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

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Received: January 7, 2025.
Accepted: February 4, 2025.
Early view: February 13, 2025.

https://doi.org/10.3324/haematol.2024.286816

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In this issue of *Haematologica*, Aldoss *et al.*[1] report the results of a single-center phase I trial combining venetoclax with induction and consolidation cycles of the Cancer and Leukemia Group B (CALGB) 10403 regimen for newly diagnosed patients with Philadelphia chromosome (Ph) negative B-cell acute lymphoblastic leukemia (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 at the discretion of the treating physician including additional cycles of the CALGB 10403 regimen, blinatumomab, or underwent allogeneic stem cell transplantation.

The study enrolled 24 patients with newly diagnosed Ph$^-$ B-ALL with a median age of 31 years (range, 18-53 years). Twelve (50%) patients had Ph-like genomic rearrangements, including 11 patients with *CRLF2* rearrangement and one 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 complete remission (CR) / complete remission with incomplete count recovery (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 Ph-like ALL patients; however, NGS MRD post consolidation appeared numerically lower in Ph-like ALL at 45% *versus* 80% for the 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 chronic lymphocytic leukemia and for older adults with newly diagnosed acute myeloid leukemia. Preclinical work has identified subsets of B- and T-cell ALL who may be sensitive to BCL2 inhibition such as early T-cell precursor ALL, mixed lineage leukemia 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 relapsed/ refractory (R/R) ALL. Additionally, some trials have also evaluated the role of BCL-xL inhibition, such as with navitoclax.

Philadelphia-like ALL represents a high-risk genomic subtype of B-ALL with poor outcomes after chemoimmunotherapy.[14,15] Emerging data seem to suggest that targeted therapies such as blinatumomab, inotuzumab ozogamicin and chimeric antigen receptor (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 unde-

Table 1. Summary of prospective clinicals trials evaluating venetoclax in B- and T-cell acute lymphoblastic leukemia.

Study reference	Patient population	N of patients	Treatment regimen	Response	Survival outcomes
Luskin *et al.*, 2024[12]	Newly dx older adults or aged ≥18 years 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 dx 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 dx patients
Short *et al.*, 2024[13]	R/R aged ≥18 years 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.*, 2021[11]	R/R aged ≥4 years 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.*, 2024[1]	Newly dx B-ALL (aged 18-54 years)	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 were 91% and 96%, respectively

B-ALL: B-cell acute lymphoblastic leukemia; CALGB: Cancer and Leukemia Group B; CR: complete remission; CRi: CR with incomplete count recovery; CRp: CR with low platelet count; DFS: disease-free survival; dx: diagnosed; LFS: leukemia-free survival; mini-hyper-CVD: cyclophosphamide, vincristine and dexamethasone with alternating cycles of cytarabine and methotrexate; MRD: measurable residual disease; N: number; OS: overall survival; RFS: relapse-free survival; R/R: relapsed/refractory; T-ALL: T-cell acute lymphoblastic leukemia; Rx: radiotherapy.

tectable MRD by MFC, though, at the end of consolidation, the 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. These data are certainly encouraging and provide a rationale for clinical use of BCL2 inhibitor for patients with Ph-like ALL. However, as the authors appropriately pointed out, these data are 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 a 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 under clinical development for various hematologic malignancies, and their role in B- and T-ALL remains to be investigated.

Disclosures

NJ reports research funding from Pharmacyclics, AbbVie, Genentech, AstraZeneca, BMS, Pfizer, ADC Therapeutics, Cellectis, Adaptive Biotechnologies, Precision Biosciences, Fate Therapeutics, Kite/Gilead, Mingsight, Takeda, Medisix, Loxo Oncology, Novalgen, Dialectic Therapeutics, Newave, Novartis, Carna Biosciences, Sana Biotechnology, and Kisoji Biotechnology, and Advisory Board / Honoraria from Pharmacyclics, Janssen, AbbVie, Genentech, AstraZeneca, BMS, Adaptive Biotechnologies, Kite/Gilead, Precision Biosciences, Beigene, Cellectis, MEI Pharma, Ipsen, CareDX, MingSight, Autolus, and Novalgen. EJ reports research grants from Abbvie, Adaptive Biotechnologies, Amgen, Ascentage, Novartis, Pfizer, and Takeda, and consultancy fees from Abbvie, Adaptive Biotechnologies, Amgen, Ascentage, Novartis, BMS, Genentech, Incyte, Novartis, Pfizer, and Takeda. MK reports consulting for AbbVie, AstraZeneca, Boehringer Ingelheim, Eli Lilly, F. Hoffman La-Roche, Genentech, Gilead, Janssen, Legend, MEI Pharma, Novartis, Redona, Sanofi, Stemline, and Vincerx, research contracts from AbbVie, Allogene, AstraZeneca, Genentech, Gilead, ImmunoGen, MEI Pharma, Precision, Rafael, Sanofi, and Stemline, clinical trials for AbbVie, AstraZeneca, Genentech, Janssen, Sanofi,

and Stemline, Advisory Boards for AbbVie, Auxenion, Bakx, Dark Blue Therapeutics, F. Hoffman La-Roche, Genentech, Gilead, Stemline, and Vincerx, and Principal Investigator for Reata Pharmaceutical.

Contributions

All authors contributed equally.

Funding

NJ is supported by the Leukemia and Lymphoma Society Career Development Award. This research is supported in part by the MD Anderson Cancer Center NIH/NCI Cancer Center Support Grant P30 CA016672.

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