Dear Editor,

Autoimmune cytopenias are a frequently encountered complication of chronic lymphocytic leukemia (CLL). Here we report, for the first time, the successful use of venetoclax in the treatment of 2 patients with refractory immune thrombocytopenia (ITP).

CLL manifests as a clonal proliferation of CD5+, mature B-lymphocytes involving the peripheral blood, lymphatic organs, and bone marrow. Autoimmune cytopenias are observed in 5% to 10% of patients with CLL, and may precede, occur at time of diagnosis or develop as a complication of therapy. Autoimmune hemolytic anemia (AIHA) and ITP are the most common autoimmune events. Evans syndrome, concurrent AIHA and ITP, occurs in <1% of patients with CLL.1 Front-line therapy consists of corticosteroids with or without anti-CD20 antibody rituximab for both AIHA and ITP. Additionally, intravenous immunoglobulin is an effective treatment for ITP.2 In patients where corticosteroids are ineffective, or additional indications to treat CLL are present, chemoimmunotherapy (CIT) regimens may lead to resolution of autoimmune cytopenias.3 Several small case series4 have demonstrated safety and moderate efficacy with the Bruton tyrosine kinase (BTK) inhibitor ibrutinib.1-4 By contrast, the BCL2 inhibitor venetoclax has not been studied in treatment of AIHA or ITP.

Venetoclax is approved by the US Food and Drug Administration and European Medicines Agency for the treatment of relapsed/refractory (r/r) CLL. US indications include patients with or without del(17p) who have received one prior line of therapy, while in Europe, venetoclax is approved as a single agent in patients with del(17p) or TP53 aberrancy who have progressed or are not candidates for BTK inhibitors, or in patients who have progressed after CIT and BTK inhibitor. In a phase II trial of 158 patients with r/r CLL, the objective response rate with venetoclax was 77%. AIHA was reported in 5% of patients on study while ITP was not reported.5 We are not aware of any reports of ITP treated with venetoclax, and only 1 case report of AIHA treated with venetoclax.6 Here we present our experience with venetoclax in 2 patients with CLL and refractory autoimmune cytopenias, one with ITP and the other with Evans syndrome.

Patient 1 was a 54-year-old man diagnosed with CLL in August of 2016 after presenting with fever, night sweats, and abnormal blood counts (Fig. 1). White blood cells (WBC) were 82 × 10^9/L (normal 3.5–10.8 × 10^9/L), absolute lymphocyte count (ALC) 80 × 10^9/L (normal 1.0–4.8 × 10^9/L), hemoglobin 8.3 g/dl (normal 13.5–17.5 g/dl), and platelets 36 × 10^9/L (normal 150–400 × 10^9/L). Lactate dehydrogenase (LDH) and Coombs tests were normal/negative. Flow cytometric evaluation of peripheral blood demonstrated a population of CD5, CD19, CD20, and CD23 positive cells which were kappa restricted. Fluorescent in situ hybridization (FISH) demonstrated del(11q) in 21.5% of the cells. Further studies revealed presence of a complex karyotype. He received experimental therapy with a combination of CD20 antibody and PI3K inhibitor. Treatment was discontinued due to adverse events after 10 months. Platelets were 205 × 10^9/L at the start of therapy and remained in normal range. In November 2017, he presented with undetectable platelets consistent with ITP and was treated with IVIG and dexamethasone (40 mg daily) for 4 days. Platelets increased to 32 × 10^9/L. Bone marrow biopsy demonstrated a hypercellular marrow (80%) with residual trilineage hematopoiesis, increased megakaryocytes and extensive involvement by CLL (60–70% of total marrow cellularity). One month later, he returned with undetectable platelets and was treated with high-dose methylprednisolone 1 g/m^2 for 3 days and rituximab. Platelets remained undetectable and R-CVP was started with a long steroid taper. He completed 5 cycles of R-CVP; however, ITP relapsed after steroids were tapered off and he underwent splenectomy. After initial normalization of platelet count, he developed thrombocytopenia within 2 months (23 × 10^9/L). Venetoclax was started in July 2018 at standard ramp-up reaching 400 mg daily without clinical or laboratory tumor lysis syndrome. Platelet count recovered within 3 weeks (during ramp-up dosing). Six months later, patient remains in complete remission on venetoclax, and platelet count is within normal range (Fig. 1).

Patient 2 was a 34-year-old man diagnosed with CLL and Evans syndrome in February 2017 after presenting with weight...
loss, fatigue, and adenopathy. Labs showed WBC $14 \times 10^9/L$, ALC $9.2 \times 10^9/L$, hemoglobin of 4.4 g/dL, and platelets of $38 \times 10^9/L$ (Fig. 2A, B). Additional labs included undetectable haptoglobin, LDH 539 U/L (normal < 250), elevated indirect bilirubin and negative Coombs test. A high sensitivity Coombs was positive (C3d, polyspecific IgG). FISH demonstrated del (11q) in 14% of the cells. He had unmutated IGHV. Bone marrow biopsy demonstrated low-level involvement (5%) by a monoclonal B-cell population which was CD5, CD19, dim CD20, CD23, and dim kappa positive. CT scan showed diffuse adenopathy and mild splenomegaly. He received blood transfusions and was treated with obinutuzumab (6 cycles) and prolonged steroid taper between February and August 2017. In May 2018, he was again noted to have cytopenias with a hemoglobin of 6.0 g/dL for which he received 2 units of red blood cells, and platelets of $142 \times 10^9/L$. Other labs were significant for undetectable haptoglobin and LDH of 572 U/L. He was treated with prednisone and 4 weekly cycles of rituximab without response. Venetoclax was initiated in June 2018 with a standard ramp-up followed by 400 mg daily. The patient manifested full resolution of anemia within 4 weeks of venetoclax therapy (during ramp-up) and remains in complete remission on therapy 6 months later (Fig. 2A, B).

