Venetoclax for treating refractory autoimmune hemolytic anemia in chronic lymphocytic leukemia: report of two cases in Spain

Chronic lymphocytic leukemia (CLL) is often associated with autoimmune complications. Indeed, autoimmune cytopenias (AIC) such as autoimmune hemolytic anemia (AIHA), immune thrombocytopenia (ITP), pure red cell aplasia and autoimmune granulocytopenia may be present in 5% to 9% of CLL patients.[1,2] Among the different AIC, AIHA is the most prevalent in CLL patients.[1] AIC refractory to steroids supose a criteria of treatment in patients with CLL according to iwCLL18.[3]

In the era of patient-tailored approach therapies, some targeted drugs such as ibrutinib, acalabrutinib, idelalisib, and venetoclax have been used in CLL treatment. There is evidence reporting positive outcomes in patients with preexisting AIC, especially with ibrutinib, an irreversibly inhibitor of the Bruton tyrosine kinase.[2,4] Regarding B-cell lymphoma 2 (BCL-2) inhibitors, there is little evidence of about their use in CLL-associated autoimmune cytopenias.[2] To our knowledge, no clinical trials have directly studied the role of these novel signal inhibitors in the management of AIC in patients with CLL.[1]

The current paper aims to present two patients with CLL who developed AIHA and underwent treatment with the BCL-2 inhibitor venetoclax.

Case 1

A 63-year-old woman diagnosed with CLL in May 2014, without alterations in fluorescence *in situ* hybridization (FISH), normal karyotype, wild-type *TP53* and unknown immunoglobulin heavy chain (IGHV). In March 2016, the patient developed non-autoimmune anemia (hemoglobin: 8.5 g/dL) and splenomegaly (18.7 cm) that was treated with a total of six cycles of fludarabine, cyclophosphamide, and rituximab (FCR), achieving complete remission for 4 years. In September 2021, she presented a relapse with AIHA (hemoglobin 6 g/dL, lactate dehydrogenase [LDH] 666 UI/L, indirect bilirubin 3.04 mg/dL) and IgG C3d in direct Coombs test, associated with generalized lymphadenopathy, and hepatomegaly (17 cm) and splenomegaly (20 cm). After not responding to the first-line treatment with corticosteroids (1 mg/kg/day of prednisone), the patient began treatment with venetoclax plus rituximab according to the MURANO trial scheme.[5]

To date, the administration of venetoclax has been maintained at a dose of 400 mg per day. At the last follow-up visit (December 10, 2022), the patient has shown complete remission according to iwCLL 2018,[3] over the 16 months of follow-up. There has been a clinically significant improvement, with normalization of red blood count (13.2 g/dL of hemoglobin) (Figure 1), biochemical parameters (LDH 232 UI/L, indirect bilirubin 0.8 mg/dL), and resolution of lymphadenopathy and hepatosplenomegaly; without relevant adverse effects. Table 1 summarizes the main clinical outcomes.

Case 2

A 70-year-old man diagnosed with CLL in May 2016, with chromosome 13q deletion. He presented an episode of AIHA, serum hemoglobin of 8.5 g/dL (IgG in direct Coombs test), refractory to corticosteroids (1 mg/kg/day of prednisone) that responded to rituximab (375 mg/m^2 per week for 4 weeks), reaching levels of 15 g/dL. In June 2018, there was a worsening of the disease, with a general deterioration of his performance status and relapsed AIHA, that was treated with the combination of obinituzumab-chlorambucil.[7] After the first dose of obinutuzumab, the patient suffered worsening of AIHA, with hemoglobin of 5.1 g/dL, LDH 331 UI/L and indirect bilirubin of 2.89 mg/dL, and non–ST-elevation acute myocardial infarction, which led to obinutuzumab withdrawal. The patient started treatment with corticosteroids plus rituximab (4 cycles) that led to a complete remission according to iwCLL 2018.[3]

In April 2020, the patient presented a relapsed of AIHA, with hemoglobin 6.9 g/dL, LDH 318 UI/L, indirect bilirubin 1.5 mg/dL and IgM C3d in direct Coombs test, refractory to corticoids (prednisone 1 mg/kg/day). Unmutated IGHV and wild-type *TP53* were determined, so venetoclax plus rituximab was started following the same scheme aforementioned.[5]

The patient has remained asymptomatic for 32 months with the combination of venetoclax plus rituximab. At the last follow-up visit (December 14, 2022), the patient showed complete remission of the disease, with normalization of red blood count (14.6 g/dL of hemoglobin) (Figure 2) and biochemistry parameters (LDH 196 UI/L and indirect bilirubin 0.55 mg/dL), without adverse effects (Table 1).

