REGULAR ARTICLE

blood advances

Nelarabine combination therapy for relapsed or refractory T-cell acute lymphoblastic lymphoma/leukemia

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Key Points

- Nelarabine combination therapy is a safe and effective bridge to transplant in children and adults with R/R T-ALL/LBL.
- Nelarabine combination therapy vs monotherapy is associated with improved survival in patients with R/R T-ALL/LBL.

Nelarabine, an antimetabolite prodrug, is approved as monotherapy for children and adults with relapsed and refractory T-cell acute lymphoblastic leukemia and lymphoma (R/R T-ALL/LBL), although it is often used in combination regimens. We sought to understand differences in efficacy and toxicity when nelarabine is administered alone or in combination. We retrospectively analyzed 44 consecutive patients with R/R T-ALL/LBL; 29 of whom were treated with combination therapy, most with cyclophosphamide and etoposide (23, 79%) and 15 with monotherapy. The median age was 19 years (range, 2-69), including 18 children (<18 years). After a median of 1 (range, 1-3) cycle of treatment, 24 patients (55%) achieved complete remission, 62% (18/29) with combination therapy and 40% (6/15) with monotherapy (P = .21). Most responders (21, 88%) pursued allogeneic stem cell transplant (alloSCT). Overall survival (OS) was 12.8 months (95% confidence interval, 6.93-not reached) in the entire cohort and was higher in the combination therapy than in the monotherapy group (24-month OS, 53% vs 8%; P = .003). The rate of neurotoxicity was similar between groups (27% vs 17%; P = .46) and grade 3/4 anemia and thrombocytopenia were more frequent in the combination group (76% vs 20%; P < .001% and 66% vs 27%; P = .014, respectively). In a multivariate analysis, nelarabine combination therapy and alloSCT post nelarabine were associated with improved OS (hazard ratio, 0.41; P = .04 and hazard ratio, 0.25; P = .008, respectively). In conclusion, compared with monotherapy, nelarabine combination therapy was well tolerated and associated with improved survival in pediatric and adult patients with R/R T-ALL/LBL.

Introduction

T-cell acute lymphoblastic leukemia/lymphoma (T-ALL/LBL) comprises approximately 15% of ALL cases and most commonly occurs in adolescent and young adult males, although the early T-cell precursor (ETP) subtype occurs in both younger and older patients.[1,2] The majority of patients with T-ALL/LBL initially respond to chemotherapy, and many, particularly younger patients able to receive intensive pediatric-style regimens, achieve cure with modern treatment.[3-5] However, T-ALL/LBL that is

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The full-text version of this article contains a data supplement.

refractory to or relapses after initial therapy has a dismal prognosis owing to few treatment options and chemotherapy resistance.[4-10]

Nelarabine is the only drug approved for patients with relapsed or refractory (R/R) T-ALL/LBL. Nelarabine is a prodrug that is demethylated by adenosine deaminase to the deoxyguanosine analog, 9-b-D-arabinofuranosylguanine. T-lymphoblasts are highly sensitive to the cytotoxic effects of deoxyguanine and its analogs.[11-13] The accumulation of deoxyguanosine triphosphate and resulting inhibition of ribonucleotide reductase leads to impaired DNA synthesis and cell death.[11,14,15] Nelarabine was studied in both children and adults with R/R T-ALL/LBL. Among children with first or second relapse of T-ALL/LBL, the response rates were 55% and 27%, respectively.[16] In adults, approximately one-third of patients in first or later relapse achieved complete remission (CR).[17,18] Based on these studies, nelarabine was approved in 2005 by the US Food and Drug Administration for patients with R/R T-ALL/LBL after 2 previous regimens (third-line therapy). The pediatric and adult dosing of nelarabine is 650 mg/m^2 per day for 5 consecutive days and 1500 mg/m^2 per day on days 1, 3, and 5, respectively, repeated in 21-day cycles, with neurotoxicity found to be the dose-limiting toxicity.

To improve response rates, nelarabine has been combined with cyclophosphamide and etoposide (NECTAR). In a pilot study of 7 patients aged 2 to 19 years with R/R T-ALL/LBL, the CR rate was 71% and the overall response rate was 100%.[19] A phase 1 trial of NECTAR in 19 children with R/R T-ALL/LBL demonstrated 25% and 44% overall response rates in T-LBL and T-ALL, respectively, with 9 patients subsequently undergoing allogeneic stem cell transplantation (alloSCT).[20] A case series of 5 adult patients with R/R T-ALL/LBL treated with NECTAR reported a CR in 3 patients.[21] Given these small studies, the safety and efficacy of the NECTAR regimen remains poorly defined.[22-24] In this study, we report our experience with nelarabine and nelarabine combination regimens in adults and pediatric patients with R/R T-ALL/LBL.

