Risk of hepatitis B virus reactivation in chronic lymphocytic leukemia patients receiving ibrutinib with or without antiviral prophylaxis. A retrospective multicentric GIMEMA study

Several reports have highlighted the risk of hepatitis B virus (HBV) reactivation in patients with lymphoproliferative disorders undergoing cytotoxic treatment. This risk is particularly relevant in chronic lymphocytic leukemia (CLL) patients with occult HBV infection (OBI), especially during treatment with anti-CD20 monoclonal antibodies. Moreover, CLL is one of the B-cell lymphoproliferative diseases with the highest risk of HBV reactivation. Since chemo-immunotherapy treatments (CIT) of CLL patients with OBI are associated with an intermediate to high risk of HBV reactivation,[1,2] antiviral therapy as prophylaxis is recommended. Currently, lamivudine is universally used as prophylaxis due to its low cost and toxicity profile. As HBV reactivation can occur up to 12-18 months after the end of the chemotherapy,[3] the antiviral prophylaxis is indicated from the beginning of the specific CLL chemotherapy up to 18 months after the end of treatment.

HBV reactivation has also been anecdotally reported in CLL patients with OBI treated with a B-cell receptor inhibitor (BCRi), such as ibrutinib, although the evidences remain limited to individual reports and the incidence of HBV reactivation in this setting is still unknown.[4-7] Ibrutinib seems to modestly increase the risk of infections in general and to be associated with a moderate risk for HBV reactivation (1-10%);[8] however, it is unclear whether HBV reactivation is due to ibrutinib treatment *per se*, considering that this drug is often used in patients who have previously been subjected to CIT. Another unanswered question is whether the cumulative risk of a HBV reactivation is high enough to ask for a routine HBV-DNA monitoring or a HBV prophylaxis during or after ibrutinib therapy.

We performed a retrospective analysis of 109 CLL patients with OBI from 22 Italian GIMEMA centers treated with single agent ibrutinib prior to 31 January 2019, with at least 1 year of follow-up from the first administration. These patients were identified among a cohort of 789 CLL patients who had been analyzed for HBV serum markers before starting ibrutinib, resulting in an overall prevalence of OBI seropositivity of 14%.

Inclusion criteria included a CLL diagnosis according to the IwCLL guidelines[9] and HBV serum markers suggestive of a seropositive OBI (HBsAg negative, presence of antibodies towards the HBV core antigen [anti-HBc] with or without antibodies towards the HBsAg [anti-HBs] in the serum)[10] at the time of ibrutinib initiation. All enrolled patients were HBV-DNA negative at baseline. Patients who had a concomitant HCV infection, HIV infection and/or any other liver disease were excluded.

The primary endpoint of the study was the rate of HBV reactivation, defined as a HBsAg seroconversion and/or an increase of serum HBV-DNA by at least one log above the lower limit of detection of the assay, with or without liver injury, assessed by serum alanine aminotransferase levels.[12] For all patients, serological markers for HBV infection (including HBsAg, anti-HBs antibody, anti-HBc antibody, HBeAg, and anti-HBe antibody) and serum HBV-DNA were assayed prior to the start of treatment with ibrutinib and every 3 months thereafter.

The study was conducted in agreement with the Declaration of Helsinki and was approved by the Local Ethical Committee of each participating institution. Documented informed consent was obtained for all patients included in the study before they were registered or randomized at the GIMEMA Data Center. Data were collected from the medical files and entered into case record forms by treating physicians. Study data were collected and managed using REDCap electronic data capture tools hosted GIMEMA Foundation.[11,12]

Among the 109 enrolled patients, one was excluded because of missing information regarding the management of OBI during ibrutinib. For the 108 analyzed patients, baseline demographic and disease characteristics for the two cohorts segregated by therapy (i.e., prophylactic antiviral therapy with lamivudine administered at the standard dose of 100 mg daily [n=73] *vs*. monitoring of HBV serum markers [n=35]) are shown in Table 1.

