Occult HBV reactivation induced by ibrutinib treatment : a case report

Patrick de Jésus Ngoma[1], Benoît Kabamba[2], Geraldine Dahlqvist[1], Christine Sempoux[3], Nicolas Lanthier[1], Tony Shindano[1], Eric Van Den Neste[4], Yves Horsmans[1]

(1) Department of Hepato-gastroenterology, (2) Department of Microbiology, (3) Department of Pathology, (4) Department of Hematology, Cliniques universitaires Saint Luc, Université Catholique de Louvain, Brussels, Belgium.

Abstract

Ibrutinib is a small molecule that has been recently developped for the treatment of B cell malignancies. Common side effects are diarrhoea, nausea, fatigue, infections, neutropenia and thrombocytopenia. Here we report the first case of Hepatitis B virus reactivation in a 80 years old chronic lymphocytic leukaemia patient receiving ibrutinib, suggesting that such treatment must be associated with HBV screening. (Acta gastroenterol. belg., **2015**, 78, **424-426**).

Key words : hepatitis B virus, reactivation, ibrutinib, chronic lymphocytic leukaemia.

Introduction

Reactivation of hepatitis B virus (HBV) is a well-described complication in patients with chronic HBV infection undergoing cytotoxic or immunosuppressive chemotherapy for hematologic malignancies (1). This phenomenon has been frequently reported with rituximab (2,3).

Cases of HBV reactivation in hematologic patients receiving tyrosine kinase inhibitors (TKI) therapy have been recently described (4,5). However, to the best of our knowledge, HBV reactivation induced by ibrutinib, a Bruton's tyrosine kinase inhibitor, has never been reported. Ibrutinib is a small molecule that is under development (Pharmacyclics, Inc. and Janssen Biotech, Inc., USA) for the treatment of B cell malignancies, including chronic lymphocytic leukaemia (CLL), mantle cell lymphoma and diffuse large B cell lymphoma, as well as multiple myeloma, follicular lymphoma and Waldenstrom's macroglobulinemia.

Diarrhoea, nausea, fatigue, infections, neutropenia and thrombocytopenia are common side effects associated with ibrutinib (6).

Here we report the first case of HBV reactivation in a 80 year-old CLL patient receiving ibrutinib.

Case report

In June 2010, an 80 year-old man was diagnosed with CLL Binet stage C with a 17p deletion presence in 27% of FISH cores. The karyotype was normal.

His past medical history is marked by diabetes mellitus, hypertension, benign prostatic hypertrophy and stroke. In 2005 and 2008, HBV serologies showed positive anti-HBs and anti-HBc antibodies (Ab).

He was treated for CLL from February 2013 with bendamustine, an alkylating agent. The dose administered in the second cycle was reduced due to grade IV thrombocytopenia occurrence. Bendamustine was not proved to be active on the disease.

On June 2013, a treatment with ibrutinib 420 mg/day was initiated. On May 7th the patient had a biological profile characterized by negative HBsAg, positive anti-HBc Ab, positive anti-HBs Ab at a title of 85 I.U/μL and a HBV DNA level at 420 I.U/mL (Abbott HBV Real-Time assay ; Abbott Laboratories, North Chicago, IL, USA), serum transaminases level was normal (AST : 25 IU/L, normal < 50 IU/L and ALT : 21 IU/L, normal < 50 IU/L) suggesting a profile of occult hepatitis B.

Laboratory tests showed a hemoglobin level at 12.2 g /dl, red blood cells at 3980000/μL, white blood cells at 92,500/μL (neutrophils : 930, lymphocytes : 91,580), platelets at 48000 /μL on May 7th. The bone marrow aspiration showed no signs of prolymphocytic acceleration nor changes into aggressive lymphoma.

The 2 weeks treatment with ibrutinib induced bruising and petechiae, warranting drug discontinuation for 1 week. It was then resumed with a lower dose of 280 mg/day.

This treatment reduced nodes and spleen sizes, stabilization of the lymphocytosis and increased rate in blood platelets.

