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RESEARCH ARTICLE

A phase 1 trial of venetoclax in combination with liposomal vincristine in patients with relapsed or refractory B-cell or T-cell acute lymphoblastic leukemia: Results from the ECOG-ACRIN EA9152 protocol

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Abstract

Introduction: Relapsed or refractory (r/r) acute lymphoblastic leukemia (ALL) or lymphoblastic lymphoma (LL) remains a therapeutic challenge. Preclinical data in both B- and T-ALL suggests synergy of venetoclax (VEN) with vincristine (VCR). We designed a phase I/II trial (EA9152) of the combination of L-VCR and VEN for patients with r/r B-or T-cell ALL or LL. Here, we report the safety and efficacy outcomes of the phase I portion of this trial (NCT03504644).

Methods: In a 3+3 dose escalation design, r/r ALL subjects were given single-agent VEN doses reaching 400, 600, or 800 mg for the three respective dose levels. Weekly L-VCR at 2.25 mg/m^2 IV was started on D15 of cycle 1. The primary phase I objective was to determine the maximum tolerated dose (MTD) of the combination.

Results: Among the 18 patients in phase I, grade ≥ 3 treatment-related adverse events were reported in 89% of treated patients. Two patients (two of three) at dose level 3 experienced dose-limiting toxicities. Therefore, the MTD of the combination was determined to be dose level 2 (VEN 600 mg). Twenty-two percent of evaluable patients ($N = 4$) achieved a complete response, with two of them showing no evidence of measurable residual disease (MRD).

Conclusion: The combination of VEN and L-VCR was found to be safe for patients with r/r ALL and encouraging preliminary efficacy, including MRD negative responses. With the removal of L-VCR from the US market, the phase 2 portion of this trial is actively enrolling with vincristine sulfate.

KEYWORDS
acute leukaemia, BCL-2, clinical trials

1 | INTRODUCTION

Acute lymphoblastic leukemia (ALL) is a blood cancer characterized by the rapid growth of immature lymphoid cells in the bone marrow [1]. While high rates of remission are seen in patients with ALL following traditional chemotherapy regimens, some will experience recurrence or have refractory disease which is associated with poor outcomes [2–6].

Therapies targeting apoptosis, the process of programmed cell death, have been studied and approved for various types of hematologic malignancies [7–14]. B-cell lymphoma (BCL-2) protein family members regulate the intrinsic pathway of apoptosis [15]. Upon the initiation of this pathway through diverse stimuli, anti-apoptotic BCL-2 protein members are inhibited by "initiator" BH3-only proteins of the BCL-2 family. This allows pro-apoptotic BCL-2 family proteins to migrate to the mitochondria, where the outer membrane is permeabilized, allowing for the subsequent release of cytochrome C from the mitochondria, and consequently, apoptosis of the cell [16–19]. Overexpression of BCL-2 has been observed in many hematopoietic cancers, including ALL, providing a rationale for the treatment of these diseases with BCL-2 inhibitors [14, 20–23].

Venetoclax (VEN) is an inhibitor of the anti-apoptotic BCL-2 protein. It acts by binding directly to BCL-2, hindering its ability to bind to and inhibit pro-apoptotic proteins, thus enabling apoptosis to proceed [7]. VEN is approved for the treatment of chronic lymphocytic leukemia or small lymphocytic lymphoma and in combination with azacitidine, decitabine, or low-dose cytarabine for the treatment of newly diagnosed acute myeloid leukemia.

The combination of a BCL-2 inhibitor with a potent, standard chemotherapeutic agent in ALL, such as vincristine (VCR), is an attractive option with the potential for increased apoptosis of leukemic blasts [24]. We designed a Phase 1b/II multi-institutional study combining the BCL-2 inhibitor, VEN, with liposomal VCR (L-VCR) through the Eastern Cooperative Oncology Group-American College of Radiology Imaging Network (ECOG-ACRIN) as part of the United States National Clinical Trials Network (NCTN). We are now reporting the results of the phase 1b portion of the EA9152 trial, which determined the maximum tolerated dose (MTD) of VEN with L-VCR in patients with relapsed or refractory (r/r) ALL or lymphoblastic lymphoma (LL).