Methods

Patients

We retrospectively identified consecutive patients with R/R T-ALL/LBL who were treated with at least 1 dose of nelarabine chemotherapy between August 2006 and November 2021 at the Boston Children's Hospital (BCH), Dana-Farber Cancer Institute/Brigham and Women's Cancer Center (DFCI), or Massachusetts General Hospital (MGH). A diagnosis of ALL and LBL was made per standard hematopathology criteria. We excluded patients who were treated with nelarabine during initial therapy. Patient and treatment characteristics were collected from the electronic medical record. This research was approved by the Dana-Farber Cancer Institute Institutional Review Board and conducted in accordance with the Declaration of Helsinki.

Outcomes

CR was defined as resolution of all medullary and extramedullary disease and complete recovery of peripheral blood counts. Partial remission (PR) was defined as improvement, but not resolution, of disease without appearance of new lesions. Overall response rate included patients with CR or PR. Response assessments were determined by the treating physician. Measureable residual disease (MRD) was assessed by multicolor flow cytometry and fewer than 0.01% lymphoblasts was defined as negative MRD. Overall survival (OS) was defined as time from nelarabine therapy until date of death from any cause, with censoring at last follow-up for patients last known alive. Relapse-free survival (RFS) was defined as time from achievement of CR to relapse or death, with patients censored on the date of last follow-up. Additional end points were rate of alloSCT and occurrence of hematologic and nonhematologic adverse events (AEs). All AEs were classified according to the Common Terminology Criteria for Adverse Events version 5.0.

Statistics

Categorical variables are summarized as numbers and percentages, and comparisons were made by Pearson chi-square or Fisher exact tests. Continuous variables are summarized as median and range, and comparisons were made by Mann-Whitney tests. OS and RFS were estimated by the Kaplan-Meier method, with confidence intervals (CIs) estimated using the log-log method. The log-rank test was used to compare survival outcomes. Cox proportional hazards regression models were fitted to assess the effect of covariates on survival outcomes in univariate and multivariate models. AlloSCT post nelarabine administration was included as a time-dependent variable. Predefined covariates of nelarabine treatment type (monotherapy vs combination therapy) and alloSCT were included in the multivariate analysis. An additional landmark analysis for all comparisons was performed at day 30 after nelarabine initiation to address potential immortal time bias. For all analyses, CIs were calculated at the (2-sided) 95% level of confidence. A 2-sided P value of $<.05$ was considered statistically significant. All statistics were performed with R version 4.0.

Results

Patients

Between 2006 and 2021, 44 patients were treated with nelarabine for R/R T-ALL/LBL at BCH (n = 17), DFCI (n = 21), and MGH (n = 6). Of the nelarabine-treated patients, 29 (66%) were treated with a nelarabine combination (combination group) and 15 (34%) were treated with single agent nelarabine (monotherapy group). The median patient age at diagnosis was 19.2 years (range, 2-69) including 18 patients (41%) under 18 years of age and 8 patients (18%) over 40 years of age. The majority (n = 33, 75%) of patients were male. Additional patient characteristics are shown in Table 1. Pediatric and adult patients were equally represented in the combination and monotherapy groups.

The initial diagnosis was LBL in 13 patients (30%). In total, 13 (30%) patients had central nervous system (CNS) involvement at diagnosis (either CNS-2 or CNS-3). Higher rates of T-ALL (vs LBL) and CNS involvement were seen in the combination group than in the monotherapy group (79% vs 47%; $P = .04$% and 45% vs 0%; $P = .003$, respectively). Complete pathologic and genetic characterization was available for 26 patients, among whom 14 (54%) had immunophenotypic and molecular findings consistent with ETP ALL/LBL, as previously defined,[25] and 7 (27%) had a complex karyotype (5 or more chromosome abnormalities).