With regard to HBV, hepatitis B virus reactivation occurred 5 months after starting ibrutinib treatment : biological tests done in November 2013 showed positive HBsAg, antiHbs Ab at 71 IU/L, positive anti-HBc Ab, positive anti-HBe Ab, negative HBe Ag and elevated HBV-DNA level (23,076,000 U.I/ml).

Due to HBV reactivation, serum transaminase levels were regularly monitored. In February 2014, after 8 months of ibrutinib administration, several biological controls showed moderate increases in serum transaminase levels (AST : 71 IU/L, normal < 50 IU/L, ALT : 103 IU/L, normal < 50 IU/L).

Correspondence to : Y. Horsmans, M.D., Ph.D., Departement of Hepato-gastroenterology, Cliniques universitaires Saint Luc, avenue Hippocrate 10, 1200 Brussels, Belgium. E-mail : yves.horsmans@uclouvain.be

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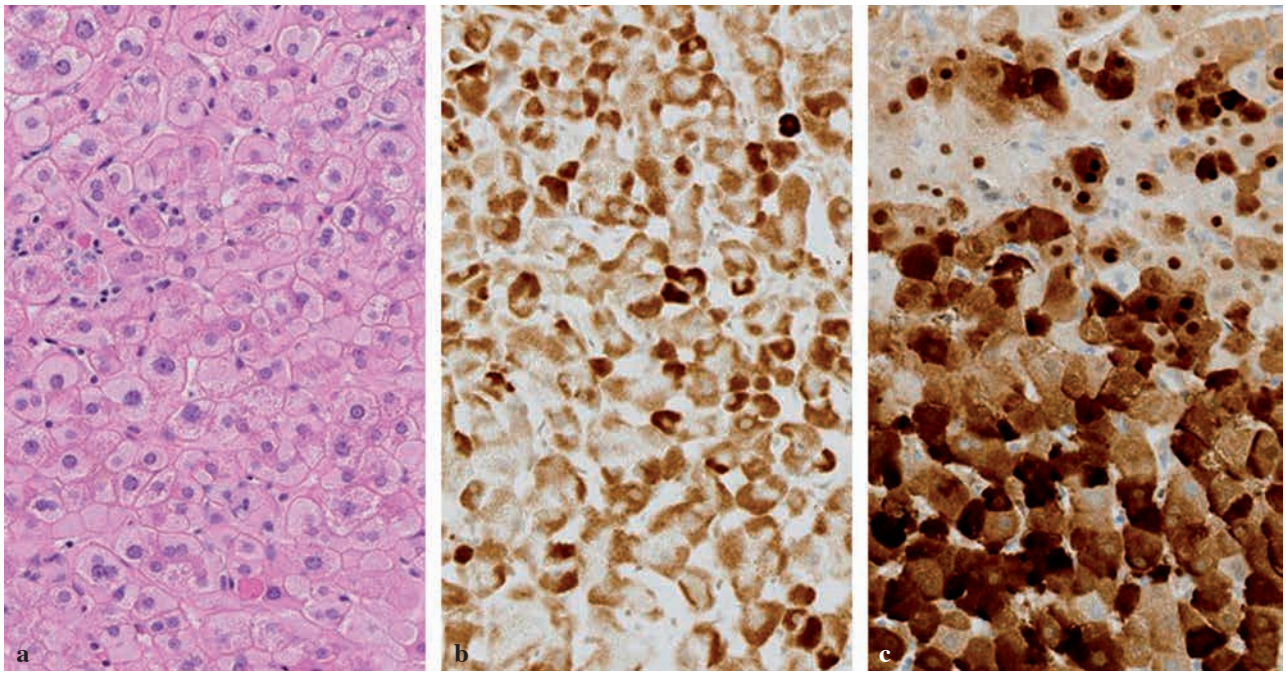

Fig. 1. — Liver biopsy (Original Magnification ×25). (a) On Hematoxylin-eosin routine staining, spotty necrosis and lobular inflammation is observed, alongue side with numerous hepatocytes showing a "ground-glass" appearance of the cytoplasm. (b) HBs immunostaining is diffusely positive in the hepatocytes cytoplasm. (c) HBc immunostaing shows a strong positivity within the cytoplasm and within the nuclei of numerous hepatocytes, underlying the intense viral replication.

