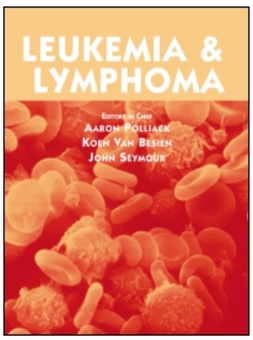

Leukemia & Lymphoma

ISSN: 1042-8194 (Print) 1029-2403 (Online) Journal homepage: https://www.tandfonline.com/loi/ilal20

Risk of hepatitis B reactivation under treatment with tyrosine-kinase inhibitors for chronic myeloid leukemia

Ester Maria Orlandi, Chiara Elena & Elisa Bono

To cite this article: Ester Maria Orlandi, Chiara Elena & Elisa Bono (2017) Risk of hepatitis B reactivation under treatment with tyrosine-kinase inhibitors for chronic myeloid leukemia, Leukemia & Lymphoma, 58:7, 1764-1766, DOI: 10.1080/10428194.2016.1260127

To link to this article: https://doi.org/10.1080/10428194.2016.1260127

LEUKEMIA & LYMPHOMA, 2017
VOL. 58, NO. 7, 1764–1766
http://dx.doi.org/10.1080/10428194.2016.1260127

Taylor & Francis
Taylor & Francis Group

LETTER TO THE EDITOR

Risk of hepatitis B reactivation under treatment with tyrosine-kinase inhibitors for chronic myeloid leukemia

Ester Maria Orlandi[a], Chiara Elena[a,b] and Elisa Bono[c]

[a]Department of Oncology-Hematology, Hematology Unit, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; [b]Department of Molecular Medicine, University of Pavia, Pavia, Italy; [c]Department of Oncology-Hematology, School of Hematology, University of Pavia, Hematology Unit, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

ARTICLE HISTORY Received 19 October 2016; accepted 6 November 2016

In February 2016, the European Medicines Agency (EMA) released a document stating that, according to available evidence, the marketing authorization holders of BCR-ABL tyrosine-kinase inhibitors (TKI), namely imatinib, dasatinib, nilotinib, bosutinib, and ponatinib-containing medical products should amend the product information to provide supplementary information on the risk of hepatitis B virus (HBV) reactivation (http://www.ema.europa.eu/docs/en_GB/document_library/PRAC_recommendation_on_signal/2016/). The EMA document recommends that patients should be tested for HBV infection before initiating treatment with TKIs as reactivation of hepatitis B in chronic carriers of this virus has occurred after these patients received BCR-ABL TKIs. Some cases resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or a fatal outcome. In Italy, hematologists are particularly conscious of the risk of hepatitis B virus (HBV) reactivation under treatment for hematologic malignancies. In our country HBsAg prevalence is about 2%, that is a lower-intermediate endemicity level according to Schweitzer et al. [1]; on the other hand, the seroprevalence of resolved infection (HBsAg negative, HBcAb positive, HBsAb positive/negative) ranges from 8% to 36.9%, and is higher than that in other Western Europe countries.[2–4] HBV reactivation under chemo/immunochemotherapy is most common in HBsAg carriers; however, the risk is not negligible in HBsAg negative patients with resolved infection. In this setting, reactivation is related to the persistence of replication-competent HBV in the form of covalently closed circular DNA within the nuclei of hepatocytes [5] and is more likely to occur in patients receiving monoclonal antibodies and high-dose steroids. [6] To what extent BCR-ABL TKIs might represent a trigger for HBV reactivation is not known. In a recent issue of Leukemia & Lymphoma, Sorà et al. [7] have reported on 122 patients with chronic myeloid leukemia (CML) treated with BCR-ABL TKIs: none of the 11 patients with resolved infection experienced reactivation. We would like to provide additional information adding our experience on this specific issue in a larger number of patients.

Based on the high national seroprevalence for HBV infection in Italy, since the '90s patients with hematologic malignancies have been screened for HBV at our institution before starting treatment. Taking advantage from this institutional policy, we retrospectively collected data in 187 consecutive patients with early or late chronic-phase CML who started TKI treatment between January 2000 and December 2015 at our institution. We were able to assess the prevalence of HBV infection and the incidence of HBV reactivation in 157 cases; 30 patients could not be included because of incomplete data on HBV status (20) or because vaccinated (10). Clinical characteristics are detailed in Table 1. Patients HBV negative at TKI treatment start (baseline) were not systematically reassessed during follow-up, but all alive patients had HBV status completely reassessed at the time the present study was planned. Serum HBV DNA level was serially evaluated in HBsAg positive patients, while patients with resolved infection were monitored outside a predefined schedule. HBV reactivation was defined as a marked increase in HBV replication ($\geq$2log increase from baseline levels or a new appearance of HBV DNA to a level of $\geq$100 IU/ml) in a person with previously stable or undetectable level, reverse HBsAg seroconversion or appearance of HBV DNA in serum in the absence of HBsAg.[8] HBV status was assessed using commercially available kits. Concurrently with evaluation for HBV, our patients underwent assessment for hepatitis C virus (HCV) serological status. As per clinical practice, liver enzymes were evaluated every 3–4 months under TKI therapy, along with a comprehensive biochemical panel. This retrospective study was approved by the Ethics Review Board at our Institution.

