DOI: 10.4274/vhd.galenos.2024.2024-1-1
Viral Hepatitis Journal 2024;30(1):19-22

Hepatitis B Virus Reactivation with Ibrutinib Treatment in a Patient with Chronic Lymphocytic Leukemia: A Case Report and Literature Review

Kronik Lenfositik Lösemili Bir Hastada İbrutinib Tedavisi ile Hepatit B Virüsü Reaktivasyonu: Olgu Sunumu ve Literatür Değerlendirmesi

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ABSTRACT

Chronic lymphocytic leukemia (CLL) is a common hematological neoplasm in adults with an abnormal increase in monoclonal B lymphocytes. Ibrutinib is a small molecule class oral cancer drug that inhibits Bruton's tyrosine kinase (BTK) enzyme. They are widely used for treating CLL. Ibrutinib suppresses peripheral lymphocytes, causing both lymphopenia and neutropenia. It has little effect on serum immunoglobulin levels and reportedly does not cause reactivation of tuberculosis or opportunistic infections. Hepatitis B prophylaxis during treatment remains controversial. However, there have been cases of acute liver failure and severe hepatitis B reactivation associated with its widespread use. In this case report, we report a patient with no previous history of immunosuppressive therapy who developed hepatitis B reactivation in the early period after ibrutinib treatment for CLL.

Keywords: Chronic lymphocytic leukemia, ibrutinib, hepatitis B, reactivation

ÖZ

Kronik lenfositik lösemi (KLL), monoklonal B lenfositlerde anormal artışla seyreden ve yetişkinlerde sık görülen hematolojik bir malignitedir. İbrutinib, Bruton tirozin kinaz enzimini inhibe eden küçük molekül sınıfı bir oral kanser ilacıdır. Günümüzde KLL tedavisinde yaygın olarak kullanılmaktadır. İbrutinib, periferik lenfositleri baskılayarak hem lenfopeniye hem de nötropeniye neden olur. Serum immünoglobulin düzeyleri üzerinde çok az etkisi vardır ve tüberküloz veya fırsatçı enfeksiyonların yeniden aktivasyonuna neden olmadığı bildirilmektedir. Tedavi sırasında Hepatit B profilaksisi tartışmalıdır. Ancak, yaygın kullanımı ile birlikte akut karaciğer yetmezliği ve ciddi hepatit B reaktivasyonu olguları bildirilmiştir. Bu olgu sunumunda, daha önce immünosüpresif tedavi öyküsü olmayan ve KLL için ibrutinib tedavisi sonrası erken dönemde hepatit B reaktivasyonu gelişen bir olgu bildirilmektedir.

Anahtar Kelimeler: Kronik lenfositik lösemi, ibrutinib, hepatit B, reaktivasyon

Cite this article as: Altunçekiç Yıldırım A, Kurt C, Ülküden B, Çetinkol Y. Hepatitis B Virus Reactivation with Ibrutinib Treatment in a Patient with Chronic Lymphocytic Leukemia: A Case Report and Literature Review. Viral Hepatitis Journal 2024;30(1):19-22

Introduction

Chronic lymphocytic leukemia (CLL) is the most commonly observed hematological neoplasia in adults and is characterized by an abnormal increase in the mature appearance of small monoclonal B lymphocytes in peripheral blood, bone marrow, or lymphoid tissue. Ibrutinib is a cancer medication in the small molecule class that is used orally and displays an effect by inhibiting Bruton's tyrosine kinase (BTK). An essential component

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of the B-cell receptor signal path, BTK enzyme is essential for B-cell proliferation and survival of leukemic cells (1). In the United States, it was approved for refractory mantle cell lymphoma in 2013 and for the treatment of refractive CLL in 2014. Side effects are common but usually mild to moderate. Elevated liver enzyme levels may be observed at 20-30% rates; however, this is generally self-limiting. Ibrutinib suppresses peripheral lymphocytes, causing both lymphopenia and neutropenia, has minimal effect on serum immunoglobulin levels, and is not associated with reactivation of tuberculosis or opportunistic infections (2). However, acute liver injury cases are reported, like acute liver failure and severe hepatitis B virus (HBV) reactivation, have been reported with the popularization of their use. In this case report, we present a patient with a CLL diagnosis who began ibrutinib treatment with no previous immunosuppressive treatment and developed HBV reactivation in the early period.