A transjugular liver biopsy was performed on March 5th, 2014, showing active lobular inflammation with spotty necrosis, minimal fibrosis (Score F1 according to METAVIR scoring system), and, by immunohistochemistry, a strong expression of HBs antigen and a diffuse cytoplasmic and nuclear HBc positive staining, confirming the active viral replication (Fig. 1). A treatment with entecavir 0.5 mg/day was then initiated allowing a decrease in HBV-DNA and transaminases after 3 months of treatment (HBVDNA : 76,134 U.I/ml, AST : 53 IU/L and ALT : 82 IU/L) and after 6 months, transaminases level was normalized associated with a HBV-DNA level at 10,270 IU/ml.

Discussion

To the best of our knowledge, this is the first description of hepatitis B virus reactivation in a patient treated with ibrutinib in the context of CLL.

Hepatitis B reactivation is defined as a huge increase in viral replication in a patient with inactive or resolved hepatitis B. HBV reactivation can be clinically silent, but often causes a sudden worsening of liver disease that can result in acute hepatic failure. Most reactivations spontaneously resolve, but in case of prolonged immune suppression, re-establishment of chronic hepatitis occurs and can lead to cirrhosis (7).

In a prospective study of 626 patients undergoing cytotoxic chemotherapy, Yeo *et al*. found that HBV reactivation occurs in nearly 20% of them and accounted for 44% of hepatitis cases. The risk factors identified include male sex, younger age, HBeAg seropositivity, and the diagnosis of lymphoma (1). A low anti-HBsAb title (<100 IU/L) in patients who underwent more than one line of chemotherapy has also been described as a risk factor (8). Reactivation predominantly occurs among HBsAg-positive patients.

HBV reactivation in patients with negative HBsAg but positive anti-HBc and anti-HBsAb and in patient with occult anti-HBcAb may occur but is an uncommon condition therefore routine antiviral prophylaxis is not recommended in such situations. It is advised that these patients are prospectively evaluated and treated if HBV-DNA becomes detectable (7).

The specific mechanism of TKI-induced HBV reactivation remains unclear due to limited case reports (4).

Ibrutinib acts by blocking B-cell antigen receptor signalling, thereby reducing malignant proliferation of B cells and inducing cell death (9). Dubovsky *et al*. showed that ibrutinib irreversibly binds IL-2–inducible kinase (ITK) and inhibits activation of Th2 cells after T-cell receptor (TCR) stimulation. This inhibition is specific to Th2-polarized CD4 T cells, because redundant resting lymphocyte kinase (RLK) remains functional, thus providing a compensatory platform for activation of Th1 and CD8 T cells (10).

Regard to HBV in the context of chemotherapy, there is no agreement between the different international

guidelines even if a preventive treatment is frequently recommended. For example, European Association for the Study of the Liver (EASL) 2009 consensus is in favour of vaccinating all HBV seronegative patients and evaluating HBV-DNA level before starting chemotherapy. In other situations, proposing pre-emptive therapy with antiviral treatment for least 12 months after chemotherapy (11).

It has been suggested that HBsAg-negative patients with positive anti-HBc Ab and undetectable HBV DNA level who receive chemotherapy and/or immunosuppression should be followed carefully by means of ALT and HBV DNA testing and treated with nucleoside/nucleotide analogues upon confirmation of HBV reactivation before ALT elevation (11).

For patients with occult hepatitis B virus infection, early identification of viral reactivation is recommended to start antiviral therapy and prevent the occurrence of hepatitis B (12-14).

