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Letter to the Editor

Hepatitis B reactivation during treatment of tyrosine kinase inhibitors—Experience in 142 adult patients with chronic myeloid leukemia

Letter to editor

Target therapy is currently one of the major trends in treatment for cancer. Chronic myeloid leukemia (CML) is a clonal myeloproliferative disorder characterized by *BCR* gene fusion with *ABL*. Imatinib is a first-generation tyrosine kinase inhibitor (TKI) for CML and significantly improves survival and quality of life [1,2]. Second-generation TKIs such as dasatinib and nilotinib are commonly used to treat CML. Hepatitis B is an infectious disease worldwide and is especially common in East Asia and sub-Saharan Africa. Monitoring for the reactivation of hepatitis B virus (HBV) during or after chemotherapy and immunotherapy has been suggested in several guidelines concerning patients with hematological malignancy [3–6]. HBV reactivation in TKIs for CML has been sporadically reported in several studies [7–11]. Little research has been conducted on the epidemiology of HBV reactivation in patients with CML using TKI. Most guidelines do not indicate whether patients carrying HBV require antiviral prophylaxis during treatment with TKIs. The role of TKIs in HBV reactivation remains unclear. Taiwan has a high prevalence of HBV infection, and this study investigated the epidemiology of HBV reactivation in patients with CML treated with TKIs.

We retrospective reviewed the clinical and laboratory data, HBV serology, HBV DNA data, and outcome results of adult patients with CML at National Taiwan University Hospital (NTUH) during the period from January 2008 to July 2018. The patients without HBV serology were not enrolled. The patients with blastic crisis or receiving allogeneic transplantation were excluded from this study. This research conformed to the Helsinki Declaration, and local legislation was approved by the Institutional Review Board of the NTUH's Research Ethics Committee (201606132RIND).

HBV reactivation was defined as a greater than 10-fold increase in the nadir levels of HBV DNA [12] or the reappearance of HBsAg in the serum for patients whose baseline HBsAg was negative [13]. If baseline HBV DNA was unavailable, we defined HBV DNA of more than 20000 IU/mL as HBV reactivation [4,14,15]. HBV-related hepatitis was defined as a greater than 100 U/L of the serum alanine aminotransferase (ALT) level (the upper normal limit is 41 U/L at NTUH) accompanying or following HBV reactivation. The methods have already been described in our previous study [16].

A total of 142 adult patients with CML were enrolled in this study. Of these patients, 78 were men and 64 were women, with a median age of 48 years (range 18–97 years), and 24 (16.9%) patients were more than 65 years old. The median follow-up period was 44 months (range 1–129 months). The TKIs received by the patients were as follows: 43 (30.3%) imatinib, 37(26.1%) nilotinib, 48 (33.8%) dasatinib, 1 (0.7%) ponatinib, and 13 (9.2%) had exposure to two or more TKIs. At the time of diagnosis of CML, 19 (13.4%) of the 142 patients tested positive for HBsAg (HBV). Of the 123 non-HBV carriers, 118 (95.9%) had tested for anti-HBs Ab, 71 (60.2%) of 118 whom were positive for anti-HBs Ab. Additionally, 68 (55.3%) of the 123 non-HBV carrier had anti-HBc Ab test, 36 (52.9%) of 68 whom tested positive for anti-HBc Ab. Of the 19 who underwent testing for HBeAg, all 3 who were HBV carriers tested positive for HBeAg. In total, 6 of the 19 patients who were HBV carriers received antiviral prophylaxis treatment. Univariate analysis revealed a significant difference in reactivation in HBV carriers than others (5/19 vs. 0/123, $p < 0.001$) (Table 1).

In total, 5 (26.3%) of the 19 HBV carriers had 6 episodes of HBV reactivation, and 3 experienced HBV-related hepatitis (more than 100 U/L of ALT). Only one of the 19 HBV carrier patient underwent antiviral prophylaxis before HBV reactivation (case 3), and the other patients did not undergo primary prophylaxis of HBV. No HBV reactivated in patient who was positive HBcAb without HBsAg-positivity in this study.

The details are presented in Table 2. HBV reactivation in HBV carriers was detected between 3 and 51 months after TKI use (cases 1–5). Three cases (case 1, 2, and 5) presented with HBV-related hepatitis and were treated with 0.5 mg of entecavir soon after HBV reactivation. They recovered without hepatic failure or death. The incidence of HBV reactivation was 10.8 per 100 person-years in CML patients who were HBV carriers in this retrospective cohort study.

Chemotherapy, corticosteroids, anti-CD20 antibody and stem cell transplantation have been associated with the risk of HBV reactivation depending on the type and intensity of immunosuppression caused by various medical interventions [17]. TKIs are one of modern novel molecular agents against cancer. The role of TKI-related HBV reactivation in patients with CML is unclear. Two Italian studies have reported a low risk of HBV reactivation in patients with CML treated with TKI [1,18]. These studies reported that 5 (4.0%) of 126 patients with CML [18] and 0 (0%) of 122 patients with CML were HBV carriers [1], respectively. No HBV reactivation is reported. However, HBV reactivation during TKI treatment had been reported in the literatures [7–11]. 19 (13.4%) of the 142 CML patients in this retrospective cohort study were HBV carriers, and we noted 5 cases of HBV reactivation in this study. We considered this difference of HBV reactivation to possibly be related to the relatively more numbers of HBV carriers in this study. The high prevalence of HBV in Taiwan may have resulted in the detection of a low HBV reactivation rate in patients with CML.