Relapsed CLL with cytogenetic abnormalities predictive of a poor response to CIT (eg, del(17p)/TP53 mutation, del(11q), complex karyotype and unmutated IGHV) is now routinely treated with targeted agents such as ibrutinib or venetoclax. Autoimmune cytopenias occurring in this setting, particularly when refractory to corticosteroids represent a therapeutic challenge. Newer targeted therapies have not been well studied for treatment of AIHA or ITP. While some reports suggested that ibrutinib, a BTK inhibitor, may be efficacious in treatment of autoimmune cytopenias, others documented that AIHA/ITP may emerge in patients receiving ibrutinib. Similarly, an analysis of 350 patients treated with venetoclax reported a 5% rate of AIHA while on therapy, with 2 patients ultimately discontinuing therapy due to AIHA. Depth of response in patients with recurrent or new onset AIHA was not reported in this dataset. Incidence of ITP was similarly not commented on. It is possible that autoimmune cytopenias in patients treated with targeted agents (ibrutinib or venetoclax) emerge due to incomplete CLL control.

The recently published results of the MURANO trial demonstrated superior efficacy with venetoclax-rituximab compared with bendamustine-rituximab, when venetoclax was stopped after 2 years. It is unclear whether the combination of venetoclax-rituximab would have similar or superior activity when compared to single agent venetoclax for the treatment of
autoimmune cytopenias, particularly in those who had received prior rituximab. Here we for the first time report on the efficacy of the BCL2 inhibitor venetoclax in treatment of multiple-refractory ITP and Evans syndrome in 2 patients with CLL. Our limited experience with venetoclax suggests it is a safe and effective treatment in this setting and should be a strong consideration for therapy in patients with autoimmune cytopenias, particularly those who have other indications to treat CLL. Control of autoimmune cytopenias with venetoclax is likely due to activity against underlying CLL; however, a direct immunological mechanism cannot be fully excluded and therefore deserves further study. Finally, prospective evaluation would be desirable to establish clear recommendations for the management of these patients.

References
1. D’Arena G, Guariglia R, La Rocca F, et al. Autoimmune cytopenias in chronic lymphocytic leukemia. Clin Dev Immunol. 2013;2013:730131.
2. Deloughery TG. The “platelet boilermaker” is an option for quickly raising platelet counts in IVIG refractory ITP. Blood. 2014;124:5023.
3. Rossignol J, Michallet AS, Oneric L, et al. Rituximab-cyclophosphamide-dexamethasone combination in the management of autoimmune cytopenias associated with chronic lymphocytic leukemia. Leukemia. 2011;25:473–478.
4. Hampel PJ, Larson MC, Kabat B, et al. Autoimmune cytopenias in patients with chronic lymphocytic leukaemia treated with ibrutinib in routine clinical practice at an academic medical centre. Br J Haematol. 2018;183:421–427.
5. Vitale C, Ahn IE, Siwina M, et al. Autoimmune cytopenias in patients with chronic lymphocytic leukaemia treated with ibrutinib. Haematologica. 2016;101:e254–e258.
6. Rogers KA, Ruppert AS, Bingman A, et al. Incidence and description of autoimmune cytopenias during treatment with ibrutinib for chronic lymphocytic leukemia. Leukemia. 2016;30:346–350.
7. Stilgenbauer S, Eichhorst B, Scheteilg J, et al. Venetoclax for patients with chronic lymphocytic leukemia with 17p deletion: results from the full population of a phase II pivotal trial. J Clin Oncol. 2018;36:1973–1980.
8. Lacerda MP, Guedes NR, Yamakawa PE, et al. Treatment of refractory autoimmune hemolytic anemia with venetoclax in relapsed chronic lymphocytic leukemia with del(17p). Ann Hematol. 2017;96:1577–1578.
9. Hallek M, Cheson BD, Catovsky D, et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. Blood. 2018;131:2745–2760.
10. Manda S, Dunbar N, Marx-Wood CR, et al. Ibrutinib is an effective treatment of autoimmune haemolytic anaemia in chronic lymphocytic leukaemia. Br J Haematol. 2015;170:734–736.
11. Davids MS, Hallek M, Wierda W, et al. Comprehensive safety analysis of venetoclax monotherapy for patients with relapsed/refractory chronic lymphocytic leukemia. Clin Cancer Res. 2018;24:4371–4379.
12. Seymour JF, Kipps TJ, Eichhorst B, et al. Venetoclax-rituximab in relapsed or refractory chronic lymphocytic leukemia. New Engl J Med. 2019;378:1107–1120.