Discussion

Sometimes the diagnosis of AIHA in CLL patients can be difficult due to hemolysis findings in blood counts or biochemical tests may be distorted in CLL due to disease progression or therapy.[1]

The development of targeted therapies for treating AIHA in CLL patients is continuously evolving.[8] To date, there is not enough evidence to recommend one or another in CLL-as-

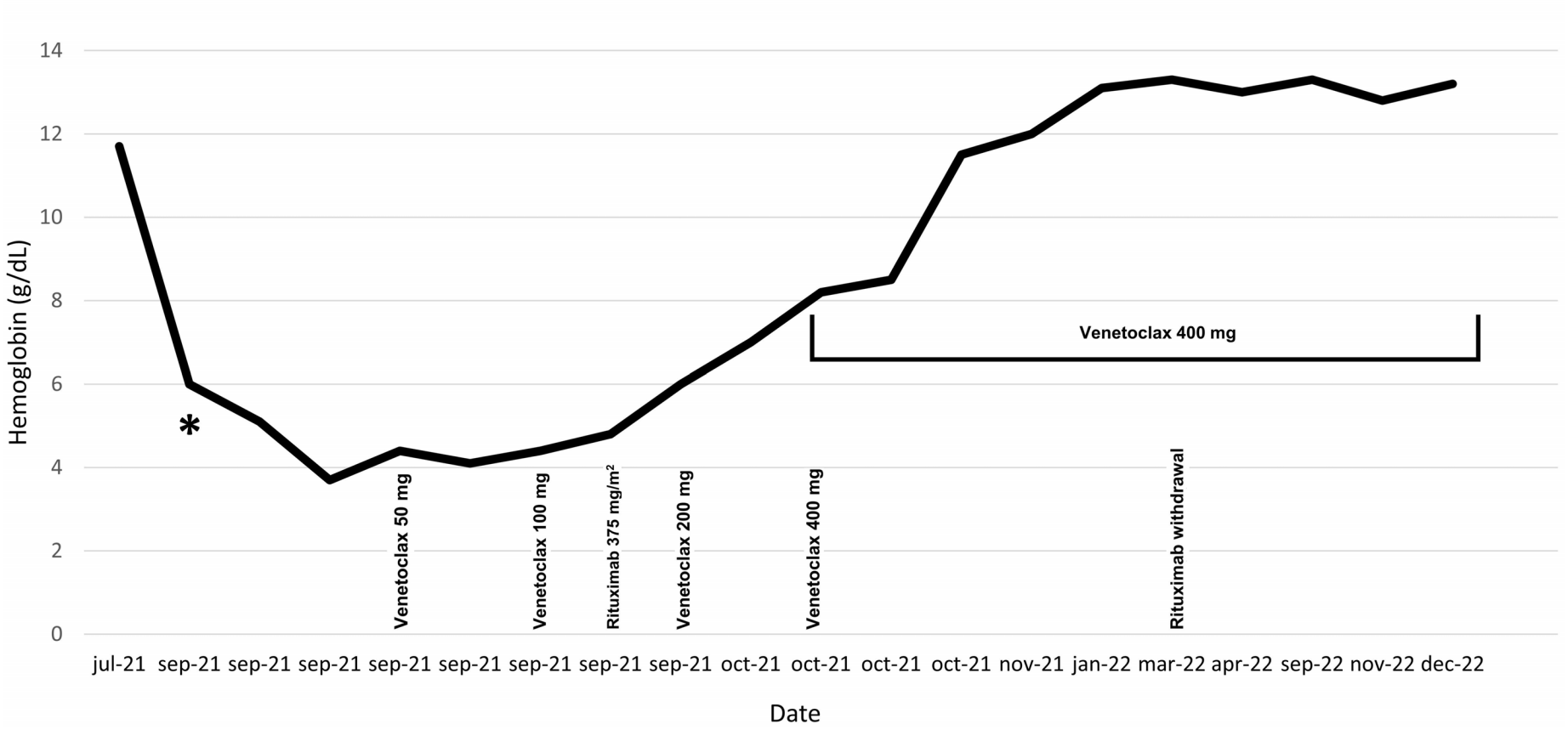

Figure 1. Evolution of hemoglobin levels and associated treatments of a 63-year-old woman diagnosed with chronic lymphocytic leukemia throughout the patient follow-up. *Autoimmune hemolytic anemia presentation. Prednisone 1 mg/kg/day + venetoclax ramp up (20 mg). jul: July; sep: September; oct: October; nov: November; jan: January; mar: March; apr: April; dec: December.