2 | METHODS

2.1 | Study design and treatment

This open-label phase 1b study evaluated the safety and preliminary efficacy of the combination of VEN with L-VCR in the treatment of patients with r/r T-cell and B-cell ALL/LL (ClinicalTrials.gov identifier: NCT03504644). The primary objective of this study was to determine the MTD and the recommended phase 2 dose (RP2D) of VEN. Preliminary efficacy, safety, and toxicity assessment after the combination treatment with VEN and L-VCR were evaluated. This study followed a 3+3 dose escalation design with VEN given orally once daily in each dose arm. The VEN dose arms were as follows: Arm A (dose level 1): 20, 50, 100, and 200 mg on Days 1, 2, 3, and 4 and 400 mg on Days 5–70; Arm B (dose level 2): 50, 100, 200, and 400 mg on Days 1, 2, 3, and 4 and 600 mg on Days 5–70; Arm C (dose level 3): 100, 200, 400, and 600 mg on Days 1, 2, 3, and 4 and 800 mg on Days 5–70.

After a two-week lead-in phase, patients were administered a fixed, weekly standard dose of intravenous L-VCR at 2.25 mg/m2 × 4 weeks (Cycle 1 = 42 days). Assessment of each dose level required 3 patients as a cohort, and a total of six patients per dose level were required to confirm the MTD of VEN. Escalation was continued until > 33% of patients in a particular dose arm experienced a dose-limiting toxicity (DLT). A bone marrow biopsy was performed on day 42 ± 2 days. Cycle 2 was held for up to 2 weeks (14 days) to obtain the results of the day 42 bone marrow biopsy, while VEN was continued. All patients continued on to a second 28-day cycle of the combination therapy (Cycle 2 = 28 days). A bone marrow biopsy was again performed on day 70 ± 2 days.

Patients who achieved at least a stable disease response continued with 28-day cycles of combination therapy until disease progression.

By protocol, patients were required to take at least 75% of VEN doses and 75% of L-VCR doses during the DLT evaluation period (i.e., Cycle 1 of the protocol treatment) to be considered evaluable for the MTD assessment. Safety monitoring criteria and stopping rules for toxicity were protocol-defined. The study protocol was approved by the institutional review board at participating institutions and informed consent was obtained from all patients.

The key eligibility criteria of patients for this study were a pathological diagnosis of r/r B-cell or T-cell ALL/LL or if less than 5% of lymphoblasts were present on morphologic evaluation, positivity for measurable residual disease (MRD), defined as the presence of $> 10^{-3}$ lymphoblasts by flow cytometry after multiagent chemotherapy. To be eligible for enrollment, the patients had to be at least 18 years of age with an ECOG performance status of 0–2. Key exclusion criteria included the use of strong or moderate CYP3A inhibitors or inducers within 7 days prior to the first dose of the study drug on account of interaction with VEN.

2.1.1 | Adverse events

AEs were graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 and reported by the treating physician at scheduled times during a trial and for ≥30 days after the last dose of trial therapy or initiation of another anticancer therapy. The MTD was the highest dose at which < 2 of ≥6 patients experienced a DLT. A DLT was defined by the occurrence of any of the following toxicities assessed according to the NCI CTCAE version 5.0 criteria as possibly, probably, or definitely related to the study medication or their combination occurring within the first cycle (i.e., ≤ 42 days of the first dose of study drug). Patient's bone marrow samples were evaluated for tumor response as complete remission (CR), complete remission with incomplete hematologic recovery (CRi), partial response (PR), or relapsed/refractory (REL) [25]. The preliminary efficacy of VEN in combination with L-VCR was evaluated by morphology at the individual institutional level and reviewed centrally.

2.2 | Statistical analysis

The primary toxicity analysis was based on all patients who started the protocol regardless of eligibility for MTD determination. A preliminary efficacy analysis was performed on eligible patients who started protocol treatment. Descriptive statistics (frequency, percentage, median, and/or range) were used to characterize patient demographics, disease characteristics, adverse events, and responses.