Case Report

A 70-year-old male patient was diagnosed with modified RAI system staging stage 4 high risk, Binet stage C CLL from the hematology clinic in July 2019. There were accompanying progressive bone marrow failure symptoms, widespread lymphadenopathy, and massive splenomegaly. Follow-up and treatment could not be provided because the patient did not come for clinical check-ups until May 2020. The patient's incomplete examinations were completed on this date, and 420 mg/day ibrutinib treatment was initiated. Fluorescence *in situ* Hybridization deletion 17 p negative. Ibrutinib was chosen as the treatment because of its ability to use oral medication during the pandemic and the accompanying chronic obstructive pulmonary disease. In the comparative evaluation of thoracic and abdominal computed tomography performed in July 2019 (diagnosis) and June 2020, a regression in lymph node size of 50% was detected and was considered a partial response.

In the past medical records of the patient, hepatitis B surface antigen (HBsAg) was negative and anti-HBs was positive. The anti-HBc IgG test was not available. The patient's Infectious Diseases Polyclinic evaluation was only possible at the end of June. The control serology is shown in Table 1. HBsAg positive, anti-HBs negative, hepatitis B e antigen positive (previously negative), and HBV-DNA 8.28 105 international unit (IU)/mL (Roche Light Cycler® 480, Roche Molecular Systems, Inc., Branchburg, NJ). Were detected in control tests. Liver function tests were normal during this period. The patient began antiviral treatment with tenofovir alafenamid fumarate. The patient did not attend follow-up examinations on the recommended dates. Medication compliance was poor according to the anamnesis and prescription dates. Serologic follow-up revealed dynamic changes. HBV-DNA negativity under treatment was observed at the end of the second year. The patient was last evaluated in September 2023. Antiviral drug use continued and HBV-DNA was found to be negative.

Discussion

Patients infected with hepatitis B may have reactivation observed during immunosuppressive treatment or when these treatments are stopped and the immune system returns to normal. The risk of HBV reactivation in patients receiving immunosuppressive therapy is related to the HBV serological status, viral load, underlying disease, type, dose, and duration of the immunosuppressive agent used. The most common HBV reactivations are reported in patients receiving chemotherapy because of hematological malignancies and in patients undergoing hematopoietic stem cell transplantation (3). In terms of reactivation, situations increasing risk are male sex,

Table 1. Hepatitis serology follow-up

Tarih	HBsAg (ng/mL)	Anti-HBs (IU/L)	HBeAg (S/CO)	Anti-HBe (S/CO)	Anti-HBc IgM (S/CO)	Anti-HBc IgG (S/CO)	HBV-DNA (IU/mL)	ALT/AST (U/L)
02.01.2019	0.716 (negative)	**17.08 (positive)**	0.134 (negative)	1.63 (positive)				
02.07.2019	0.546 (negative)	**26.48 (positive)**						
08.06.2020	**7.21 (positive)**	**222.6 (positive)**	**129.0 (positive)**		**0.064 (positive)**	**0.735 (positive)**		10/25
30.06.2020	**4.91 (positive)**	**292.7 (positive)**	**58.60 (positive)**	**1.86 (positive)**	**0.065 (positive)**	**0.177 (positive)**	**$8.28x10^5$**	12/20
06.08.2020	**13.09 (positive)**	**215 (positive)**					**$5.69x10^2$**	16/25
13.06.2022	**15.05 (positive)**	4.66 (negative)	**49.19 (positive)**	1.64 (negative)	0.072 (negative)	1.32 (negative)	<1.00 (negative)	
11.09.2022	**9.22 (positive)**	**24.70 (positive)**						54/45
17.04.2023	**6.78 (positive)**	7.06 (negative)						17/25
13.09.2023	**4.39 (positive)**	<2.00 (negative)	**14.94 (positive)**	1.57 (negative)	0.053 (negative)	1.84 (negative)	<1.00 (negative)	18/23

Values in bold to indicate reactivation date and positive values, HBsAg: Hepatitis B surface antigen, HBeAg: Hepatitis B e antigen, HBV: Hepatitis B virus, IU: International unit, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase

Table 2. Reactivation cases related to ibrutinib reported in the literature

References	Diagnosis	Patients (age, sex)	History of İ.T.*	Reactivation time
de Jésus Ngoma et al. (11)	CLL	80, M	+	20 week
Hammond et al. (12)	CLL CLL	57, M 75, M	+ +	42 week 22 week
Malek et al. (13)	NHL	68, M	+	24 week
Herishanu et al. (14)	CLL	79, M	+	48 week
Akkurd et al. (15)	MCL	54, M	+	36 week
İskender et al. (16)	CLL	58, M	+	48 week
Lam et al. (17)	CLL	61, F	+	16 week
Choi et al. (18)	CLL	81, F		12 week