Table 1. Overview of the main clinical characteristics and outcomes of the two clinical cases and their comparison with Lacerda *et al.*[6]

Patient	Age in yrs	Sex	FISH	IGHV	*TP53*	Type of AIHA	N of previous lines for CLL	Regimen	Best response	Progression-free survival in mth
1	68	F	neg	NA	WT	IgG C3d	1	Venetoclax + rituximab	CR	16
2	70	M	del 13q	un	WT	IgM C3d	1	Venetoclax + rituximab	CR	32
3[6]	63	M	del 17p	NA	NA	IgG C3d	2	Venetoclax	CR	10

Yrs: years; FISH: fluorescence *in situ* hybridization; N: number; mth: months; M: male; F: female; AIHA: autoimmune hemolytic anemia; CLL: chronic lymphocytic leukemia; IGHV: mutational status of immunoglobulin heavy-chain variable; neg: negative; NA: not applicable; WT: wild-type; un: unmutated; CR: complete remission*(*according to the iwCLL2018 criteria[3]).

sociated AIC.[2] Although there is evidence suggesting rapid and durable responses when ibrutinib was used to treat autoimmune cytopenias associated with CLL, clinical experience with idelalisib or venetoclax is limited.[2,9]

The current paper describes two patients diagnosed with CLL that present a refractory AIHA crisis, who were successfully managed with venetoclax in combination with rituximab in second-line therapy.

Apart from the Lacerda *et al.*[6] paper, these are the only clinical cases demonstrating the efficacy and safety of venetoclax in refractory AIHA in patients with CLL. In addition, venetoclax has been shown to be effective in treating multiple-refractory idiopathic thrombocytopenic purpura and Evans syndrome in two patients with CLL[10] and in other two patients with not-specified pre-existing AIC.[2]

Some cases of treatment emergent AIC were reported after treatment with these new targeted drugs,[2,8,11,12] with two cases of treatment-emergent AIC in CLL patients during treatment with venetoclax in monotherapy.[11,12] However, it has been recently pointed out that treatment-emergent AIC during administration of targeted drugs is manageable in most patients without interruption of treatment.[2]

Venetoclax is a molecule, capable of binding and antagonizing BCL-2 family anti-apoptotic proteins by mimicking the BH3 domain of pro-apoptotic proteins.[13] Venetoclax is strongly cytotoxic to CLL lymphocytes due to the high ex-