3 | RESULTS

3.1 | Patient characteristics

Eighteen patients from nine ECOG-ACRIN institutions were enrolled (three, 12, and three to Arms A, B, and C, respectively) from 2018 to 2021. Among those enrolled, the median age was 42 years (range: 22–77) with 44% being female (Table 1). The majority were White (80%) and non-Hispanic (78%). Upon entry, 13 (72%) patients were diagnosed with r/r B-ALL, 1 (4%) with T-ALL and 4 (22%) had relapsed LL. 78% of the patients had an ECOG performance status of 1. Note that, 94% of patients had received prior chemotherapy including two who had received a previous stem cell transplant.

3.2 | MTD determination

Of the 18 patients who initiated study treatment, 12 were evaluable for MTD determination. Six patients not included in MTD determination were excluded due to rapid progression of disease ($N = 2$) or withdrawal of consent ($N = 4$) prior to receiving the prespecified number of doses of study medication but were included in safety and efficacy analyses. The most common toxicity (see Table 2) reported across all three arms was grade 3 anemia (2/3, 4/12, and 3/3 patients from Arm A, B, and C, respectively) followed by febrile neutropenia (3/12 and 2/3 patients in Arms B and C, respectively). Several treatment-related grade 4 hematologic toxicities, such as a decrease in white blood cells, neutrophils, and platelet counts were reported in all three arms. In arms, A and B, no protocol-defined DLTs were observed. In arm C, two patients developed DLTs, including refractory grade 3 hypocalcemia and grade 3 heart failure. As a result, the RP2D was decided to be 600 mg of VEN. No instances of clinical tumor lysis syndrome were observed in any of the three arms.

3.3 | Efficacy

The best overall response was evaluated among all 18 patients who started protocol treatment (Table 3). Four CRs were observed (one on Arm A, two on Arm B, and one on Arm C) with the remaining patients being non-responders. Three patients were not evaluable for response due to early death or withdrawal of consent and were considered non-responders. Four patients were reported with stable disease (two on Arm A and two on Arm B) and seven with disease progression (six on Arm B and one on Arm C). Two of four patients in CR were found to be MRD negative by multiparameter flow cytometry (<0.01% of lymphoblasts in the bone marrow).

4 | DISCUSSION

The results of this early phase investigation of VEN with L-VCR in r/r ALL or LL demonstrated that the combination had an acceptable safety profile. The majority of adverse events seen in this experimental regimen were hematologic in nature as was expected based on prior experience with the drugs. Although no new safety signals were seen, we noted significant cardiac toxicity at the 800 mg VEN dose potentially supporting concerns raised by other groups. [26] We have determined that 600 mg of VEN daily will be tested in the phase II

TABLE 1 Patient characteristics.

	Arm A ($n = 3$)	Arm B ($n = 12$)	Arm C ($n = 3$)	Total ($n = 18$)	Total %
Gender					
Female	3	4	1	8	44.4%
Male	0	8	2	10	55.6%
Race[a]					
Black or African American	1	2	0	3	20%
White	2	8	2	12	80%
Ethnicity					
Hispanic or Latino	0	3	1	4	22.2%
Not Hispanic or Latino	3	9	2	14	77.8%
ECOG Performance Status					
0	2	1	0	3	16.7%
1	1	11	2	14	77.8%
2	0	0	1	1	5.5%
Patient diagnosis					
Lymphoblastic lymphoma	0	4	0	4	22.2%
B-cell ALL	2	8	3	13	72.2%
T-cell ALL	1	0	0	1	5.6%
Prior Chemotherapy Administered—Yes	3	11	3	17	94.4%
Transplant received -Yes	0	1	1	2	11.1%
Age (years) Median	73	33	32	42	
Blasts, Blood (%)[b] Median	6.0	17.5	69.0	17.5	
Blasts, Bone marrow (%) Median	64	80	96	80	
Cellularity, Bone marrow (%) Median	52.5	90	90	90	

[a]Value missing for the first five patients enrolled to step 1 as this piece of information was collected in the case report form afterward.
[b]Values missing/unknown for two patients in Arm B.

