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Letters to *Blood*



TO THE EDITOR:

# Risk of hepatitis B virus reactivation in patients treated with ibrutinib

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Certain therapies for hematologic malignancies, including anti-CD20 monoclonal antibodies and allogeneic hematopoietic cell transplantation (allo-HCT), are associated with increased risk of hepatitis B virus (HBV) reactivation in patients previously infected with HBV.[1,2] Past HBV infection is defined by concurrent detectable HBV core immunoglobulin G antibodies (HBcAb), undetectable HBV surface antigen (HBsAg), and undetectable HBV DNA. HBV reactivation in patients with hematologic malignancies with past HBV infection being treated with new, targeted cancer therapies has been reported, but its incidence is unknown.

One such agent, ibrutinib, inhibits Bruton tyrosine kinase and thereby interrupts B-cell receptor signaling. Ibrutinib gained US Food and Drug Administration approval for treatment of mantle cell lymphoma in 2013,[3] chronic lymphocytic leukemia (CLL) in 2014,[4] Waldenstrom macroglobulinemia in 2015,[5] and marginal zone lymphoma[6] and chronic graft-versus-host disease in allo-HCT[7] in 2017. Patients with past or chronic HBV were excluded from clinical trials of ibrutinib. With widespread use in a real-world population, infectious diseases complications that were not commonly seen in clinical trials have been reported. These include invasive aspergillosis involving the central nervous system[8] and atypical *Pneumocystis jirovecii* pneumonia.[9] Two case reports have described fulminant HBV reactivation in patients with serologic evidence of previous HBV infection treated with ibrutinib for CLL.[10,11] In contrast, a case series reported no reactivation among 7 HBcAb-positive patients treated with ibrutinib, with median follow up of 24 months.[12] Thus, it remains unclear whether ibrutinib treatment is associated with increased risk of HBV reactivation in patients with past HBV infection.

After observing HBV reactivation in a patient treated with ibrutinib at our institution, we designed this retrospective study to systematically assess the incidence of HBV reactivation among patients with past HBV infection and hematologic malignancy during and after ibrutinib therapy. We identified patients treated with ibrutinib at Dana-Farber Cancer Institute (DFCI) between 1 January 2010 and 31 December 2016 with serologic evidence of past HBV infection. Clinical characteristics were collected including previous therapy with anti-CD20 antibodies (rituximab, ofatumumab, or obinutuzumab) and allo-HCT. HBV monitoring is routinely performed on patients receiving anti-CD20 therapy or undergoing allo-HCT at DFCI; liver function test results are routinely monitored in all patients with hematologic malignancy.

HBV reactivation was defined as development of HBV DNA >100 IU/mL on 2 consecutive measurements with or without reappearance of HBsAg in patients with evidence of past HBV infection. Data were censored on 31 March 2017. This research was approved by the Dana-Farber/Harvard Cancer Center Office for Human Research Studies.

During the study period, 412 patients were treated with ibrutinib at DFCI, of whom 21 (5.1%) had evidence of past HBV infection and were thus at risk for reactivation. Median duration of ibrutinib therapy among those at risk for HBV reactivation was 9.5 months (range, 1-49 months), and median duration of follow up from the time ibrutinib started was 18.3 months (range, 2-69 months). Two patients developed HBV reactivation; thus, the cumulative incidence of HBV reactivation was 9.5% among those at risk (95% confidence interval, 1.2% to 30.4%); risk in the entire cohort including those without past HBV infection was 0.5% (95% confidence interval, 0.06% to 1.7%). Demographic, oncologic, and HBV-related characteristics of the at-risk cohort are described in Table 1.

The index patient is a 57-year-old man diagnosed with CLL 12 years before reactivation. At baseline, he was HBcAb positive, and HBsAb was >10 IU/L. Six years before HBV reactivation, he was treated with fludarabine and rituximab for 6 cycles, the last 2 of which included cyclophosphamide. Approximately 19 months later, he started therapy with ibrutinib for CLL progression. HBsAb had declined to <5 IU/L at this time. Forty-two months after starting ibrutinib, he developed detectable HBV DNA at 120 IU/mL that persists between 120 and 920 IU/mL with undetectable HBsAg. The patient has been monitored closely without antiviral therapy, and alanine and aspartate aminotransferase levels have remained normal on continued ibrutinib 47 months after starting therapy.