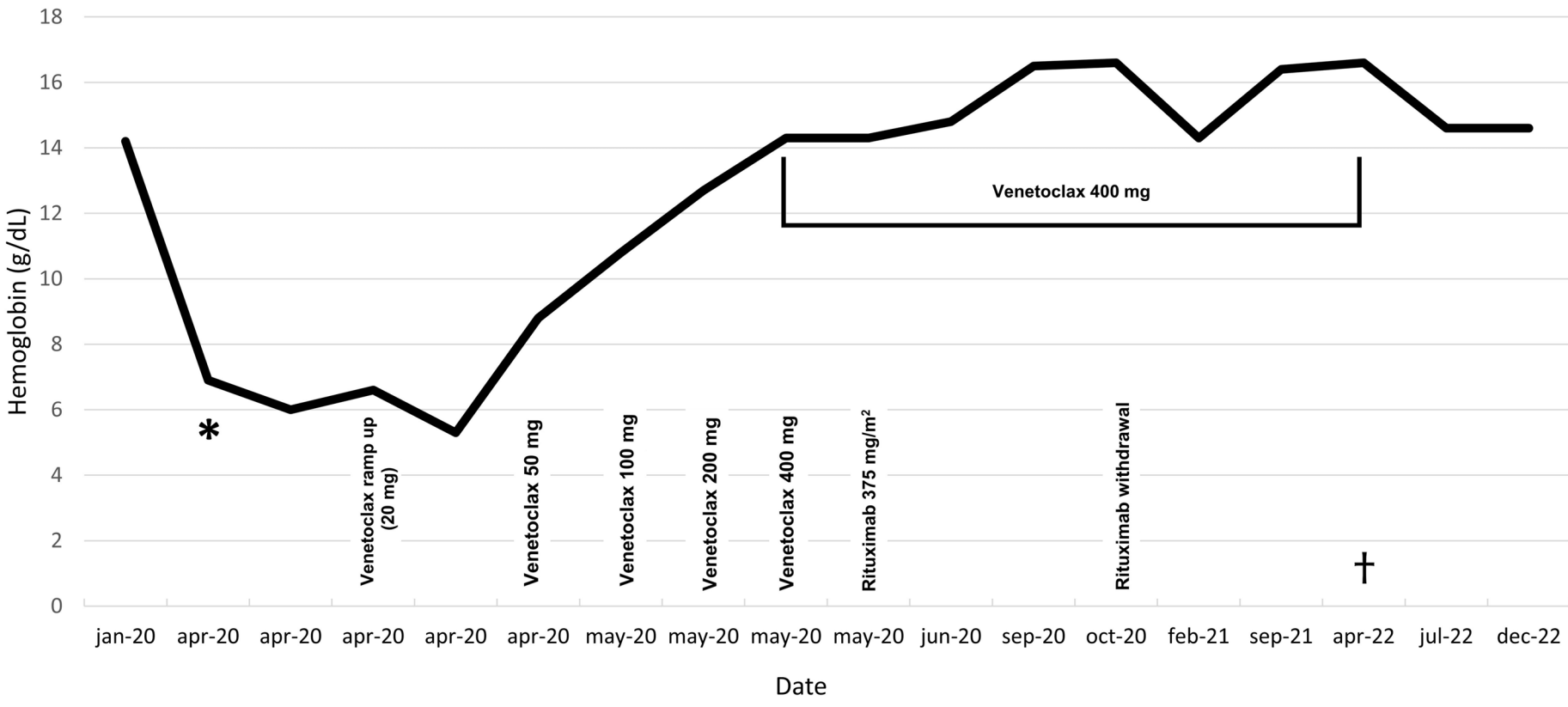

Figure 2. Evolution of hemoglobin levels and associated treatments of a 70-year-old man diagnosed with chronic lymphocytic leukemia throughout the patient follow-up. *Autoimmune hemolytic anemia presentation. Prednisone 1 mg/kg/day. †End venetoclax scheme. Jan: January; apr: April; may: May; jun: June; sep: September; oct: October; feb: February; jul: July, dec: December.

pression levels of BCL-2 family proteins.[14] That could be the reason why venetoclax can easily control a first-time AIHA crisis. The microenvironment plays a big part in CLL pathogenesis and is AIHA related. CLL cells process and present red blood antigen to T cells that will induce a formation of polyclonal antibodies by normal B cells against erythrocytes.[15] Furthermore, CLL cells loose tolerance to cytokine inhibition by the innate system.[15] For that reason, the leukemic microenvironment induces some kinds of resistance mechanisms to venetoclax, which are either CD40 ligand resistance or BCL-XL expression.[14] These mechanisms can be overcome by anti-CD20 antibodies without affecting the expression of BCL-2 family proteins.[14] It is only a hypothesis, but could be the pathophysiology mechanism why these two cases are responding to venetoclax in combination with rituximab. Moreover, this combination showed a good safety profile. As observed in the MURANO trial, only three patients in the venetoclax-rituximab arm required treatment withdrawal.[2,7]

Despite the good results obtained in our patients, further prospective studies are needed to identify the best profile and the best targeted drug or combination for CLL patients with AIHA.

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Contributions

PG-N developed the concept, visualized the research, analysed data, supervised the project and wrote the original draft. AD-G developed the concept and methodology, and visualized the research. MÁR-G analyzed data, was responsible for project administration, developed the methodology, and reviewed and

edited the manuscript. JMP-P acquired funding, was responsible for project administration, supervised the research, and reviewed and edited the manuscript.

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Data-sharing statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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