At the start of ibrutinib treatment, nine, 51 and 43 patients were in Binet stage A progressive, B and C, respectively; five patients had missing data. Twenty-five (23%) patients were treatment-naïve at the start of ibrutinib, whereas 83 (77%) had been previously treated; among the latter, 42 (39%), 18 (17%) and 23 (21%) patients had received one, two or more than two lines of CIT, respectively. In the group of previously treated patients, 52 started ibrutinib more than 12 months after the last chemotherapy, while 31 received it prior than 12 months from the end of chemotherapy. The median duration of ibrutinib treatment was 12 months (range, 1-64 months).

Only two of the 108 patients (1.9%) witnessed a HBV reac-

Table 1. Patients' characteristics and results.

	22 Italian GIMEMA centers			Prophylactic antiviral therapy with lamivudine and HBV-DNA monitoring		
Characteristics	Overall, 108 patients			No = 35	Yes = 73	*P*-value
	Sex: M/F, n		73/35	23/12	50/23	0.83
	Median age (range)		64 (39-83)	63 (48-81)	65 (39-83)	0.41
	Binet stage, n (%) 103/108	A B C	9 (9) 51 (49) 43 (42)	1 (3) 21 (60) 13 (37)	8 (12) 30 (44) 30 (44)	0.20
	IGHV, n (%) 81/108	Unmutated Mutated	57 (70) 24 (30)	22 (81) 5 (19)	35 (65) 19 (35)	0.20
	FISH, n (%) 103/108	Normal karyotype Del 13q Tris 12 Del 11q Del 17p	31 (30) 19 (18) 12 (12) 13 (13) 28 (27)	11 (31) 7 (20) 3 (9) 4 (11) 10 (29)	20 (29) 12 (18) 9 (13) 9 (13) 18 (26)	0.97
Time to ibrutinib, n (%) 108/108	Ibrutinib 1st line		25 (23)	8 (23)	17 (23)	0.50
	After less than 12 months from the last treatment		31 (29)	13 (37)	18 (25)	
	After more than 12 months from the last treatment		52 (48)	14 (40)	38 (52)	
Overall reactivation by therapy, n (%)	Overall reactivation		2 (1.9)	1 (2.9)	1 (1.4)	0.55
Details for patients with reactivation, n	Ibrutinib 1st line		0	0	0	
	Ibrutinib 2nd or subsequent lines*		2	1	1	

*After more than 12 months from the last treatment. HBV: hepatitis B virus; M: male; F: female; IGHV: immunoglobulin heavy chain variable region; FISH: fluorescence *in situ* hybridization.

tivation, one occurring in the HBV prophylaxis group (1/73, 1.4%) and another in the HBV monitoring group (1/35, 2.9%) (*P*=0.55); the two patients had been previously treated with CIT (2/83, 2.4%). Both reactivations were detected during the first 6 months of ibrutinib treatment. The patient who experienced a reactivation in the prophylactic lamivudine group was a 69-year-old male who started treatment with ibrutinib and lamivudine 15 months after receiving front-line treatment with rituximab and second-line treatment with fludarabine-rituximab. The serological status at the start of ibrutinib was as follows: HBcAb, HBsAb and HBeAb positive, HBsAg and HBeAg negative, and HBV-DNA undetectable. After 1 month of ibrutinib treatment, the patient showed a detectable HBV-DNA (76 UI/mL), whereas the other serum HBV markers were unchanged and serum transaminase levels remained within the normal range. During the following months, the patient was carefully monitored and all liver function parameters remained normal. Antiviral therapy with entecavir at the dose of 0.5 mg/daily was started after 7 months of ibrutinib treatment when the HBV-DNA raised to 350 UI/mL, and ibrutinib was reduced to 280 mg/daily because of severe diarrhea. HBV-DNA became undetectable after 3 months from the beginning of entecavir. Ibrutinib treatment was stopped after 1 year because of atrial fibrillation. Two months later, the patient started treatment with venetoclax that is still ongoing together with entecavir administration.