The second patient is a 75-year-old man diagnosed with CLL 9 years before HBV reactivation. At baseline, he was HBcAb positive and HBsAb was 51.7 IU/L. He was treated with 2 cycles of rituximab and lenalidomide 7 years before reactivation, followed by observation. Four and a half years before reactivation, he was treated with rituximab and bendamustine for 1 cycle, which was complicated by a severe allergic reaction to rituximab, followed by 1 cycle of bendamustine, after which he was again observed. Due to increased bulky lymphadenopathy 3 years before reactivation, he was treated with 2 cycles of bendamustine. He was then switched to ibrutinib, which was stopped 9 months later due to neurologic toxicity. He has been observed without CLL therapy since. Twenty-two months after stopping ibrutinib

**Table 1. Characteristics of patients with past HBV infection treated with ibrutinib (N = 21)**

| Characteristic | No. of patients |
|---|---|
| Male sex | 15 (71) |
| Age, median (range), y | 66 (50-83) |
| **Hematologic malignancy** | |
| CLL | 15 (71) |
| Mantle cell lymphoma | 4 (19) |
| Waldenstrom macroglobulinemia | 2 (10) |
| Duration of ibrutinib (mo), median (range) | 9.5 (1-49) |
| Anti-CD20 therapy* in previous 2 y | 10 (48) |
| **Allo-HCT** | 5 (24) |
| Before ibrutinib | 2 (10) |
| After ibrutinib | 3 (14) |
| **Baseline HBV surface antibody >10 IU/L†** | 17 (89) |
| Quantitative HBsAb, median (range),† IU/L | 260 (<5, >1000) |
| HBV prophylaxis‡ | 1 (5) |

Data are presented as n (%) of patients unless indicated otherwise.

*Anti-CD20 therapy given within 2 years before ibrutinib started included rituximab, ofatumumab, or obinutuzumab.

†Includes information from 19 patients; baseline surface antibody before ibrutinib was not checked in 2 of 21 patients.

‡One patient was on HBV prophylaxis with entecavir that was started during a course of rituximab <1 year before ibrutinib was started. Entecavir continued during the entire ibrutinib course for this patient.

he was noted on routine labs to have alanine and aspartate aminotransferase levels ~2× normal. Further testing revealed HBV reactivation, with positive HBsAg and HBV DNA >170 000 000 IU/mL. He was asymptomatic. Treatment with entecavir resulted in a prompt reduction in HBV DNA.

In this retrospective assessment of patients with evidence of past HBV infection treated with ibrutinib, we have observed 2 cases of HBV reactivation to date, both of which occurred years after starting ibrutinib. Our retrospective observations are limited by interpatient variability in HBV monitoring. Nonetheless, this is the largest study assessing HBV reactivation in at-risk patients treated with ibrutinib. HBV reactivation in patients treated with ibrutinib has been described only in 2 case reports,[10,11] and the only case series to assess this population included 7 patients who had no reactivation events.[12] The cumulative incidence of reactivation in our larger cohort was 9.5%. Given that our median follow-up was relatively short (18 months) and both cases occurred after this, it is possible that with longer follow-up, the reactivation rate in our cohort will be higher.

Many questions remain about the impact of ibrutinib on HBV reactivation in this population. For example, what is the mechanism underlying this increased risk of reactivation? For how long after discontinuing ibrutinib does increased risk persist? Rituximab is known to increase risk for HBV reactivation in patients with past HBV infection for 1 year or more after therapy stops. Patient 2 in this cohort and another patient reported by Herishanu et al[10] developed reactivation several months after ibrutinib stopped, which suggests that, as with rituximab, the reactivation risk may linger for months to years after ibrutinib ends. Another important question is: how important is HBV viremia without HBsAg reverse seroconversion in a patient on ibrutinib? The index cohort patient had fluctuating levels of HBV DNA for 6 months without developing abnormalities in aminotransferases or reverse seroconversion. Is it possible that low-level viremia during ibrutinib is of no clinical importance and may resolve without antiviral therapy? Another unanswered question is whether the cumulative probability of HBV reactivation is high enough to merit routine HBV DNA monitoring or HBV prophylaxis during or after therapy.

In conclusion, we demonstrate that HBV reactivation may be a risk during and after ibrutinib therapy in those with past HBV infection. We recommend that practitioners systematically screen patients for HBV infection before starting ibrutinib therapy. Further studies are needed to understand the mechanism, timing of risk, impact of underlying hematologic malignancy and pretreatment, importance of low-level viremia during ibrutinib therapy, and optimal monitoring strategies for patients at risk for HBV reactivation on this effective, widely used novel therapy.


