The NEW ENGLAND JOURNAL of MEDICINE

Please review the Supplemental Files folder to review documents not compiled in the PDF.

BCL2 inhibition in refractory hairy cell leukemia

Journal:	*New England Journal of Medicine*
Manuscript ID	22-15613.R2
Article Type:	Letter NOT about NEJM Article
Date Submitted by the Author:	n/a
Complete List of Authors:	Forconi, Francesco; University Hospital Southampton NHS Foundation Trust, Cancer Science Unit & Haematology Dept Ashton-Key, Margaret; Southampton University Hospitals NHS Trust Meakin, Nicola; Southampton University Hospitals NHS Trust
Abstract:	Hairy-cell (HC) leukemia (HCL) is a mature B-cell lymphoid cancer, whose diagnostic mainstays are its unique morphology and phenotype, and the acquisition of BRAF-V600E mutation.[1] Commonly treated with purine-analogues, hairy cell leukemia patients also benefit significantly from BRAF-V600E-specific inhibitors (BRAFi).[2,3] However, purine-analogues are toxic and BRAFi alone do not eradicate the disease and HCL will recur. Another fundamental, but unexplored feature of HCL is the remarkable overexpression of the antiapoptotic protein BCL2,[4] determining prolonged survival of the leukemic cells. BCL2 levels in HCL are as high as in the most common mature B-cell leukemia chronic lymphocytic leukemia (CLL) (**Figure 1A**), where the BH3-mimetic venetoclax successfully prevents the excessive sequestration of proapoptotic molecules by the overexpressed BCL2 and, by rapidly rebalancing the leukemic cells towards death, leads to undetectable disease in the large majority of patients.[5] However, its clinical efficacy in HCL has not been reported. We used venetoclax in a 56-year-old male patient with refractory HCL requiring treatment. The patient had received a diagnosis of HCL in 2007, failed response to interferon-alfa and had a partial response to cladribine (2008), complicated by bacterial pneumonia, and rituximab (2013). In 2018 the patient developed fatigue and night sweats and blood counts revealed dropping platelets (59,000/µl) and neutrophils (300/µl). A computed-tomography scan revealed a splenomegaly (17x16cm). Bone marrow infiltration by BRAF V600E+ve HCs was 80% with grade-2 reticulin fibrosis. BCL2 overexpression in the HCs was demonstrated (**Figure 1B**). The patient started venetoclax 5-week escalation in November 2018, followed by venetoclax 400 mg/daily until the current time. Fatigue disappeared and peripheral blood counts met the complete remission criteria within 5 weeks (**Figure 1C**). Spleen size and HCs in the bone marrow gradually decreased at 1, 6, 12, 24, and 36 months and a complete morphological, phenotypic and molecular remission (1% BRAF-V600E c.1799T>A by droplet digital PCR, below detection limit) was obtained at 48 months (**Figure 1D**). The patient

	experienced no clinical or laboratory tumour-lysis or haematological toxicity. No infective complication, Covid-19 infection, was observed throughout the entire pandemic. Serum SARS-CoV2 functional IgG antibodies were present at month 48 of venetoclax, 10 months from the last vaccination (**Figure 1E**), and T-cell subsets all normalised (**Figure 1F**). The prolonged efficacy and safety of venetoclax were remarkable. This case suggests that therapeutic BCL2 inhibition can offer a new chemotherapy-free alternative in those HCL patients where BRAFi are not available or can be used in combination.

BCL2 inhibition in refractory hairy cell leukemia

TO THE EDITOR:

Hairy-cell leukemia (HCL) is a mature B-cell lymphoid cancer. Diagnostic mainstays are its unique morphology and phenotype, and the acquisition of BRAF-V600E mutation.[1] Commonly treated with purine-analogs, HCL patients also benefit significantly from BRAF-V600E-specific inhibitors (BRAFi).[2,3] However, purine-analogs are toxic and BRAFi alone do not eradicate the disease.

Another fundamental feature of HCL is the overexpression of the antiapoptotic protein BCL2.[4] BCL2 levels in HCL are as high as in the most common mature B-cell leukemia, chronic lymphocytic leukemia, where the BH3-mimetic venetoclax successfully prevents the excessive sequestration of proapoptotic molecules by the overexpressed BCL2 and leads to leukemic cell death and undetectable disease in the large majority of patients.[5] However, its clinical efficacy as a single agent in HCL has not been reported.

We used venetoclax in a 56-year-old male patient with refractory HCL requiring treatment. The patient had received a diagnosis of HCL in 2007. Interferon-alfa failed to produce a remission and he had a partial response to cladribine (2008), complicated by bacterial pneumonia, and to rituximab (2013). In 2018 the patient developed fatigue and night sweats and blood counts revealed dropping platelets (59,000/μl) and neutrophils (300/μl). A computed tomography scan revealed a splenomegaly (17x16cm). Bone marrow infiltration by BRAF V600E+ve leukemia cells was 80% with grade 2 reticulin fibrosis. BCL2 overexpression in the tumor cells was demonstrated (**Figure 1A**). The patient started venetoclax 5-week escalation in November 2018, followed by venetoclax 400 mg/daily until the current time. Fatigue disappeared and peripheral blood counts met the complete remission criteria within 5 weeks (**Figure 1B**). Spleen size and leukemic cells in the bone marrow gradually decreased at 1, 6, 12, 24, and 36 months and a complete morphological, phenotypic, and molecular remission (1% BRAF-V600E c.1799T>A by droplet digital PCR, below detection limit) was obtained at 48 months. The patient experienced no clinical or laboratory tumor lysis or hematological toxicity. No infectious disease complication or Covid-19 infection was observed throughout the entire pandemic. Serum SARS-CoV2 functional IgG antibodies were present at month 48 of venetoclax, 10 months from the last vaccination, and T-cell subsets all normalized.

