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ORIGINAL PAPER

Efficacy of lamivudine prophylaxis in preventing hepatitis B virus reactivation in patients with resolved infection undergoing allogeneic SCT and receiving rituximab

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Abstract

Purpose Hepatitis B virus (HBV) reactivation during immunosuppressive therapy is common in patients with hematological malignancies, even in case of resolved infection. Prophylaxis of HBV reactivation is universally recommended in stem cell transplant (SCT) recipients and patients treated with anti-CD20 agents (i.e., rituximab). Despite its well-established favorable safety profile, lamivudine (LAM) use in prophylaxis has been debated because of the possible emergence of resistant viral strains. The aim of this study was to investigate the efficacy of LAM in preventing HBV reactivation in allogeneic SCT recipients with a resolved HBV infection.

Methods Patients who received first allogeneic SCT in years 2009–2016 were evaluated. Sixty-three patients with resolved infection received LAM prophylaxis and were included in the study. Baseline and post-SCT characteristics were recorded, including rituximab exposure, length of LAM prophylaxis, and time from transplant to the last clinical and virological follow-up.

Results Overall, 39 patients (62%) were male, 39 (62%) had acute myeloid leukemia, 38 (60%) received transplant from haploidentical donor, 29 (53%) received myeloablative conditioning, and 15 (24%) received rituximab post-transplant. Median clinical follow-up was 24 months after SCT (range 0.3–97); median virological follow-up 16 months (range 0.3–78), and median length of LAM prophylaxis of 14.5 months (range 0.3–78). No patient experienced HBV reactivation while on LAM prophylaxis. One patient experienced reactivation 8 months after discontinuing prophylaxis.

Conclusions In this high-risk population, LAM prophylaxis was effective in preventing HBV reactivation in patients with resolved infection. It should be considered a reasonable first-line prophylactic agent to be administered in this setting.

Keywords LAM · HBV · Anti-CD20 · Hematological · HBcAb · Transplant

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Introduction

Hepatitis B virus (HBV) reactivation during immunosuppressive therapy is common and may result in hepatitis flares, hepatic decompensation, and liver failure [1]. Moreover, these complications pose problems in differential diagnosis of causes of liver damage and may interrupt or cancel ongoing or planned chemotherapy, thus leading to important negative impact on the outcome of the underlying disease. Due to the persistence of HBV as covalently closed circular DNA in hepatocytes and other tissues [2, 3], reactivation can occur in both HBV surface antigen (HBsAg)-positive patients and, less frequently, in those with a resolved infection [defined as HBsAg-negative/anti-HB core antibody (anti-HBc)-positive patients, with or without HBV surface antibodies (anti-HBs) and usually negative serum HBV-DNA] [4].

With regard to the latter group, two settings of high risk of reactivation have been identified: stem cell transplant (SCT), especially allogenic, and patients, usually but not exclusively with lymphoma, treated with anti-CD20 agents such as rituximab [5].

Rates of reactivation in SCT recipients range from 3 to 43% [6–10]. Besides the different strategy of monitoring for reactivation adopted in singular studies (i.e., serum HBV-DNA vs HBsAg testing), such an important variability is likely due to the differences in severity of graft versus host disease (GvHD) and intensity of immunosuppression [6–10]. The risk of reactivation persists for years after transplant and the timing of evaluation matters, as demonstrated by Knoll and colleagues who reported that six of seven long-term survivors experienced HBV reactivation, even as late as over 3 years after SCT [11].

Similarly, due to prolonged B-cell depletion and impaired humoral function, HBV reactivation rates have been reported to reach figures as high as 41.5% in lymphoma patients treated with rituximab [12, 13].

Therefore, in these settings, most international guidelines recommend prophylaxis with nucleos(t)ide analogues over pre-emptive therapy for at least 12–18 months after the completion of chemotherapy [4, 5, 14].

