Ribavirin for Chronic Hepatitis E Virus Infection in Ibrutinib-Exposed Patients

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Ibrutinib is an oral first-in-class Bruton's tyrosine kinase inhibitor approved for the therapy of various B-cell lymphoid malignancies. Among ibrutinib-related infections, viral hepatitis are poorly described. We report our single-center experience with 4 cases of chronic hepatitis E virus infection and their management with ribavirin.

Keywords. hematological malignancies; hepatitis E virus; ibrutinib; immuno-deficiency; ribavirin.

Hepatitis E virus (HEV) is a ribonucleic acid (RNA) virus mainly transmitted by the fecal-oral route. Hepatitis E virus is a major cause of viral hepatitis in developing countries and is highly prevalent in our area (seroprevalence of anti-HEV antibodies being 52.5% among blood donors [1]). Hepatitis E virus infection is generally associated with self-limiting acute hepatitis, without persistence of latent virus in hepatocytes. Yet, HEV genotypes 3 and 4 might develop into chronic infection in solid organ transplant recipients, leading to cirrhosis. Ribavirin is considered the standard treatment of chronic HEV in solid organ recipients, and it is also highly effective when initiated at the acute phase in patients with hematological malignancies [2].

Ibrutinib is an oral tyrosine kinase inhibitor targeting the Bruton tyrosine kinase, activated downstream the B-cell receptor, but also some Toll-like receptors and chemokine receptors, therefore affecting both tumoral and normal immune cells activation (including T and B cells, macrophages, natural killer

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cells, neutrophils, basophils, and eosinophils) [3]. This therapy is now considered to be the gold standard therapy for relapsed chronic lymphocytic leukemia (CLL), and it is also increasingly used in the first-line setting. Both in the context of registration trials and real-world evidence, serious infections are common, up to 56% of patients in a large meta-analysis (20% of which were pneumonia) [4], leading to permanent treatment discontinuation in 11% of patients. Viral hepatitis is not only underreported in published clinical trials, but also in the largest single-center experience of 412 ibrutinib-exposed patients reported so far [5], which found only 2 reactivations of hepatitis B virus (HBV) (9.5%) among 21 patients with past HBV infection (and thus at risk of reactivation) [6]. In this study, we report our single-center experience of 4 cases of HEV infection, which occurred in CLL patients exposed to ibrutinib (1 in the frontline and 3 in the relapse setting).

METHODS

One hundred fifty consecutive patients with CLL received ibrutinib in our institute from 2014 to 2019. Local monitoring included a twice-monthly assessment of whole blood counts, transaminases, bilirubin, and creatinine levels from initiation of ibrutinib to 3 months, then monthly for months 3 to 6, and then every 3 months thereafter. All patients with abnormal liver blood tests (4 of 150) were tested for viral hepatitis in the laboratory of Virology of the University Hospital of Toulouse, France, which is the French Reference Center for hepatitis E virus (HEV). Serology for HEV was performed using the HEV immunoglobulin (Ig)M and IgG kits from Wantai (Wantai Biological Pharmacy Enterprise Co., Beijing, China). Hepatitis E virus RNA was detected in plasma samples by real-time reverse transcription-polymerase chain reaction (RT-PCR) as previously described [5]. Limit of detection of HEV RT-PCR is $2 \log_{10}$ copies/mL. Sequencing of the ORF2 region of HEV indicated that all of the HEV samples were HEV 3.

RESULTS AND DISCUSSION

Characteristics of our patients are summarized in Table 1. Overt HEV infection was diagnosed early after ibrutinib initiation (2–6 months). Patient no. 3 had a preexisting history of chronic HEV infection and received ribavirin therapy for 3 months (1 month before ibrutinib initiation, he had no detectable plasmatic HEV viral load by PCR). Ibrutinib was deemed mandatory for the management of CLL by the referent hematologist; therefore, per our published algorithm [7], we started ribavirin very early because immunosuppression could not be withheld. The median time between HEV diagnosis and initiation of