Single-agent venetoclax demonstrated prolonged safety and efficacy in this case. Therapeutic BCL2 inhibition can offer an alternative in HCL patients in whom other therapies have failed.

Francesco Forconi, University of Southampton Hospital Trust

Margaret Ashton-Key, University of Southampton Hospital Trust

Nicola Meakin, University of Southampton Hospital Trust

Supported by a grant (ECRIN-M3 accelerator award C42023/A29370) from Cancer Research UK

References

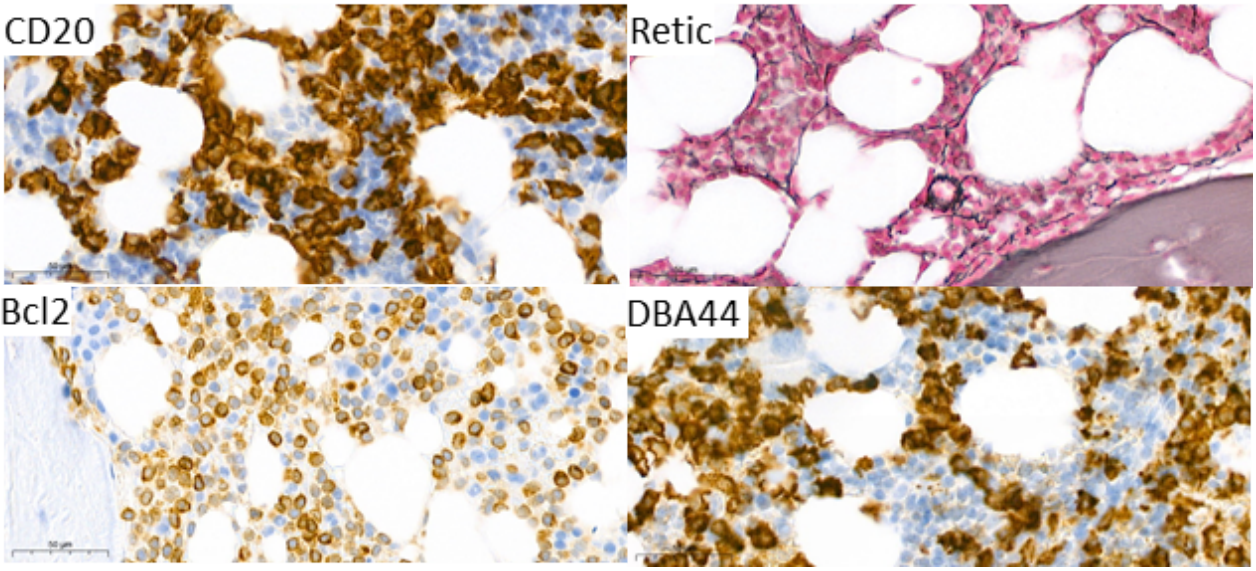
1. Grever MR, Abdel-Wahab O, Andritsos LA, et al. Consensus guidelines for the diagnosis and management of patients with classic hairy cell leukemia. Blood 2017;129:553-60.
2. Tiacci E, Park JH, De Carolis L, et al. Targeting Mutant BRAF in Relapsed or Refractory Hairy-Cell Leukemia. N Engl J Med 2015;373:1733-47.
3. Tiacci E, De Carolis L, Simonetti E, et al. Vemurafenib plus Rituximab in Refractory or Relapsed Hairy-Cell Leukemia. N Engl J Med 2021;384:1810-23.
4. Zaja F, Di Loreto C, Amoroso V, et al. BCL-2 immunohistochemical evaluation in B-cell chronic lymphocytic leukemia and hairy cell leukemia before treatment with fludarabine and 2-chloro-deoxy-adenosine. Leuk Lymphoma 1998;28:567-72.
5. Roberts AW, Davids MS, Pagel JM, et al. Targeting BCL2 with Venetoclax in Relapsed Chronic Lymphocytic Leukemia. N Engl J Med 2016;374:311-22.

Figure 1. Expression of BCL2 and efficacy and safety of venetoclax in a patient with hairy-cell leukemia.

Panel A: Immunohistochemistry and reticulin staining of the bone marrow trephine before venetoclax start (November 2018), documenting abundant staining by CD20+ve, BCL2+ve, DBA44+ve hairy cells and grade 2 reticulin fibrosis (40X magnification). **Panel B:** kinetics of the peripheral blood counts including hairy cells, neutrophils, lymphocytes and monocytes (upper graph), and platelets (lower graph) from the day of venetoclax start in November 2018 to month 48 of therapy in October 2022.

Figure 1

A



B