High rate of hepatitis B reactivation during tyrosine kinase inhibitor treatment among patients with chronic myeloid leukemia in Korea

TO THE EDITOR: Hepatitis B virus (HBV) infection is a global public health issue and a major cause of liver-related morbidity and mortality [1]. Although the prevalence of HBV infection in other countries is decreasing owing to the HBV vaccination program, infection rates remain relatively high in South Korea [2]. Several treatment guidelines have proposed monitoring the potential reactivation of HBV infection among patients receiving chemotherapy or immunosuppressive therapy [3, 4]. The European LeukemiaNet 2020 recommends the assessment of hepatitis B serology before initiating tyrosine kinase inhibitor (TKI) therapy [5]. The risk of HBV reactivation in patients receiving TKI is considered moderate, considering data that support this notion [3, 4]. In patients with chronic myeloid leukemia (CML) who received TKI, HBV reactivation has been reported sporadically [6-10], and the HBV reactivation rates have differed [0% (N=157) [11] vs. 26.3% (N=142) [12]] in recent large-scale studies.

The National Health Insurance Service (NHIS) in Korea is a mandatory health insurance scheme that covers the entire Korean population, and the Korean government facilitates standardized health examinations for all individuals. Using the national medical insurance claims and biennial health examination results, the incidence of HBV reactivation after initiating TKI therapy in patients with CML and the clinical characteristics of these patients in Korea were evaluated.

Data from the NHIS database in Korea were employed. This study included patients aged ≥20 years who were diagnosed with Philadelphia chromosome-positive CML [International Classification of Diseases (ICD) code C92.1] from 2005 to 2017 and were prescribed TKIs (including imatinib, dasatinib, nilotinib, and radotinib). Patients who were prescribed TKIs within <1 month or treated with interferon prior to TKI therapy were excluded. Data such as ICD code, age, sex, list of prescribed medications, and date of death were extracted. C921 did not differentiate the phase of CML; this included all-phase CML. Except

Table 1. Characteristics of the participants.

	Total (N=2,278)
Median age (yr)	52 (20–91)
Sex male (N, %)	1,386 (60.8)
Median duration of TKI treatment, months (range)	51.3 (1–160.5)
TKI	
Imatinib, N (%)	1,563 (68.6)
Dasatinib, N (%)	825 (36.2)
Nilotinib, N (%)	678 (29.8)
Radotinib, N (%)	154 (6.8)
N of TKIs	
1 TKI, N (%)	1,552 (68.1)
2 TKIs, N (%)	533 (23.4)
3 TKIs, N(%)	171 (7.5)
4 TKIs, N (%)	22 (1.0)
HBV infection, N (%)	143 (6.3)
HBV reactivation, N (% of HBV carrier)	33 (23.1)
During imatinib[a], N	24
During dasatinib, N	6
During nilotinib, N	1
During radotinib, N	0
HBV reactivation events/1,000 patients-year	
Imatinib[a], events/1,000 patients-year	3.5
Dasatinib, events/1,000 patients-year	3.0
Nilotinib, events/1,000 patients-year	0.6
Radotinib, events/1,000 patients-year	0
Median interval (mo) from TKI initiation to HBV reactivation, (range)	2 (0–67)
Death, N (%)	466 (20.5)

[a]This included one patient treated with imatinib alone, and HBV reactivation occurred after the discontinuation of imatinib in one patient. See Fig. 2 (patient 7).
Abbreviations: HBV, hepatitis B virus; TKI, tyrosine kinase inhibitor.

for hepatitis B surface antigen (HBsAg) positivity (+) in patients who underwent general health examinations, laboratory data were unavailable. The expenses for antiviral agents for hepatitis B, such as lamivudine, clevudine, telbivudine, entecavir, adefovir, tenofovir disoproxil, tenofovir alafenamide, and besifovir, can be claimed only in the following cases:1) HBeAg (+) and HBV-DNA level ≥20,000 IU/mL, 2) hepatitis B e antigen (HBeAg) (-) and HBV-DNA level ≥2,000 IU/mL and alanine aminotransferase (ALT) level >80 IU; 3) HBV-DNA level ≥2,000 IU/mL in compensated liver cirrhosis; and 4) HBV-DNA (+) in decompensated liver cirrhosis or hepatocellular carcinoma. In previous studies, HBV reactivation was defined as an increase in serum ALT levels to ≥3 times the baseline level and ALT levels >100 IU/L, and either one of the following: 1) exacerbation of chronic hepatitis B was defined as a 100-fold increase in serum HBV-DNA levels when compared with the baseline level; 2) relapse of previous HBV infection was defined as seroreversion from HBsAg (-) to HBsAg (+) or detectable HBV-DNA in a patient with previously undetectable levels [4, 13]. Thus, in the present study, HBV infection was defined as 1) prescription with liver medications (drug classification code 391 according to the Ministry of Health and Welfare, which can be initiated either 1) aspartate aminotransferase (AST) or ALT is ≥60 U/L, or 2) AST/ALT is maintained ≥40 U/L for >3 months when AST or ALT fluctuates between 40 and 60 U/L [14] owing to a diagnosis of acute hepatitis B (ICD code B16) or chronic hepatitis B or hepatitis B viral carrier (ICD code B181), 2) HBsAg (+) based on health examinations, or 3) history of prescription of antiviral agents for hepatitis. HBV reactivation was defined as the prescription of an antiviral agent after initiating TKI therapy in patients who were not diagnosed with liver cirrhosis (ICD code K74) or hepatocellular carcinoma (ICD code C220). This study was approved by the research board of our institution and conducted in accordance with the Declaration of Helsinki.