The incidence of HBV reactivation was 10.8 per 100 person-years in patients who were HBV carriers with CML treated with TKI in this retrospective cohort study. This rate of reactivation was similar with comparison with that of HBV in other studies, which were 9.4 per 100 person-years in patients with acute myeloid leukemia [16] and 10.5 per 100 person-years in patients with lymphoma [12,16,19]. The incidence

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Table 1
Clinical characteristics of 142 patients with chronic myeloid leukemia treated with tyrosine kinase inhibitors.

	Hepatitis B Reactivation (n = 5)	No reactivation (n = 137)	P value
Age			0.589
≧65 years	0	24	
< 65years	5	113	
Gender			0.378
Man	4	74	
Woman	1	63	
Chronic myeloid leukemia			0.166
chronic phase	4	133	
accelerated phase	1	4	
Tyrosine kinase inhibitors (TKI)			0.511
Imatinib	1	42	
Nilotinib	0	37	
Dasatinib	3	45	
Ponatinib	0	1	
Exposure to two or more TKIs	1	12	
Hepatitis B carrier at diagnosis			< 0.001
HBsAg (+)	5	14	
HBsAg (−)	0	123	
Antiviral agent prophylaxis			1.000
Yes	0	6	
No	5	131	
Death			1.000
Yes	0	4	
No	5	133	

of HBV reactivation in patients with CML treated with TKI was similar with the patients with other hematological malignancies who received chemotherapy. This corresponds with the low HBV reactivation rate reported in other studies for patients treated with CML [1,19]. Recently, Loomba et al. reported treatment with tyrosine kinase inhibitors were as the moderate risk of HBV reactivation (1˜10%) [20]. The incidence of HBV reactivation rate during treatment of tyrosine kinase inhibitors need further investigation.

HBV DNA is rarely serially followed-up in patients with CML treated with TKI. Even when the dosage remained unchanged, we observed fluctuations in the levels of HBV DNA. In the case 4 of a patient who was not treated with an antiviral agent, liver function was normal, and no clinical symptoms were observed for 61 months. Based on this case, we considered that TKI may not be the only cause of HBV reactivation in patients with CML. The association of TKI and immunosuppression in CML requires further investigation.

In this study, we confirmed that HBV reactivation could develop in patients with CML who had been treated with TKI, especially in patients who are HBV carriers. The incidence rate of HBV reactivation is significantly lower than it is in hematological patients treated with chemotherapy, immunotherapy, and stem cell transplantation. However, we recommend that all patients with CML with positive HBsAg should undergo prophylaxis with an antiviral agent. The cause of HBV reactivation in patients with a resolved HBV infection who did not undergo allogeneic transplantation is unclear, and although the risk is low, further investigation is necessary.

Conflict of interests

The authors declare no conflicts of interest or financial funding relevant to this publication. The authors declare no competing interests.

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Table 2
Serial follow-up of 5 patients with CML with hepatitis B reactivation.

Case Age / gender CML status	Baseline HBV status	TKI / Interval	TKI / Antiviral agent / Interval		TKI / Antiviral agent / Interval		
Case 1	HBs: > 250.00 IU/ml	imatinib 400mg	HBV DNA: 3.7×10^7 IU/ml	Imatinib 400mg	HBV DNA < 20 IU/ml	Imatinib 400mg	HBV DNA: 62100 IU.ml
35/ man	Anti-HBs:0.47 mIU/ml	10 months	ALT: 1021 U/L	entecavir 0.5 mg		discontinued entecavir	ALT: 71 U/L
CML, CP	ALT: 40 U/L		(1^{st} reactivation)	60 months		7 months	(2^{nd} reactivation)
Case 2	HBs: 62.31 IU/ml	dasatinib 100 mg	HBV DNA: 87700 IU/ml	dasatinib 100 mg	HBV DNA: 8180 IU/ml	dasatinib 100 mg	HBV DNA < 20 IU/ml
53/ man	Anti-HBs:0.00 mIU/ml	3 months	ALT: 109 U/L	entecavir 0.5 mg	ALT: 20 U/L	entecavir 0.5 mg	ALT: 21 U/L
CML, AP	ALT: 10 U/L		(reactivation)	1 month		42 months	
Case 3	HBs: > 250.00 IU/ml	imatinib 400 mg	HBV DNA < 20 IU/ml	dasatinib 100 mg	HBV DNA:1.33×10^6 IU/ml	dasatinib 100 mg	HBV DNA < 20 IU/ml
22/ woman	HBe: 1.245(+)	entercavir 0.5 mg	ALT: 16 U/L	entecavir 0.5 mg	ALT: 83 U/L	tenofovir 300mg	ALT: 17 U/L
CML, CP	ALT: 33 U/L	31 months		46 months	(reactivation with drug resistance HBV)	entecavir 1.0 mg 17 months	
Case 4	HBs:94.22 IU/ml	dasatinib 100 mg	HBV DNA:1.9×10^4 IU/ml	dasatinib 100 mg	HBV DNA:1020 IU/ml	dasatinib 100 mg	HBV DNA:32100 IU/ml
41/ man	Anti-HBs: 1.43 mIU.ml	51 months	ALT: 17 U/L	4 months	ALT: 17 U/L	3 months	ALT: 16 U/L
CML, CP	Anti-HBc: 12.04			(observation)		(observation)	(reactivation)
	HBV DNA: 722 IU/ml						
	ALT: 15 U/L						
Case 5	HBs: > 250.00 IU/ml	dasatinib 100 mg	HBV DNA: 2.9×10^5 IU/ml	dasatinib 100 mg	HBV DNA 9300 IU/ml		
53/ man	anti-HBs: 2.97 mIU/ml	11 months	ALT: 166 U/L	6 months	ALT: 43 U/L		
CML, CP	anti-HBc:10.48		(reactivation)	(entecavir 0.5 mg)			
	ALT: 14 U/L						

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