With the availability of new molecules, the choice of the preferred antiviral is controversial. Lamivudine (LAM) has been most extensively used in this setting, but antivirals with high genetic barriers to resistance, i.e., entecavir (ETV) or tenofovir disoproxil fumarate/alafenamide (TDF/TAF), are endorsed by some experts even in case of resolved HBV infection, especially for patients candidate to immunosuppressive regimens of extended duration [4, 5, 14]. However, very limited data are available: the only two randomized trials were performed in HBsAg-positive patients [15, 16], and no trial showed superiority of novel antivirals compared to lamivudine in HBsAg-negative patients.

In this study, we aimed to report the efficacy of LAM in preventing HBV reactivation in patients with resolved infection and malignant hematological diseases undergoing allogenic SCT, including patients who were also treated with rituximab.

Methods

Patients

All patients who underwent first allogeneic SCT between 1 January 2009 and 31 December 2016 at Ospedale Policlinico San Martino in Genoa, Italy, were evaluated. Patients with serological evidence of a resolved HBV infection who received prophylaxis with LAM were included in this study.

Data were obtained retrospectively from a prospectively collected database and integrated with chart review if necessary. HBV serological markers (HBsAg, anti-HBs, and anti-HBc) and serum HBV-DNA levels were collected for both patients and donors, and results were cross-checked with an automatically filled laboratory database.

All patients gave consent for data collection for scientific purposes at transplant. The work has been carried out in accordance with the ethical standards of the Declaration of Helsinki (2000). The privacy rights of patients involved have always been observed. Written informed consent was not required due to the retrospective and observational nature of the investigation.

Data collection

Baseline characteristics such as demographic variables (age, sex), disease-related variables (type and status of the underlying disease at SCT, type of donor, type of conditioning regimen), and donor's and recipient's HBV serostatus were collected for all the patients.

For patients included in the study, the following additional data were recorded: rituximab exposure, GvHD (grade of severity and data of onset), post-transplant serum HBV testing (HBsAg and HBV-DNA), any increase in ALT for >2 weeks, clinical follow-up time (expressed as time from transplant to last clinical follow-up visit), virological follow-up time (expressed as time from transplant to the last serum HBV-DNA determination), and length of LAM administration. Follow-up was updated at June 2017.

Antiviral prophylaxis

HBsAg-negative/anti-HBc-positive/HBV-DNA-negative patients received prophylaxis with oral LAM 100 mg once

daily (adjusted appropriately in case of decreased renal function), either continuing prophylaxis administered during chemotherapy or starting before the onset of conditioning. LAM withdrawal in this setting was guided by suspension of immunosuppressive treatment and/or HBV vaccination and documented attainment of a protective anti-HBs titre (≥ 10 UI/mL).

Transplant procedures

Transplant procedures were performed as reported elsewhere [17–20]. In particular, in case of haploidentical donor, post-transplant high-dose cyclophosphamide was administered [20].

Rituximab administration

According to the local protocol, a fixed dose of rituximab (200 mg) was administered on day + 5 after transplant to prevent Epstein–Barr virus (EBV)-associated post-transplant lymphoproliferative disease (PTLD) in patients receiving GvHD prophylaxis with anti-thymocyte globulin (usually receiving transplant from matched unrelated donor, mismatched-related/unrelated donor, or cord blood) as reported elsewhere [17, 18].

Patients with severe refractory GvHD received treatment with rituximab 375 mg/m^2 once a week for 4 weeks. The same dose was administered for 2 weeks in patients with EBV DNA-emia ≥ 1000 per 10^5 polymorphonuclear cells to prevent PTLD (pre-emptive treatment). In addition, rituximab was included in chemotherapy regimens of patients diagnosed with post-transplant relapse of non-Hodgkin lymphoma (NHL).

HBV reactivation

All patients underwent clinical and virological follow-up at clinical visits, and frequent and periodical serum HBV-DNA monitoring. ALT determination was performed at least once weekly during the first 3 months after SCT, then at least once every 14 days if no GvHD was present until 6 months after SCT, at least monthly for the subsequent 6 months, and less frequently thereafter.

Post-transplant serum HBV testing (HBsAg and HBV-DNA) was performed usually every 12 months, and any time if clinically indicated at the discretion of attending physician.

HBV reactivation in patients with resolved infection was defined as reversion to HBsAg seropositivity or detectable serum HBV-DNA in patients HBV-DNA negative at transplant [5, 13]; with or without increased liver enzymes. For patients with HBV reactivation, data on liver function, full HBV serostatus, antiviral treatment, and outcome were collected.