The initial treatment varied by age. Most pediatric patients (<18 years of age; n = 18, pediatric group) received a DFCI Consortium pediatric regimen, with the remainder receiving either Children's

Table 1. Patient characteristics

Characteristics (n, %)	All patients (n = 44)	Nelarabine combination therapy (n = 29)	Nelarabine monotherapy (n = 15)
Age at diagnosis (y, median, range)	19 (2-69)	19 (2-69)	21 (3-62)
Age groups (y)			
<18	18 (41)	12 (41)	6 (40)
≥18, <30	12 (27)	7 (24)	5 (33)
≥ 30	14 (32)	10 (35)	4 (27)
Sex (male)	33 (75)	22 (75.9)	11 (73.3)
Race			
White	28 (64)	17 (59)	11 (73)
Asian	6 (14)	4 (14)	2 (13.3)
Black	5 (11)	3 (10)	2 (13.3)
Other	2 (5)	2 (7)	0 (0)
Missing	3 (7)	3 (10)	0 (0)
Diagnosis*			
ALL	30 (68)	23 (79)	7 (47)
LBL	13 (30)	5 (17)	8 (53)
MPAL T/myeloid	1 (2)	1 (4)	0 (0)
CNS involvement at diagnosis*	13 (30)	13 (45)	0 (0)
ETP immunophenotype at diagnosis†	14 (54)	11 (52)	3 (60)
Cytogenetics at diagnosis†			
Normal	11 (42)	7 (37)	4 (57)
Complex	7 (27)	4 (21)	3 (43)
Other abnormalities	8 (31)	8 (42)	0 (0)
Mutations at diagnosis‡			
Notch/FBXW7 pathway	6 (38)	6 (55)	0 (0)
RAS/PTEN pathway	4 (25)	4 (36)	0 (0)
P53	1 (6)	0 (0)	1 (20)
Upfront treatment at diagnosis§			
Pediatric/pediatric inspired	32 (77)	23 (79)	9 (60)
HyperCVAD	6 (14)	4 (14)	2 (13)
Other	6 (14)	2 (7)	4 (27)
First treatment CR	19 (43)	12 (41)	7 (47)
AlloSCT before nelarabine treatment	7 (16)	4 (14)	3 (20)
Isolated extramedullary relapse*	6 (15)	0 (0)	6 (46)
CNS involvement at relapse	8 (20)	6 (23)	2 (13)
Nelarabine line of therapy			
Second line	28 (64)	20 (69)	8 (53)
Third line	12 (27)	6 (21)	6 (40)
Fourth/fifth line	4 (9)	3 (10)	1 (7)
Time from first therapy to nelarabine therapy (mo, median, range)	6 (1-107)	4 (1-108)	10 (1-26)

AYA, adolescents and young adults; MPAL, mixed phenotype acute leukemia; WBC, white blood cells.
*$P < .05$
†Data regarding ETP and cytogenetics at diagnosis is available only for 26 patients
‡Data regarding molecular mutations is available only for 16 patients
§Full details of upfront therapies are described in supplement Table 1.

Oncology Group (COG) or United Kingdom National Randomized Trial for Children and Young Adults with ALL (UKALL) pediatric regimens. Most patients aged 18 years or older (adult group, n = 26) received a pediatric-inspired regimen (n = 14, 54%), followed by hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone, methotrexate, and cytarabine (hyper-CVAD; n = 6, 23%), or Cancer and Leukemia Group B (CALGB) 9111-based therapy (n = 6, 23%). The median number of