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## Authorship

Contribution: S.P.H. designed the study, collected and analyzed data, and drafted the manuscript; K.C. and A.P. collected data and revised the manuscript; and M.S.D., N.C.I., and F.M.M. revised the manuscript.

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## Footnote

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**TO THE EDITOR:**

# Transplant outcome for patients with acquired aplastic anemia over the age of 40: has the outcome improved?

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Age is known to be a strong negative predictor of survival in patients undergoing an allogeneic hematopoietic stem cell transplantation (HSCT) for severe acquired aplastic anemia (SAA), with higher mortality in patients >40 years of age,[1] and this has been confirmed in several large studies.[2-7]

SAA can also be treated with immunosuppressive therapy (IST), with a lower risk of early complications, and first-line IST and bone marrow transplant have been compared in different age groups.[5] Currently, the international guidelines recommend IST first line, older than the age of 40[8] or 50.[9] The question is: are these age cutoff values still valid today? In previous studies, survival after transplantation improved from 48% (in the 1976-1980 cohort) to 66% (in the 1988-1992 cohort),[4] and more recently from 61% to 76% in patients grafted before 1999 or between 1999 and 2009[10]: the latter study included both sibling (SIB) and unrelated donor (UD) grafts as well as children and adults. Improved outcome may have been the consequence of changes in graft-versus-host disease (GvHD) prophylaxis,[4] as well as changes in the conditioning regimens,[11-15] better donor selection, and a larger use of antithymocyte globulin (ATG).[2,16] Nevertheless, for patients older than the age of 40, transplant-related mortality continued to be on the order of 50% in the 1999 to 2009 period. In more recent years, supportive care has further improved and may have reduced the risk of transplant-related complications.

We have thus compared the outcome of SAA patients older than the age of 40 years, transplanted in 2001 to 2009 (n = 329), with patients transplanted in 2010 to 2015 (n = 439). Clinical characteristics of patients are outlined in Table 1. The study was approved by the Internal Review Board of the Hematology Institute, Policlinico Gemelli, Rome, Italy. In the more recent period, patients were older, with more UDs; there was a greater use of ATG or alemtuzumab (CAMP), marrow, and fludarabine. The statistical analysis was performed with NCSS software (NCSS 11 Statistical Software−2016; NCSS, LLC, Kaysville, UT; ncss.com/software/ncss). Comparisons between transplant groups were carried out using the $\chi^2$ test for categorical variables and the nonparametric Mann-Whitney *U* test for continuous variables. Univariate and multivariate analyses were carried out using the Cox proportional hazard model. Actuarial survival was calculated according to Kaplan and Meier.

Combined primary and secondary graft failure (GF) was reported in 48 and 47 patients in the 2 time periods (14.5% vs 10.7%, $P = .1$). Primary GF was twice as frequent than secondary GF (8.2% vs 4.1%). Acute GvHD grade II to IV was comparable in the 2 periods (15% vs 11%, $P = .1$), whereas chronic GvHD was reduced from 31% to 25% ($P = .01$). Extensive chronic GvHD occurred in 10% and 15% of patients grafted from identical SIBs or UD ($P = .01$).

The 5-year survival of patients grafted in 2001 to 2009 or 2010 to 2015 was 61% vs 58% ($P = .7$). In univariate analysis, significant predictors of survival were patient's age, the use of ATG or CAMP, and center experience. The 5-year overall survival of patients aged 40 to 49 years, 50 to 59 years, and >60 years was 67%, 58%, and 45%, respectively ($P < .0001$). When patients receiving either CAMP or ATG (n = 564) were compared with patients not receiving either (n = 161), the difference in survival was 63% vs 48% ($P < .0001$). Survival of patients grafted in centers with >3 patients in this study did significantly better than patients grafted in centers with 1 to 3 patients in the study (65% vs 48%, $P = .0001$). This difference was maintained in the age group 40 to 49 years (73% vs 54%, $P = .001$), in the age group 50 to 59 years (66% vs 42%, $P = .002$), but not in patients >60 years (46% vs 44%, $P = .7$). When stratifying conditioning regimens according to the use of fludarabine, there was no significant effect on survival: for patients receiving UD grafts, the 5-year survival