Table 1. Main Characteristics of Patients and of HEV Infection

	Patient No. 1	Patient No. 2	Patient No. 3	Patient No. 4
Gender/age (years)	Male/76	Male/59	Female/76	Female/68
Lines of therapy for CLL before ibrutinib initiation (previous drugs received)	6 (rituximab, alkylating agents, purine analogs, idelalisib)	2 (rituximab, alkylating agents, purine analogs)	4 (rituximab, alkylating agents, purine analogs, idelalisib)	0
Time interval ibrutinib-diagnosis of HEV (months)	6	5	3	2
Cause for PCR viral screening	Systematic liver blood tests abnormalities			
AST (N < 31 IU/L)	243	41	159	47
ALT (N < 59 IU/L)	286	95	166	64
ALP (46–116 IU/L)	157	295	533	73
Bilirubin (N: 3–17 mol/L)	14.8	42.9	28	8
PT (%)	96%	79%	96%	ND
Factor V (%)	ND	ND	ND	ND
Anti-HEV IgG/IgM	−/−	−/+	+/−	+/−
Plasma HEV RNA viral load (log_{10} copies/mL)	6.89	7.76	6.63	5.06
Stools HEV RNA	+	+	ND	ND
Genotype of HEV	3f	3f	3h	3c
Time interval diagnosis of HEV-ribavirin initiation (days)	48	21	4	9
Dose of ribavirin at initiation (mg/kg per day)	5.3	4.6	7.5	11.5
Dose modifications of ribavirin (mg/kg per day)	8	8.1	No	No
HEV viral load after 3 months of ribavirin (log_{10} copies/mL)	2.9	5.72	<2	<2
HEV viral load decline after 3 months of ribavirin (log_{10} copies/mL)	3.83	1.89	>4.63	3.06
HEV viral load at last follow-up (log_{10} copies/mL)	Undetectable	Undetectable	6.15	Undetectable
Duration of ribavirin (months)	9	7	8	3
Outcome of HEV infection	Persistent	SVR	Relapse	SVR
Patient status (February 2019)	Deceased from second cancer (aggressive cutaneous T-cell lymphoma)	Deceased from pulmonary embolism	Deceased from bacterial infection with septicemia	CLL partial response, still taking ibrutinib

Abbreviations: ALP, alkaline-phosphatases; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CLL, chronic lymphocytic leukemia; γGT, gammaglutamyl-transferases; HEV, hepatitis E virus; Ig, immunoglobulin; ND, not done; PCR, polymerase chain reaction; PD, progressive disease; PT, prothrombin time; RNA, ribonucleic acid; SVR, sustained virological response.

ribavirin was 15 days (range, 4–48 days). The ribavirin dose at initiation varied from 400 to 800 mg/day according to weight, renal function, and hemoglobin level, and ribavirin was further adapted during the follow-up with a median dose of 8 mg/kg per day to maintain adequate hemoglobin count over 11 g/dL. Plasma HEV-RNA viral load was monitored during and after ribavirin therapy. We observed a slow plasma HEV-RNA viral load decline in patient no. 1 and patient no. 2 with persistence of detection of HEV RNA in plasma after 3 months of ribavirin despite normalization of transaminases after 1 and 2 months, respectively. In patient no. 2 and patient no. 4, ribavirin was continued until HEV viral load was undetectable. Ribavirin therapy was interrupted after 7 months and 3 months, respectively. Hepatitis E virus clearance was slower in patient no. 2 and obtained after increased ribavirin dose. Sustained virological response was confirmed in both patient no. 2 and patient no. 4 three months after ribavirin discontinuation. In patient no. 3, we observed a relapse of HEV infection at ibrutinib introduction. Ribavirin allowed HEV clearance after 8 months of therapy with sustained virological response 4 months after ribavirin cessation. Unfortunately, the patient relapsed without elevation of transaminases. Ribavirin therapy was not reintroduced because of asymptomatic infection and CLL progression. Patient no. 1 received 2 months of pegylated interferon, for the management of an aggressive cutaneous T-cell lymphoma (not associated to CLL), allowing eradication of detectable plasma HEV RNA at the last sampling before cancer-related death.