HBV-DNA testing was performed with Versant® HBV-DNA 3.0 bDNA test (Siemens Healthcare Diagnostic Inc., NY, USA), Artus® HBV-RG-PCR test (Qiagen GmbH, Hilden, Germany). All HBV-DNA levels reported were expressed in UI/mL.

Statistical analysis

Frequencies and percentages were used for descriptive statistics. The Chi-squared test or Fisher's exact test when applicable was used for categorical variables. Continuous variables were expressed as median with range and compared with the Mann–Whitney test.

A p value of < 0.05 was considered statistically significant. Statistical analysis was carried out with the Statistical Package for the Social Sciences version 18.0 (SPSS Inc. Chicago, IL, USA).

Results

Patients' characteristics

During the study period of years 2009–2016, a total of 626 patients received first allogeneic SCT. All recipients were HIV-seronegative, 9 patients were HCV-seropositive, and 89 (14%) were anti-HBc positive at SCT. Seven of them were also HBsAg-positive (indicative of chronic infection or chronic hepatitis), and thus, 82 HBsAg-negative/anti-HBc-positive patients (13% of all transplant recipients; all HBV-DNA negative) with resolved infection were evaluated. Among these patients, 63 received LAM prophylaxis (77%) and were included in the study (Fig. 1).

Patients' characteristics are reported in Table 1. Overall, 39 patients (62%) were male, 39 (62%) had acute leukemia, 38 (60%) received transplant from haploidentical donor, 29 (53%) received myeloablative conditioning, and 15 (24%) received rituximab post-transplant (10 received a single lower dose for PTLD prevention and 5 received a therapeutic dose: 2 doses for pre-emptive treatment of PTLD in 3 patients; 4 doses for treatment of NHL and severe GvHD in 1 patient each).

The median clinical follow-up was 24 months (range 0.3–97). Fifteen patients died early after SCT before checking HBV-DNA post-transplant, in median 2.8 months after SCT (range 0.3–13). In none of them, HBV reactivation was clinically suspected (no persistent increase in ALT). In the remaining 48 patients who underwent HBV-DNA testing after SCT, the median virological follow-up was 16 months (range 0.3–78) (Table 1). The clinical follow-up after the administration of rituximab was 15 months (range 1–96), in

