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BCL2 inhibition in adult acute lymphoblastic leukemia: ready for primetime?

Nitin Jain,[1] Elias Jabbour,[1] Marina Konopleva [2]

1. Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX USA
2. Department of Leukemia, Montefiore Einstein Comprehensive Cancer Center, New York, NY USA

Corresponding Author:
Nitin Jain, MD
Department of Leukemia
The University of Texas MD Anderson Cancer Center
Houston, TX USA 77030
njain@mdanderson.org

In this issue of *Haematologica*, Aldoss *et al.*[1] report the results of a single-center phase 1 trial combining venetoclax with induction and consolidation cycles of CALGB 10403 regimen for newly diagnosed patients with Philadelphia chromosome negative B-cell ALL (B-ALL). Venetoclax was administered at 400 mg daily on days 1-14 of induction with a 3-day dose ramp-up during induction (days 1-7 for patients requiring extended induction) and on days 1-14 of consolidation cycle. Venetoclax was not given during interim maintenance, delayed intensification, or maintenance cycles. Post consolidation cycle, patients received additional therapies as per treating physician discretion including additional cycles of CALGB 10403 regimen, blinatumomab, or undergo allogeneic stem cell transplantation.

The study enrolled 24 patients with newly diagnosed Philadelphia chromosome negative B-ALL with a median age of 31 years (range, 18-53 years) with 12 (50% of the cohort) patients having Ph-like genomic rearrangements, including 11 patients with *CRLF2* rearrangement and 1 patient with a *JAK2* fusion. Notably, 92% of the patients were of Hispanic ethnicity reflecting the geographic location of the treating center.

Addition of venetoclax was found to be safe with no excess myelosuppression noted with median time to absolute neutrophil count and platelet recovery post induction of 20 and 21 days, respectively. A total of 23/24 (96%) patients achieved CR/CRi after induction/re-induction (re-induction was required in 2 patients both of whom had Ph-like ALL). At the end of induction, 11/23 (48%) patients who achieved CR/CRi had undetectable measurable residual disease (MRD) by flow-cytometry (MFC, sensitivity 10^{-4}) and 27% had undetectable MRD by next-generation sequencing (NGS, 10^{-6} sensitivity). Twenty-two patients received consolidation cycle; post consolidation undetectable MRD rate by MFC and by NGS were 91% and 62%, respectively. Notably, high rates of CR/CRi and MRD by MFC post consolidation cycle was noted among patients Ph-like ALL; however, NGS MRD post consolidation appeared numerically lower in Ph-like ALL at 45% versus 80% for non-Ph-like group. The majority (74%) of patients received blinatumomab as the immediate post study treatment which is appropriate given the emerging data with blinatumomab as consolidation therapy. With a median follow-up of 11.8 months, the estimated 1-year leukemia-free survival (LFS) and overall survival (OS) were 91% and 96%, respectively. The investigators also performed BH3 profiling on pre-treatment bone marrow samples and report that Ph-like ALL blasts are more BCL2-dependent compared to non-Ph-like ALL (p=0.06). Notably, none of the pretreatment samples assessed were BCL-xL dependent.

Venetoclax, a BCL2 inhibitor is currently approved for patients with CLL and for older adults with newly diagnosed AML. Preclinical work has identified subsets of B-cell and T-cell ALL who may be sensitive to BCL2 inhibition such as early T cell precursor ALL, MLL rearranged ALL, *TCF3::HLF* fusion, hypodiploid ALL, and hyperdiploid ALL.[2-10] Several ongoing/completed prospective clinical trials are evaluating the role of venetoclax in both B- and T-ALL (Table 1).[11-13] Not unexpectedly, trials evaluating venetoclax in patients with newly diagnosed ALL are reporting high CR/CRi rates versus trials in R/R ALL. Additionally, some trials have also evaluated the role of BCL-xL inhibition such as with navitoclax.

Ph-like ALL represents a high-risk genomic subtype of B-ALL with poor outcomes after chemoimmunotherapy.[14,15] Emerging data seems to suggest that targeted therapies such as blinatumomab, inotuzumab ozogamicin and chimeric antigen receptor T (CAR T) cell therapy may overcome the negative prognostication of Ph-like ALL. In the current trial, 12 patients with Ph-like ALL genomics were included and they had high rates of CR/CRi and undetectable MRD by MFC, though the end of consolidation undetectable NGS MRD rate was lower at 45%. The authors also report higher BCL2-dependence of Ph-like ALL blasts compared to non-Ph-like ALL. This data is certainly encouraging and provides a rationale for clinical use of BCL2 inhibitor for patients with Ph-like ALL. However, as authors appropriately pointed out, this data is derived from a relatively small number of patients with limited follow-up. Additionally, the use of blinatumomab as post protocol therapy could have improved the long-term outcomes of patients, particularly among the Ph-like ALL subgroup where a substantial proportion of patients had detectable MRD by NGS at the completion of protocol therapy (i.e. post consolidation cycle).

Targeting BCL2 and BCL-xL has remained an active area of research for patients with B- and T-ALL. This is especially important in T-ALL where there is lack of targeted therapies. Besides venetoclax and navitoclax, several additional BCL2 inhibitors (such as sonrotoclax, lisaftoclax), BCL-xL degraders (DT2216) and dual BCL2/BCL-xL inhibitors (LP-118) are in clinical development for various hematologic malignancies, and their role in B- and T-ALL remains to be investigated.

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Table 1. Summary of Prospective Clinicals Trials Evaluating Venetoclax in B- and T-ALL

Study Reference	Patient population	Number of patients	Treatment Regimen	Response	Survival outcomes
Luskin et al. Blood Advances 2024[12]	Newly diagnosed older adults or age ≥18 year R/R disease; Both B- and T-ALL included	19 (newly dx, n=11, B-cell 8; T-cell 3; R/R, n=8, B-cell 3, T-cell 5)	Mini-hyper-CVD + venetoclax	CR/CRi = 10/11 (91%) among the newly diagnosed patients with all CR/CRi patients achieving undetectable MRD by flow cytometry CR/CRi = 3/8 (38%) among the R/R cohort	2-year DFS 90% for the newly diagnosed patients
Short et al. Blood Advances 2024[13]	R/R age ≥18 year B- and T-ALL	22 (B-cell 18, T-cell 4) Median 2 prior lines of Rx	Mini-hyper-CVD + venetoclax	CR/CRi = 12/21 (57%) 5/11 (45%) of responding patients with marrow involvement at baseline achieved undetectable MRD by flow cytometry	Median RFS 5.3 months Median OS 7.1 months
Pullarkat et al. Cancer Discovery 2021[11]	R/R age ≥4 year B- and T-ALL	47 (B-cell 26, T-cell 21) Median 4 prior lines of Rx	Venetoclax + navitoclax + Pegasparaginase + vincristine + dexamethasone	CR/CRi/CRp = 28/47 (60%) Undetectable MRD by flow cytometry noted in 16 (34%) patients	Median OS 7.8 months
Aldoss et al. Haematologica 2024[1]	Newly diagnosed B-ALL (age 18-54)	24	CALGB 10403 + venetoclax	CR/CRi = 23/24 (96%) 11/23 (48%) patients who achieved CR/CRi post induction had undetectable MRD by flow-cytometry	1-year LFS and OS was 91% and 96%, respectively