*İ.T.: Immunosuppressive treatment, CLL: Chronic lymphocytic leukemia, NHL: Non-Hodgkin's lymphoma, MCL: Mantle cell lymphoma

advanced age, hepatitis B e antigen (HBeAg), HbsAg positivity, and HBV-DNA elevation. In many guidelines, immunosuppressive treatments are classified in terms of the risk of reactivation and the need for prophylaxis (4,5,6). With the introduction of many new agents, the issue of HBV reactivation needs to be updated. There should be a clear recommendation regarding ibrutinib. However, there are increasing numbers of publications reporting the risk of HBV reactivation and recommending serologic tests for HBV before treatment.

The guidelines state the risk of HBV reactivation with the use of tyrosine kinase inhibitors and ibrutinib differently. It is reported as moderate, no, or uncertain (7,8,9). Ibrutinib has been shown to irreversibly inhibit T helper 2 cell activation after T cell receptor stimulation and to cause compensatory activation of T helper cells and cytotoxic T lymphocytes (10). This dynamic change in the immune response after ibrutinib treatment may be a clue for HBV reactivation in this setting. However, these mechanisms remain unclear. Case reports of reactivation with ibrutinib are increasing (11,12,13,14,15,16,17,18) (Table 2). When the cases were evaluated, most patients were over 50 years of age and mostly male. Except for two patients with non-Hodgkin's lymphoma and mantle cell lymphoma, all patients were diagnosed with CLL and had a history of immunosuppressive treatment before ibrutinib. Our patient was similar to these patients in terms of CLL diagnosis and age. The fact that our patient was HBsAg negative, anti-HBc IgG and anti-HBsAg positive, HBeAg negative, and anti-HBe positive has been shown to be included in the natural immune profile. Patients who receive immunosuppressive treatment with HBsAg positivity have a higher risk of reactivation. As a result, our patient actually had a lower risk of reactivation. In published cases, the mean time between the use of ibrutinib and the determination of reactivation was 34 weeks (20-48 weeks). In this patient, the interval between ibrutinib initiation and HBsAg positivity was 34 days. We believe that the advanced stage of the patient's primary disease and the late initiation of treatment are the reasons for the short duration of this period.

Dynamic changes in hepatitis serology in the patient are also noticeable. HBsAg became positive, anti-HBs became negative, and anti-HBc IgG became negative in the follow-up. Anti-HBc is a sensitive and widely used marker for detecting HBV exposure. Hepatitis B core antigen is not normally found in serum. It occurs in liver cells or HBV particles in serum. It triggers the humoral and cellular immune response and leads to anti-HBc. Anti-HBc negativity may result from immunosuppression, core promoter gene mutations, infection by vertical transmission, and analytical test errors (19,20). This rare serological condition was evaluated by Avettand-Fenoel et al. (21) in 39 patients, and it was reported that HBsAg detection without HBc antibodies may occur in highly immunocompromised patients. We believe that HBV serology and HBV-DNA requirement should be carefully evaluated in immunosuppressed patients. Hepatitis B reactivation is usually recognized by an increase in serum alanine aminotransferase or aspartate aminotransferase levels with or without symptoms. It is characterized by an earlier increase in HBV-DNA frequency. With awareness of serologic variations in our patient, HBV-DNA was requested and it was identified as 8.28x10.5 IU/mL. Check-up serology observed HbsAg positivity and HBeAg positivity. We think that beginning antiviral treatment before liver function tests prevented active hepatitis. The moderate increase observed at follow-up may be related to additional factors and drug compliance problems.

Conclusion

In conclusion, although there are cases reported in the literature, we believe that this case is the most clear example that indicates the ibrutinib-reactivation relationship. Our patient did not receive immunosuppressive therapy before, and reactivation developed after short-term use. Therefore, we believe it is appropriate to assess the hepatitis serology of patients before ibrutinib treatment and to begin prophylactic treatment in the patient group with contact with the HBV.

Ethics

Informed Consent: Informed consent form was obtained.

Authorship Contributions

Surgical and Medical Practices: A.A.Y., C.K., B.Ü., Y.Ç., Concept: A.A.Y., C.K., Design: A.A.Y., C.K., Data Collection or Processing: A.A.Y., C.K., B.Ü., Analysis or Interpretation: A.A.Y., C.K., B.Ü., Literature Search: A.A.Y., C.K., Writing: A.A.Y., C.K.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declare no financial support.

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