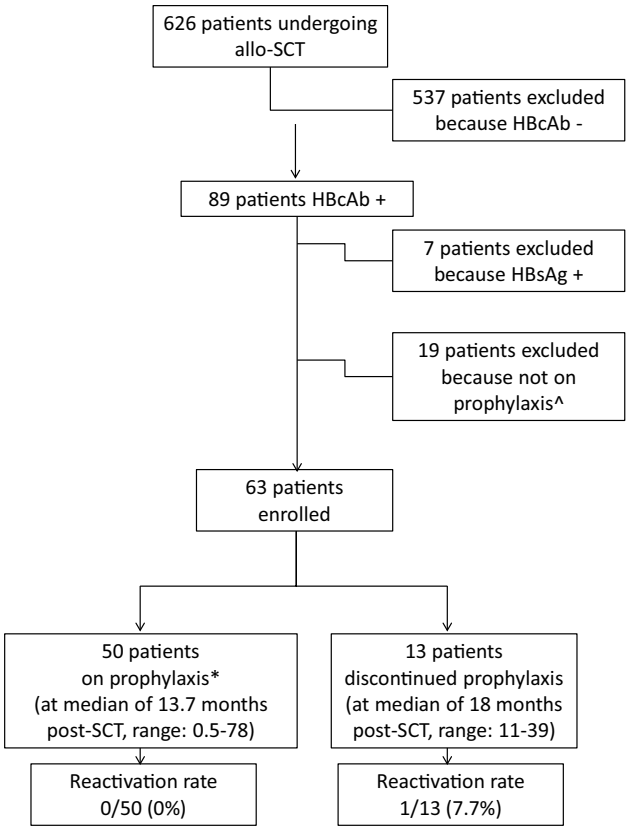

Fig. 1 Distribution of patients according to HBV serostatus and viral reactivation rates in patients with resolved infection on lamivudine prophylaxis enrolled in the study. ^LAM prophylaxis non-administered by mistake or based on decision of the attending hematologist; among these 19 patients 2 had borderline anti-HBc positivity; 5 deceased within 100 days from SCT, 6 deceased within 2 years from SCT, all without HBV reactivation; among 6 undergoing regular monitoring, and 3 experienced HBV reactivation. *Including 21 patients still on prophylaxis at the last follow-up at median 33 month post-SCT (range 2.4–78) and 29 patients who continued prophylaxis until death at median of 6 months after SCT (range 0.5–50)

particular 19.5 months in those who received a single lower dose and 12 months in those who received treatment doses.

Incidence of HBV reactivation

No patient experienced HBV reactivation while on LAM prophylaxis, independently from rituximab exposure. The median duration of antiviral prophylaxis was 14.5 months after SCT (range 0.3–78) (Table 1).

At the last follow-up, 21 patients were still receiving LAM prophylaxis (median follow-up post-SCT 33 months; range 2.4–78) and 29 have died under prophylaxis due to HBV unrelated causes, mainly leukemia relapse (median follow-up post-SCT 6 months; range 0.5–50), while 13 had discontinued LAM prophylaxis at a median of 18 months post-SCT (range 11–39). Three of them discontinued

Table 1 Main baseline and outcome data of recruited patients

Characteristics	$N=63$ (%)
Baseline variables	
Gender, male	39 (62)
Median age, years (range)	54 (20–67)
Underlying disease	
Acute myeloid leukemia	39 (62)
Acute lymphoid leukemia	7 (11)
Myelofibrosis	7 (11)
Chronic lymphocytic leukemia	5 (8)
Chronic myeloproliferative disease	2 (3)
Severe aplastic anemia	2 (3)
Non-Hodgkin lymphoma	1 (1.5)
Phase at SCT	
Complete remission	38 (60)
Active disease	25 (40)
Donor	
Matched related	14 (22)
Matched/mismatched-unrelated	3 (4.7)
Mismatched-related	1 (1.6)
Cord blood	7 (11)
Haploidentical	38 (60)
Conditioning regimen	
Myeloablative	31 (49)
Reduced intensity	32 (51)
Rituximab administration post-transplant	
Yes	15 (24)
For prophylaxis of PTLD	10 (16)
For pre-emptive treatment of PTLD	3 (5)
For relapsed NHL	1 (1.6)
For GvHD treatment	1 (1.6)
No	47 (75)
Donor's HBV immunity	
No exposure (anti-HBs negative/anti-HBc negative)	34 (54)
HBV vaccination (anti-HBs positive/anti-HBc negative)	15 (24)
Resolved infection (anti-HBc positive)	10 (16)
Missing	4 (6)
Recipient's HBV immunity (%)	
Anti-HBs ≥ 10 UI/mL	37 (58.7)
Anti-HBs < 10 UI/mL	25 (39.7)
Level unknown	1 (1.6)
Outcome variables	
Alive	32 (51)
Median clinical follow-up, months (range)	24 (0.3–97)
Median virological follow-up, months (range)[a]	16 (0.3–78)
Median duration of LAM prophylaxis, months (range)	14.5 (0.3–78)

SCT stem cell transplant, *PTLD* post-transplant lymphoproliferative disease, *NHL* non-Hodgkin lymphoma, *GvHD* graft versus host disease, *HBV* hepatitis B virus, *anti-HBs* hepatitis B surface antibodies

[a]15 no determination after SCT in patients who died early after SCT before repeating HBV-DNA post-transplant

prophylaxis after HBV vaccination and obtaining protective anti-HBs antibody titers, other ten discontinued before completing the vaccination course, at the discretion of attending physician because of complete remission of the underlying disease and the absence of immunosuppressive treatment for GvHD. These 13 patents were subsequently followed after discontinuing LAM (median of 34 month post-SCT; range 7–64).