TABLE 2 Common treatment-related toxicities by grade 1.

	Treatment arm								
	A ($n = 3$)			B ($n = 12$)			C ($n = 3$)		
Grade	3	4	5	3	4	5	3	4	5
Anemia	2			4			3		
Febrile neutropenia				3			2		
Alanine aminotransferase increased				1			1		
Aspartate aminotransferase increased				2			1		
Lymphocyte count decreased					1			1	
Neutrophil count decreased		3			6			3	
Platelet count decreased		1			1			2	
White blood cells decreased		3			4			3	
Hypokalemia				1			1		
Generalized muscle weakness				1			1		
Peripheral sensory neuropathy	1			1			1		

TABLE 3 Best overall response.

Response	Arm assignment			Total
	A	B	C	
Complete remission	1	2	1	4 (22%)
Complete remission incomplete	0	0	0	0
Partial remission	0	0	0	0
Stable disease	2	2	0	4 (22%)
Relapse/Progression	0	6	1	7 (39%)
Unevaluable	0	2	1	3 (17%)
Total	3	12	3	18

portion of this trial. Given that no evidence of tumor lysis was seen, in-patient dose escalation is not recommended to be continued in the phase II portion of the trial. However, frequent monitoring for tumor lysis during the first cycle is required. Response rates in the phase 1b portion (CR/CRi) were encouraging for the combination with 4/18 patients (22%) achieving a CR, and 50% of responders achieving MRD negativity.

Since this study's inception in 2015, a number of new drugs and combinations have been studied in r/r ALL, including combinations with VEN. Particularly, mini-hyper-CVD- an anthracycline-free regimen consisting of cyclophosphamide 150 mg/m^2 q12 h on days 1–3, steroids, and vincristine alternating every 21 days with methotrexate 250 mg/m^2 day 1 and intravenous cytarabine 0.5 g/m^2 q12 h on days 2 and 3 – has been safely combined with VEN 400–600 mg in *BCR::ABL1*-negative ALL [27, 28]. Response rates reported from these studies have ranged from 38% to 65% in the relapsed setting to as high as 100% for newly diagnosed patients. While these data compare favorably to our reported response rate, the use of these combinations is limited to centers with experience in complex, inpatient chemotherapy and to still relatively "fit" patients, as up to a third of patients were transplant-eligible once in remission. In relapsed *BCR::ABL1*-positive disease, VEN has been successfully combined with ponatinib and steroids with high reported overall response rates (~90%) though with prominent cytopenias associated [29, 30]. This emerging data in *BCR::ABL1*-positive disease highlights a drawback of our tyrosine kinase inhibitor-free trial design. Additionally, as agents like blinatumomab and inotuzumab are moved into the frontline setting, the development of new r/r strategies becomes more of an unmet need [31, 32]. In T-ALL, the development of new drugs has lagged dramatically behind B-cell disease. This trial represents one of only a handful of experimental strategies for r/r T-ALL, besides nelarabine combinations, anti-CD7 or anti-CD38 CAR-T, and other VEN-containing regimens. [33]

As the liposomal formulation of vincristine is no longer available for use, the dose expansion phase of the combination is being conducted with standard vincristine in place of the L-VCR. The phase II portion of the trial will focus on determining the efficacy of this simple, outpatient regimen for r/r ALL, and future directions include correlating response to particular molecular subtypes (e.g., *BCR::ABL1*-positive ALL, *BCR::ABL1*-like ALL, and standard risk) and immunophenotypic profiles.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study can be requested by contacting the ECOG-ACRIN Cancer Research Group.

ETHICS STATEMENT

The study protocol was approved by the institutional review board at participating institutions.

PATIENT CONSENT STATEMENT

Written informed consent was obtained from all patients.

CLINICAL TRIAL REGISTRATION

Registered as NCT03504644 at clinicaltrials.gov

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