In total, 2,278 patients were included in the present study (Table 1), with national health examination data available for 1,576 patients. The median age of participants was 52 (20–91) years, and approximately 61% were males. The median duration of treatment with TKI (such as imatinib, dasatinib, nilotinib, and radotinib) was 51.3 (1–160.5) months. Imatinib, dasatinib, nilotinib, and radotinib were prescribed to 1563 (68.6%), 825 (36.2%), 678 (29.8%), and 154 (6.8%) patients, respectively. Approximately 68% (N=1,552) of patients were taking one TKI, while the remaining patients were taking more than one TKI. Overall, 143 (6.3%) patients presented with HBV infection (Fig. 1, Table 1). The HBsAg (+) status was confirmed in 84 (3.7%) patients, and 39 were taking antiviral agents for HBV during the follow-up period. Moreover, 95 patients were treated with liver medications

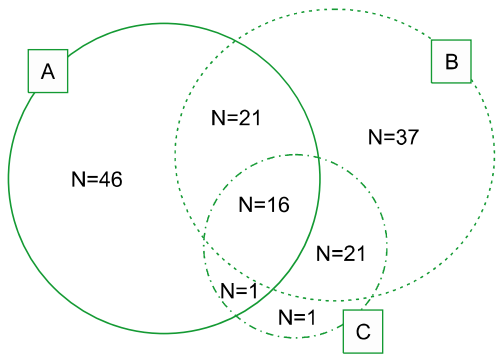

Fig. 1. Diagram showing the number of patients with hepatitis B infection (N=143). **(A)** Number of confirmed HBsAg (+) patients based on national health examinations (N=84). **(B)** Number of patients treated with hepatitis B medications (N=95). **(C)** Number of patients prescribed with antiviral agents for hepatitis B (N=39). Abbreviations: HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.

Table 2. Clinical characteristics of HBV-infected patients.

	HBV reactivation (N=33)	No HBV reactivation (N=110)	*P*
Median age at CML diagnosis, years (range)	46 (22–2)	52 (23–74)	0.12
Sex male, N (%)	23 (69.7)	75 (68.2)	0.87
Confirmed HBsAg (+), N (%)	15 (88.2)	69 (84.2)	0.67
Use of HBV medications prior to TKIs, N (%)	9 (27.3)	3 (2.7)	<0.01
Duration of TKI treatment duration, median (mo)	58 (8–156)	78 (4–156)	0.12
Liver cirrhosis, N (%)	7 (21.2)	13 (11.8)	0.17
Hepatocellular carcinoma, N (%)	10 (30.3)	14 (12.7)	0.02
Death	4 (12.1)	15 (13.6)	0.82

Abbreviations: CHB, chronic hepatitis B; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; TKI, tyrosine kinase inhibitor.

based on the diagnosis of acute or chronic hepatitis B, and 34 patients were taking antiviral agents for HBV. Except for one patient diagnosed with hepatocellular carcinoma prior to antiviral therapy, 33 (23.1%) patients initiated antiviral agents after initiating TKI therapy, that is, experienced HBV reactivation (Table 1). Among the 84 HBsAg (+) patients, 15 (17.9%) developed HBV reactivation (Table 2).

The median duration of HBV reactivation was 2 months (range, 0–67) months after TKI therapy. The duration of TKI treatment and HBV reactivation are shown in Fig. 2. Twenty-one patients (64%) were treated with one TKI, while 11 patients (36%) were treated with more than one TKI. HBV reactivation occurred during the first-line treatment, except in patients 3 and 11. HBV was reactivated during imatinib, dasatinib, nilotinib, and radotinib treatment in 24, 6, 1, and 0 patients, respectively, with incidence rates of 3.5, 3, 0.6, and 0 events/1,000 patients-year, respectively (Table 1). HBV reactivation occurred 3.2 months after imatinib discontinuation in one patient (patient 7, Fig. 2), and this patient was included in the imatinib-treated group. The cause of imatinib discontinuation remains poorly elucidated.

The clinical characteristics of the HBV-infected patients in the HBV reactivation group (N=33) and no-HBV reactivation group (N=110) are presented in Table 2. The HBV reactivation and no-HBV reactivation groups did not significantly differ considering the age at CML diagnosis and sex (P=0.12 and 0.87, respectively). However, the number of patients in the HBV reactivation group (N=9, 27.3%) with a history of antiviral treatment for HBV prior to TKI therapy was higher than that in the no-HBV reactivation group (N=3, 2.7%) ($P<0.01$). The incidence of liver cirrhosis did not differ significantly between the two groups (P=0.17). However, the incidence of hepatocellular carcinoma was higher in the HBV reactivation group (N=10, 30.3%) than that in the no-HBV reactivation group (N=14, 12.7%) (P=0.02). Nineteen patients died during the follow-up period. However, none of the deaths were related to liver disease.

