *vs* 21.3% and 50% *vs* 27.7% respectively)[65]. Other papers have reported the occurrence of death secondary to liver failure as the result of HBV reactivation, even if treated with LAM[24,26,30,33,36,51,62]. These detrimental results could be ascribed to the delayed start of LAM when viral load is already elevated and massive immunomediated hepatic damage is occurring[9,64,66], notwithstanding the baseline liver disease status that plays a pivotal role in determining outcome[2]. Applying the TP strategy, a better outcome might be expected since LAM is promptly started when HBVDNA is still low and before hepatitis has emerged[2,64]. A further chance of success is provided by the current availability of the newer nucleos(t)ide analogues (NUC) Adefovir, Telbivudine and especially the third generation NUC Entecavir (ETV), which has been shown to be effective in the management of HBV reactivation[35,40,46,52]. ETV has a higher efficacy in reducing viral load (defined "potency") and a higher genetic barrier (the characteristic of resisting to the possible selection of antiviral-resistant mutations) compared to LAM[34]. This latter characteristic may prevent the development of drug-resistant mutants in those patients in whom, following the development of high viral loads, a longer time is required to reach HBVDNA negativization.

We were able to retrieve only a few reports on the use of Tenofovir (TFV), the other currently available third generation NUC also provided with a high potency and genetic barrier, in the setting of HBV reactivation in HM patients[67,68]. In these reports, TFV was, however, used in combination with ETV. Nevertheless, given its high potency, genetic barrier profile and performance characteristics[69,70], it might be as effective as ETV in cases of HBV reactivation. In those selected cases in which, despite effective viral replication control, immunomediated phenomena sustain liver damage, glucocorticosteroids could be usefully associated[66]. Treatment with NUC should be maintained, unless stable seroconversion to anti-HBs positivity and HBsAg/HBVDNA negativity is obtained[66] and obviously if no further risk of immunosuppression is foreseen. In case viral resistances emerge, these should be managed according to currently available guidelines[12,34,71].

An alternative approach is that of UP[2], successfully adopted in NHL patients receiving Rituximab-based CHT[33,39]. However, given the reported low reactivation rates in pOBI, this approach could result in over-treatment of a substantial number of patients[41], especially in countries with a large prevalence of anti-HBc positive individuals.

A possible mediating strategy is that endorsed by the Italian guidelines, aiming at stratifying specific reactivation risks for pOBI patients[2,71], an approach also pursued by others[72]. The Italian guidelines suggest that[18,22,73] all patients with HM scheduled to receive CHT should be screened for HBV infection. Those who are anti-HBc positive should also be analyzed for HBVDNA in order to rule out false OBI[11]. The risk of reactivation is then defined by the type of CHT and patient characteristics.

HM pOBI patients scheduled to receive CHT at low immunosuppressive potential should undergo HBsAg monitoring every 1-3 mo, with the activation of TP or therapy in case of seroreversion or hepatitis reactivation, respectively. Use of HBVDNA monitoring during TP remains a controversial issue, given the lack of data on timing and duration of the surveillance. In addition, there are perplexities about the clinical significance of minimal levels of detectable viremia. Ferraro reported that low levels of HBVDNA in anti-HBc-positive patients after solid organ transplantation are not always associated with hepatitis relapse[2].

UP was instead proposed for those patients needing CHT, characterized by intense immunosuppression (fludarabine, dose-dense regimens, allogenic transplant, autologous myeloablative transplant, induction in acute leukaemia, or use of monoclonal antibodies such as Rituximab or Alemtuzumab). Chronic lymphocytic leukemia and multiple myelomas were also identified as conditions at high risk of reactivation. This approach was strongly indicated in patients with signs of advanced liver damage (chronic hepatitis/cirrhosis, either HBV-related or not). This strategy was also recommended in case of positive serum HBVDNA and/or positivity for anti-HBe antibodies at baseline evaluation and, more recently, independently from anti-HBs reactivity[74]. In case of UP, LAM is preferred for short term therapies[74], given its lower cost and efficacy in these patients with very low or absent viral replication.

Time-frames of UP remain a debated issue. If UP is selected, it should be started before CHT and administered for at least 12 mo after it has been stopped. However, as stated before, even longer periods have been proposed for patients receiving Rituximab or Alemtuzumab because of their late immune recovery[9,64] and since presently there are no reliable methods to define its occurrence.

We believe, however, that the best prevention is awareness of the problem. A recent survey, involving on-

cologists in the US, highlighted a reduced prevalence of practitioner applied universal screening for HBV infection (14%) and that only 56% were aware of the availability of prophylactic therapy[75]. In addition, it is interesting to note that in its recent provisional clinical opinion on chronic HBV infection screening in patients receiving CHT, the American Society of Clinical Oncology states that there is insufficient evidence of the net benefits and harms of routine HBV screening in these individuals. Even if they recognize that individuals with cancer who undergo certain CHT and have had prior HBV exposure may be at elevated risk of liver failure from HBV reactivation, it is only suggested that physicians should screen only those patients belonging to groups considered at risk for transmission of HBV infection or for those who will receive highly immunosuppressive CHT (such as rituximab). Screening should include testing for HBsAg. Surprisingly, it is also suggested that testing for anti-HBc should only be considered in some populations and that no evidence supports serological testing for anti-HBs in this context[76].

CONCLUSION

The event of reactivation in pOBI undergoing CHT for HM is infrequent but it might have dire consequences. Winning the battle against the tumor but failing to save lives from hepatitis represents a defeat for physicians. Appropriate management strategies have been formulated and definitions proposed. The foundations to initiate a desirable communicative network and discussion forum between different specialists involved in the care of these patients, aimed at the development of a rationale approach of this small but difficult-to-manage group of immunosuppressed patients, should be considered.

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