There was no unexpected side effect related to the combination of ribavirin and ibrutinib. As expected, anemia was the major dose-limiting toxicity, although not preventing patients from reaching 400–800 mg of ribavirin daily (median 600 mg, 8 mg/kg). Ibrutinib was not discontinued in all of our patients, yielding partial responses for CLL.

To our knowledge, these 4 patients are the first case series of HEV infections occurring in ibrutinib-exposed patients, outside a case report successfully treated with ribavirin (also in a French patient) [8]. Although 8%–14% of ibrutinib-treated patients across registration trials experienced elevation of

transaminases, usually mild in severity (grade 1–2), HEV detection was not part of the diagnostic work-up. The French Temporary Authorization for Use safety database (585 patients, 428 CLL and 157 mantle cell lymphoma) found only 1 case of HEV infection [9]. In our area, the incidence of HEV infection in solid organ transplantation recipients was of 3.2 cases per 100 person-year [10], very similar to our cohort of ibrutinib-treated patients (2.9 cases per 100 person-year). Therefore, HEV infection should be screened by PCR in plasma facing liver blood tests abnormalities in ibrutinib-treated patients, especially in endemic areas for HEV. The burden of HEV infection is expected to increase in patients treated for (1) hematological malignancies and (2) acute infection often evolving to chronic hepatitis; a high rate of morbidity and both hepatic and nonhepatic mortality are also expected to increase [11]. According to the risk factors reported in the latter series, all patients with relapsed CLL also received rituximab and alkylating agents before ibrutinib, but none underwent allogeneic stem cell transplantation or received blood transfusions before ibrutinib.

Optimal management of HEV infection in ibrutinib-treated patients is unknown. In solid organ transplant recipients, a low $CD4^+$ T-cell count was predictive for chronic hepatitis, and tapering of immunosuppression enabled HEV clearance in one third of cases. Alleviation of ibrutinib requires caution, in accordance to drug reductions recommendations. A 3-month course of ribavirin induced sustained HEV eradication in patients with hematological malignances not treated by ibrutinib [2]. Yet, unexpected poor response to ribavirin was observed after 3 months of treatment in 2 patients from our series, suggesting that dose reductions of ibrutinib could be mandated (instead of starting with low-dose ribavirin, which was associated with a reduced sustained virological response rate in the stem cell transplantation setting [2]) to avoid unwanted side effects. Still, ribavirin allowed normalization of transaminases levels after 3 months in both patients, which is an important endpoint to avoid evolution towards liver fibrosis.

Ibrutinib provides durable remissions in CLL, by disrupting tumor microenvironment, modulating the T-cell compartment, and altering the cytokine milieu. These antitumoral effects come along with an increased risk of opportunistic infections and viral reactivations. Despite being nonmyeloablative, this drug undoubtedly hampers adequate adaptive and innate immunity very early (as exemplified by rapid onset invasive fungal infections without neutropenia), presumably blunting antiviral responses and favoring persistence of HEV. On one hand, ibrutinib prevents migration of innate immune cells towards inflamed sites, reduces secretion of inflammatory cytokines, and decreases both establishment of specific $CD4^+$ and $CD8^+$ T-cell responses and serological responses against a wide variety of pathogens (including aspergillus, influenza, pneumococcus, JC virus) [12]. On the other hand, ibrutinib also partially restores immune defects induced by CLL after 6 months of therapy, avoiding long-lasting immunosuppression of chemotherapy or bone marrow transplantation.

CONCLUSIONS

In conclusion, prescribing physicians should be aware of the risk of chronic HEV infection in ibrutinib-exposed patients. Liver blood tests should be thoroughly monitored, and HEV-RNA detection should be part of the molecular workup of any abnormalities. Ribavirin coadministration with ibrutinib is safe, but the dose could be potentially constrained by pre-existing anemia. However, prolonged treatment may be required, due to a potential poor response of HEV to ribavirin in the first months of ibrutinib therapy, as we discovered in our series. Whether alleviation of ibrutinib is mandated in patients needing ribavirin therapy requires further investigation.

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