At the time of present analysis, 145 patients are alive, while 12 died (causes of death: blastic progression in 6, primary second tumor in 5, preexisting HCC in 1).

CONTACT Ester Maria Orlandi eorlandi@smatteo.pv.it Department of Oncology-Hematology, Hematology Unit, Fondazione IRCCS Policlinico San Matteo, Viale Golgi 19, 27100 Pavia, Italy

Table 1. Clinical characteristics, HBV status and HCV status of 157 patients with CML treated with TKI.

Median age (range), yrs	53 (15–81)
M/F	1.5
Median follow-up from diagnosis, months (range)	112 (8.5–379)
Previous Interferon (late chronic phase CML), *n* (%)	31 (18)
Exposure to one TKI only	
Imatinib only, *n*	112
Nilotinib only, *n*	6
Dasatinib only, *n*	5
Exposure to ≥2 TKIs	34
Median duration of TKI therapy, months (range)	95 (8.5–199)
Alive patients, *n*	145
HBV pattern	
HBV negative, *n* (%)	126 (80)
HBV positive (any marker), *n* (%)	31 (20)
HBsAg positive, *n* (%)	5 (3)
HBsAg positive, HBV DNA detectable at baseline	1
HBsAg neg- HBcAb pos- HBsAb pos/neg, *n* (%)	26 (17)
HBsAg neg- HBcAb pos- HBsAb pos/neg, and HBV DNA detectable at baseline, *n*	0
HBV reactivation (according to reference [8])	0
HCV positive, *n* (%)	7 (4)
HCV RNA positive, *n*	3

CML: chronic myeloid leukemia; HBV: hepatitis B virus; HCV: hepatitis C virus; TKI: tyrosine-kinase inhibitors.

Presently, 18 alive patients are not receiving any TKI (discontinuation in deep molecular response: 16 patients; resistance to multiple TKIs: 2). Median duration of follow-up (from diagnosis to death/last visit) was 112 months (range: 8.5–379). Median duration of TKI treatment (calculated from start to last visit for patients still on treatment or discontinuation due to any cause or progression to blast crisis) was 95 months (range: 8.5–199). Overall, at baseline HBV status (any marker) was positive in 31/157 patients (20%); transaminase levels were normal in these patients. Resolved HBV infection was detected in 26/31, while 5/31 patients were HBsAg positive. These proportions are in line with epidemiological data in Italy. Median duration of TKI treatment for HBV positive patients was 124 months (range: 8.5–199). Twenty-two out of 31 patients had received only one TKI (imatinib: 21; dasatinib: 1), 6 patients had received 2 TKIs (imatinib and dasatinib: 3, imatinib and nilotinib: 3) and 3 patients had received more than 2 TKIs. All HBsAg positive patients were HBcAb positive, and 2/5 were HBsAb negative. HBV DNA levels remained persistently undetectable in all patients with a resolved infection and in 4/5 HBsAg positive patients. Only one HBsAg positive patient showing low level HBV DNA at imatinib starting (December 2008) was prophylactically treated with lamivudine for 3 years. After lamivudine discontinuation (because of persistently undetectable HBV DNA levels), this patient showed fluctuations in HBV DNA levels always below the threshold for reactivation and without any increase in liver enzymes. The same fluctuating pattern was also observed after Imatinib discontinuation (November 2012) in stable deep molecular response (patient enrolled into a clinical trial). At the last control in persisting treatment free remission, HBV DNA was detectable at a very low level. Grade ≥3 increase in transaminases occurred in 3 HBV negative patients receiving nilotinib. Transaminitis was attributed to drug toxicity and was managed by nilotinib dose reductions.

Seven out of 157 patients (4%) were HCV antibody positive; 3 of them had detectable HCV RNA in serum. One patient affected with advanced HCV-related HCC at the time of CML diagnosis was treated with low dose imatinib, but died of liver failure and gastric bleeding. All other patients maintained undetectable or stable levels of HCV RNA without functional liver decompensation under long-term TKI therapy.