The patient who experienced a reactivation in the HBV-DNA monitoring group was a 59-year-old male who started treatment with ibrutinib 12 months after receiving the last CIT with fludarabine, cyclophosphamide and rituximab. At baseline, he was HBcAb positive, HBsAb, HBeAb and HBsAg negative, and HBV-DNA was undetectable. After 3 months of ibrutinib treatment, he developed a detectable HBV-DNA at 741 UI/mL and HBeAb became

positive; the other serological HBV markers remained unchanged and all liver function tests, including serum transaminases, remained normal. Entecavir therapy was administered at the dose of 0.5 mg daily without ibrutinib modifications. During the follow-up, HBV-DNA became undetectable after one month of therapy, whereas HBeAb became negative 1 month later. The patient continued ibrutinib and entecavir treatment until now.

The data presented in this study demonstrate a high prevalence of seropositive OBI (14%) in Italian CLL patients treated with ibrutinib, further emphasizing that the management of these patients represents a relevant clinical problem. The higher prevalence of OBI in CLL patients treated with Ibrutinib that we found, when compared with previuos data, which reported it between 8% and 10%,[13,14] is possibly explained with closer monitoring of the HBV status before initiating Ibrutinib.

The current guidelines of the European Conference on Infection in Leukemia (ECIL-5) and the American Gastroenterology Association (AGA) on the prevention of HBV reactivation provide no recommendations with regard to the management and the need for antiviral prophylaxis of patients with seropositive occult HBV infection treated with a BCRi.[15,2] A recent recommendation has been issued by acknowledging the intermediate risk of HBV reactivation and advising prophylaxis with lamivudine in HBsAg-negative, anti-HBc-positive patients starting ibrutinib treatment. However, given that ibrutinib may be administered continuously for years, the toxicity associated with prolonged antiviral prophylaxis and drug-resistance may be significant.[8]

Previous studies on much smaller series of patients reported a variable incidence of reactivation ranging from 0% to 13%.[4,6,7] In our cohort, with a median duration of ibrutinib treatment of 12 months, only two of the 108 patients developed a HBV reactivation with a cumulative incidence of 1.9%. Both patients had been previously treated with CIT, indicating that the rare cases of HBV reactivation are not necessarily related to the immunomodulatory effect of ibrutinib, but more likely to the persistent immunosuppressive effects of the previous CIT. One of the two patients was in the prophylactic lamivudine group, suggesting that lamivudine prophylaxis may reduce but does not eliminate the risk of reactivation. Considering that the risk of reactivation in HBV monitored patients is very low, the option of monitoring at 3 month-intervals the trend of HBV serum markers with the possibility to start treatment with entecavir in case of a HBV reactivation seems the most reasonable and cost-effective option, also in terms of decreased risk of adverse events from long-term treatment with entecavir.

In conclusion, we confirm that HBV reactivation may rarely occur during ibrutinib treatment in OBI/CLL patients, mainly if not only in patients previously treated with CIT. Based on the easy management with entecavir in case of HBV reactivation, we recommend, for CLL patients with OBI during ibrutinib treatment, 3-months interval monitoring of HBV serum markers rather than HBV prophylaxis.

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AV has participated in scientific board meetings held by Janssen; LT has participated in scientific board meetings and has received funding from Janssen. All other authors have no conflicts of interest to disclose.

Contributions

II, GR, AV, MC, MM, RM, RM, MG, EP, FMQ, FA, RC, MD, CI, AMF, AP, AR, VA, DDS, AT, FA, GDP, LS, FRM, AT, LT, MP, RF, PG, AC and LL collected the data; AP performed the statistical analysis. All the authors reviewed the manuscript for important intellectual contents, approved the final version of the manuscript and supervised the project.

Data sharing statement

Study data were collected and managed using REDCAP (Research Electronic Data Capture), a web-based software platform designed to support data capture for research studies. The data presented in this study are not available. Study protocol can be required to the corresponding author (luca.laurenti@unicatt.it).

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