In the present study, 143 of 2,278 CML patients were suspected to be HBV carriers or have previous HBV infection, and HBV reactivation was observed in 33 (23.1%) patients. Compared with previous studies, the current study had a high HBV reactivation rate [11, 12, 15]. Among 122 and 157 Italian patients with CML, no HBV reactivation was observed in 11 patients with resolved HBV infection [15] and 31 HBV-infected patients (HBV carriers, N=5; resolved HBV infection, N=26) [11], respectively. In a previous study undertaken in Taiwan, 5 (26.3%) of 19 HBV carriers experienced HBV reactivation [12]. However, seroconversion was also not observed in 36 patients with resolved HBV infection [12]. The underlying factors responsible for differences in HBV reactivation rates remain unclear. Ethnic differences could contribute to the observed discrepancies, given that two studies from Asian countries, Korea and Taiwan, have shown higher HBV reactivation rates than

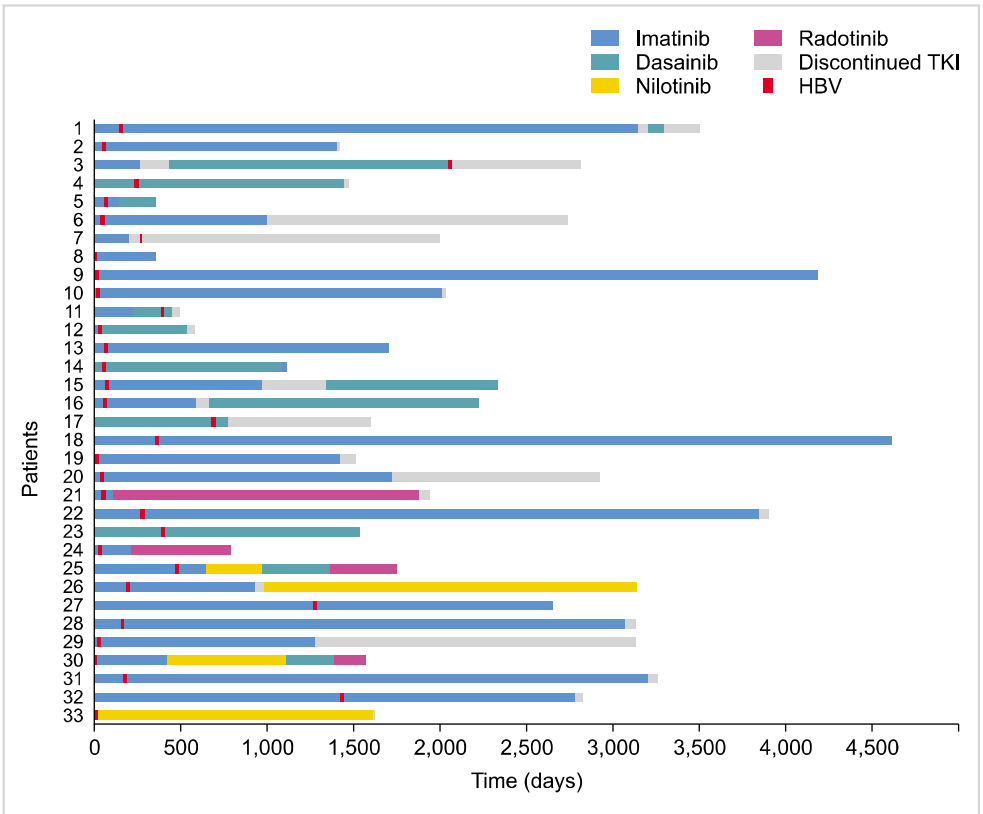

Fig. 2. Treatment with tyrosine kinase inhibitor in patients with hepatitis B reactivation.
Abbreviations: HBV, hepatitis B virus; TKI, tyrosine kinase inhibitor.

two separate studies from Italy.

According to the present study, routine screening of HBV serology prior to initiating TKI therapy should be performed to identify HBsAg-positive patients and closely monitor hepatic function and HBV serology during TKI therapy. This monitoring should be undertaken within the first two months, given that HBV reactivation occurred at a median of two months after initiating TKI therapy, especially in patients with a history of antiviral treatment for HBV.

The current study has several limitations. First, laboratory data, such as HBV serology or AST/ALT, were unavailable for all patients. Second, the use of prophylactic antiviral medications was not determined, as these agents were not covered by the NHIS. These limitations might lead to an overestimation of the HBV reactivation rate. However, the present study had a large sample size, and 3.7% of patients were positive for HBsAg, which was comparable with that of a previous report on the prevalence of HBV carriers in Korea [2]. Thus, considering the high incidence of HBV reactivation following TKI therapy, concomitant antiviral prophylaxis should be considered in HBsAg-positive patients receiving TKI treatment. Further prospective studies are required.

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Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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