Among the 13 patients who discontinued LAM prophylaxis, a single episode of HBV reactivation was recorded (7.7%) in a patient who did not receive HBV vaccination. This patient had received cord blood transplant in 2012 for myelodysplastic syndrome. He discontinued LAM prophylaxis at 14 months after transplant, together with discontinuing immunosuppressive treatment with cyclosporine and 3 months after tapering methylprednisolone started for moderate acute GvHD. HBV reactivation occurred 8 months later (22 months after SCT) with the presence of increase in ALT (max 95 U/L), HBsAg seroreversion and HBV-DNA of 7.2×10^5 IU/mL. He was successfully treated with TDF 245 mg/day, seroconverted to anti-HBs after 13 months, and discontinued antivirals after 3 years and 3 months of TDF treatment.

No other case of HBV reactivation, either virologically documented or clinically suspected due to persistent increase in ALT levels, was recorded.

Discussion

Our study showed that, in a cohort of 63 allogeneic SCT recipients with resolved HBV infection receiving immunosuppressive drugs, which included rituximab in over 25% of them, LAM prophylaxis was effective in preventing HBV reactivation.

Our findings are consistent with the results of comparable studies led in the same settings. In previously published studies evaluating the reactivation rate in anti-HBc-positive allogeneic SCT recipients, only two episodes of reactivation were reported in 70 patients receiving LAM prophylaxis (2.9%): one in a patient with poor compliance and one in a patient whose viral isolate was discovered harboring the resistance mutation L80I [9, 21–25].

Usually, concerns about the choice of LAM as the first-line prophylactic drug arise from its low genetic barrier which could predispose to the generation of treatment-resistant variants, especially in case of prolonged administration [26]. Such events have been reported in patients with chronic active HBV infection on long-term antiviral treatment, with increasing rates of mutations from 20% after 1 year to 70% after 5 years of LAM administration [27–29]. Such a phenomenon has never been reported in patients who start LAM while HBV-DNA negative.

As no study compared different nucleoside analogues in resolved HBV infection in SCT recipients so far, there are no convincing data supporting a better performance of the third-generation antivirals over LAM in this setting. Consequently, indications from international guidelines regarding the preferred antiviral in this setting are discordant [4, 5], with some of them favoring high barrier molecules on the basis of the previous experiences in patients with chronic HBV infection [5, 14, 30]. The only two randomized trials were performed in HBsAg-positive patients. In the first one, which included 121 HBsAg-positive, HBV-DNA < 2000 IU/mL patients with diffuse large B-cell lymphoma receive chemotherapy containing rituximab; the reactivation rate was significantly lower in the ETV arm compared to LAM group (respectively, 8.2% vs 23.3%) [15]. In the second, in 213 HBsAg-positive patients undergoing chemotherapy for solid tumors, LAM and ETV were equally effective in preventing HBV reactivation in a subgroup of 117 patients with HBV-DNA < 2000 IU/mL [16].

The only study comparing the efficacy of LAM versus ETV which included 25 patients with a resolved HBV infection was not randomized and found comparable outcomes for both arm [31]. No controlled trial has been performed specifically in high-risk populations such as allogeneic SCT recipients.

Our study provides reassurance that LAM can be safely used in patients with resolved HBV infection, who are almost universally non-viremic, even in case of long duration of antiviral prophylaxis (median of 14.5 months), and in the presence of severe immunodeficiency, such as occurring in allogeneic SCT recipients who, in one-fourth of cases, also received anti-CD20 treatment. Thus, treatment with third-generation antivirals may be reserved for HBV viremic or HBsAg-positive patients.

The main limitations of this study include its retrospective and nonrandomized nature which may have introduced some biases and the adoption of different prophylaxis withdrawal strategies. Nevertheless, this is, to the best of our knowledge, the largest cohort of HBsAg-negative/anti-HBc-positive allogenic SCT recipients receiving LAM prophylaxis who were closely followed for years by a single transplant center; in whom persistent ALT increases were excluded.

In conclusion, long-term LAM prophylaxis is effective in preventing HBV reactivation in HBsAg-negative/anti-HBc-positive/HBV-DNA-negative allogeneic SCT recipients, even in case of rituximab administration. The role of high barrier molecules should be defined in consideration of their long-term safety profile and economic impact.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interest.

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