In conclusion, this case report suggests that ibrutinib administration may induce HBV reactivation in hematologic patients reinforcing the view that tyrosine kinase inhibitors therapy should be administered with caution in HBV patients.

References

1. YEO W., CHAN P.K., ZHONG S., HO W.M., STEINBERG J.L., TAM J.S. *et al*. Frequency of hepatitis B virus reactivation in cancer patients undergoing cytotoxic chemotherapy : a prospective study of 626 patients with identification of risk factors. *J. Med. Virol*., 2000, **62** : 299-307.
2. YEO W., JOHNSON P.J. Diagnosis, prevention and management of hepatitis B virus reactivation during anticancer therapy. *Hepatology*, 2006, **43** : 209-220.
3. PAPAMICHALIS P., ALEXIOU A.B., DALEKOS M., RIGOPOULOU G.N. *et al*., Reactivation of resolved hepatitis B virus infection after immunosuppression : Is it time to adopt pre-emptive therapy ? *Clin. Res. Hepatol. and Gastroenterol*., 2012, **36** : 84-93.
4. LAI G.M., YAN S.L., CHANG C.S., TSAI C.Y. Hepatitis B reactivation in chronic myeloid leukemia patients receiving tyrosine kinase inhibitor. *World J. Gastroenterol*., 2013, **19** : 1318-21.
5. IKEDA K., SHIGA Y., TAKAHASHI A., KAI T., KIMURA H., TAKEYAMA K. *et al*. Fatal hepatitis B virus reactivation in a chronic myeloid leukemia patient during imatinib mesylate treatment. *Leuk. Lymphoma*, 2006, **47** : 155-7.
6. O'BRIEN S., FURMAN R.R., COUTRE S.E., SHARMAN J.P., BURGER J.A., BLUM K.A. *et al*. Ibrutinib as initial therapy for elderly patients with chronic lymphocytic leukaemia or small lymphocytic lymphoma : an open-label, multicentre, phase 1b/2 trial. *The Lancet Oncology*, 2014, **15** : 48-58.
7. HOOFNAGLE J.H. Reactivation of hepatitis B. *Hepatology*, 2009, **49** : S156-65.
8. BORENTAIN P., COLSON P., COSO D., BORIES E., CHARBONNIER A., STOPPA A. M. *et al*. Clinical and virological factors associated with hepatitis B virus reactivation in HBsAg-negative and anti-HBc antibodies-positive patients undergoing chemotherapy and/or autologous stem cell transplantation for cancer. J Viral Hepat, 2010, **17** : 807-15.
9. CAMERON F., SANFORD M. Ibrutinib : first global approval. *Drugs*, 2014, **74** : 263-71.
10. DUBOVSKY J.A., BECKWITH K.A., NATARAJAN G., WOYACH J.A., JAGLOWSKI S., ZHONG Y. *et al*. Ibrutinib is an irreversible molecular inhibitor of ITK driving a Th1-selective pressure in T lymphocytes. *Blood*, 2013, **122** : 2539-49.
11. EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER. EASL Clinical Practice Guidelines : Management of chronic hepatitis B. *J. Hepatol*., 2009, **50** : 227-242.
12. HUI C.K., CHEUNG W.W., ZHANG H.Y., AU W.Y., YUENG Y.H., LEUNG A.Y. *et al*. Kinetics and risk of de novo hepatitis B infection in HBsAg-negative patients undergoing cytotoxic chemotherapy. *Gastroenterology*, 2006, **131** : 59-68.
13. RAIMONDO G., POLLICINO T., CACCIOLA I., SQUADRITO G. Occult hepatitis B virus infection. *J. Hepatol*., 2007, **46** : 160-70.
14. ONOZAWA M., HASHINO S., IZUMIYAMA K., KAHATA K., CHUMA M., MORI A. *et al*. Progressive disappearance of anti-hepatitis B surface antigen antibody and reverse seroconversion after allogeneic hematopoietic stem cell transplantation in patients with previous hepatitis B virus infection. *Transplantation*, 2005, **79** : 616-9.