BCR-ABL TKIs represent the cornerstone of CML treatment, and are generally well-tolerated. TKIs are not classically associated with immunosuppression, although *in vitro* studies have shown that imatinib, nilotinib and dasatinib have immunological off-target effects,[9,10] and sporadic cases of HBV reactivation have been described in HBsAg positive patients receiving TKIs.[11–15] The majority of reported patients were from the East Asian region where prevalence of HBsAg positivity is high, whereas scarce data are available on the occurrence of HBV reactivation in European CML patients receiving TKIs for a long period. The study by Sorà et al. [7] on 11 CML patients with resolved HBV infection suggests a small risk of reactivation on TKI treatment. We have confirmed this finding in a larger cohort of patients and with a longer follow-up under TKI treatment. According to recently revised product labels of TKIs, HBV status should be assessed before starting TKI therapy. Combining our experience with that by Sorà et al., [7] antiviral prophylaxis is not deemed necessary in patients with resolved HBV infection, provided that appropriate surveillance could be guaranteed. This proves true particularly in patients receiving imatinib.

On the other hand, the optimal strategy is debatable in HBsAg carriers. All previously reported cases of reactivation were in the chronic infection setting, and this suggests that TKI therapy may represent a potential trigger for reactivation. In our experience, no reactivation was observed in HBsAg carriers who received TKI therapy for a long time. However, HBV DNA level fluctuations were detected in one patient and subclinical reactivation could have been missed in other cases.

More intensive post-market surveillance and timely case reports are required to define the optimal preventive strategy in HBsAg carriers, whether antiviral prophylaxis should be recommended, which drug should be selected and for how long, taking into account that TKI therapy is long-term.

Potential conflict of interest: Disclosure forms provided by the authors are available with the full text of this article online at http://dx.doi.org/10.1080/10428194.2016.1260127.

ORCID

Ester Maria Orlandi http://orcid.org/0000-0003-1588-3558

References

[1] Schweitzer A, Horn J, Mikolajczyk RT, et al. Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013. Lancet. 2015;386:1546–1555.

[2] Becker N, Schnitzler P, Boffetta P, et al. Hepatitis B virus infection and risk of lymphoma: results of a serological analysis within the European case-control study Epilymph. J Cancer Res Clin Oncol. 2012;138:1993–2001.

[3] Romanò L, Velati C, Cambiè G, et al. Hepatitis B virus infection among first-time blood donors in Italy: prevalence and correlates between serological patterns and occult infection. SIMTI study group for HBV infection among first-time blood donors. Blood Transfus. 2013;11:281–288.

[4] Taborelli M, Polesel J, Montella M, et al. Hepatitis B and C viruses and risk of non-Hodgkin lymphoma: a case-control study in Italy. Infect Agents Cancer. 2016;11:27–32.

[5] Yim HJ, Lok AS. Natural history of chronic hepatitis B virus infection: what we knew in 1981 and what we know in 2005. Hepatology. 2006;43:S173–S181.

[6] Yeo W, Chan TC, Leung NW, et al. Hepatitis B virus reactivation in lymphoma patients with prior resolved hepatitis B undergoing anticancer therapy with or without rituximab. J Clin Oncol. 2009;27:605–611.

[7] Sorà F, Ponziani FR, Laurenti L, et al. Low risk of hepatitis B virus reactivation in patients with resolved infection and chronic myeloid leukemia treated with tyrosine kinase inhibitors. Leuk Lymphoma. 2016. [Epub ahead of print]. doi: 10.1080/10428194.2016.1219906.

[8] Hwang JP, Lok AS. Management of patients with hepatitis B who require immunosuppressive therapy. Nat Rev Gastroenterol Hepatol. 2014;11:209–219.

[9] Seggewiss R, Price DA, Purbhoo MA. Immunomodulatory effects of imatinib and second-generation tyrosine kinase inhibitors on T cells and dendritic cells: an update. Cytotherapy. 2008;10:633–641.

[10] Salih J, Hilpert J, Placke T, et al. The BCR/ABL-inhibitors imatinib, nilotinib and dasatinib differentially affect NK cell reactivity. Int J Cancer. 2010;127:2119–2128.

[11] Ikeda K, Shiga Y, Takahashi A, et al. Fatal hepatitis B virus reactivation in a chronic myeloid leukemia patient during imatinib mesylate treatment. Leuk Lymphoma. 2006;47:155–157.

[12] Lakhani S, Davidson L, Priebat DA, et al. Reactivation of chronic hepatitis B infection related to imatinib mesylate therapy. Hepatol Int. 2008;2:498–499.

[13] Kang BW, Lee SJ, Moon JH, et al. Chronic myeloid leukemia patient manifesting fatal hepatitis B virus reactivation during treatment with imatinib rescued by liver transplantation: case report and literature review. Int J Hematol. 2009;90:383–387.

[14] Lai GM, Yan SL, Chang CS, et al. Hepatitis B reactivation in chronic myeloid leukemia patients receiving tyrosine kinase inhibitor. World J Gastroenterol. 2013;19:1318–1321.

[15] Walker EJ, Simko JP, Ko AH. Hepatitis B viral reactivation secondary to imatinib treatment in a patient with gastrointestinal stromal tumor. Anticancer Res. 2014;34:3629–3634.