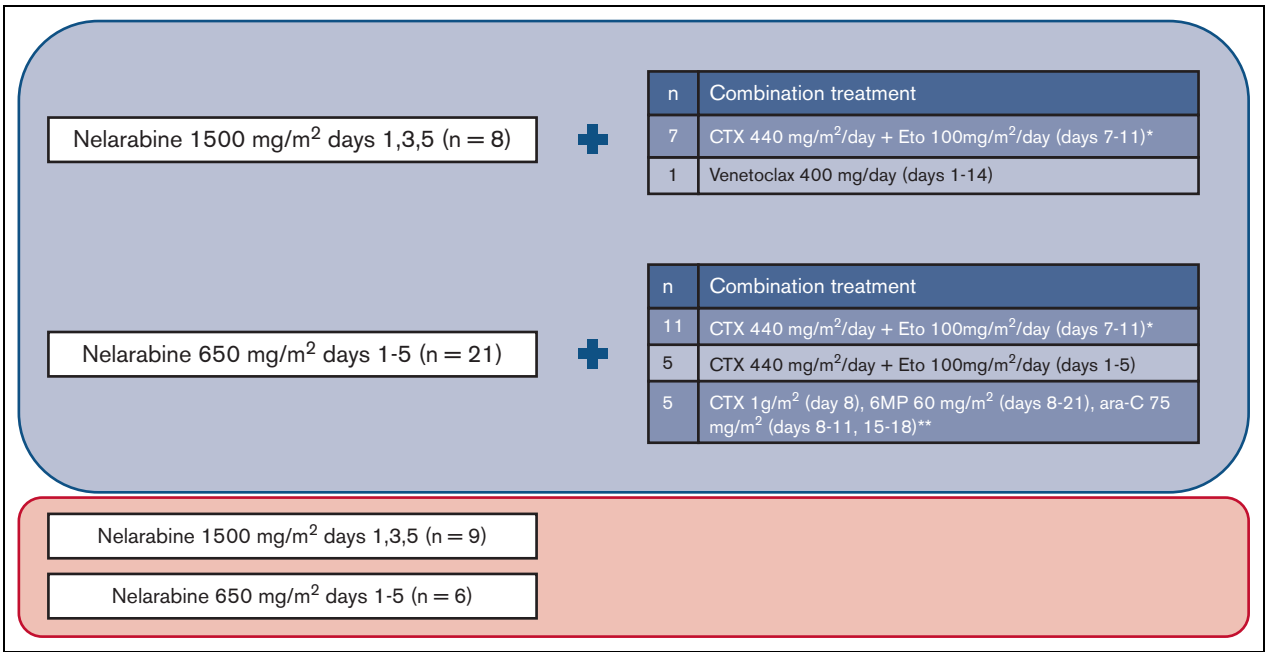

Figure 1. Nelarabine-based therapies among patients with R/R T-ALL/LBL. *Three patients received Eto and CTX first at days 1 to 5 with nelarabine given at days 7 to 11; **2 of the 5 patients were also given Pegasparaginase 2500 U/m^2 at day 22 and 1 patient was given vincristine 1.5 mg/m^2 at days 22 and 29. CTX, cyclophosphamide; Eto, etoposide; 6MP, 6-mercaptopurine; ara-C, cytarabine; P-Asp, pegylated asparaginase.

therapies before nelarabine treatment was 1 (range, 1-4). Nelarabine-based treatment was second-line therapy in 28 patients (64%), third-line therapy in 12 patients (27%), and fourth- or fifth-line therapy in 4 patients (9%). Eight patients (20%) had CNS involvement at relapse: 6 (23%) in the combination group and 2 (13%) in the monotherapy group ($P = .69$). All except 2 patients had overt hematologic relapse, either by increased blasts or extramedullary disease, whereas the other 2 patients had only recurrent MRD at relapse. The median time from first therapy to nelarabine salvage therapy was 6 (range, 1-107) months. Seven (16%) patients received alloSCT before nelarabine salvage therapy. There were no differences in prior treatment characteristics between combination and monotherapy groups.

Treatment

The nelarabine dose and schedule was either 1500 mg/m^2 per day on days 1, 3, and 5 (n = 17) or 650 mg/m^2 per day for 5 consecutive days (n = 27), with or without additional therapy, as illustrated in Figure 1. The likelihood of receiving combination therapy vs monotherapy was not different by age: 12 (67%) vs 6 (33%) in the pediatric group and 17 (65%) vs 9 (35%) in the adult group, respectively ($P > .99$). Most patients received 1 (n = 25, 57%) cycle of nelarabine-based therapy with the remainder receiving 2 (n = 16, 36%) or rarely 3 to 4 (n = 3, 7%) cycles of therapy, without statistical differences between combination and monotherapy groups ($P > .99$).

Adjuvant CNS-directed treatment was given in most patients (n = 36, 86%), either with intrathecal (IT) chemotherapy (n = 30, 72%) or combined IT chemotherapy and radiation (n = 6, 14%). Six patients did not receive any CNS-directed treatment alongside nelarabine-based therapies, and 2 patients had no data regarding CNS-directed therapy.

Adverse events

The major AEs are summarized in Table 2. The most common grade 3-4 hematologic toxicity was neutropenia in 29 (66%) patients with borderline statistical significance (76% vs 47%; $P = .053$) between combination and monotherapy groups. Grade 3-4 anemia and thrombocytopenia were more prevalent among the combination group vs the monotherapy group (76% vs 20%; $P < .001$% and 66% vs 27%; $P = .014$, respectively). Neurotoxicity was documented in 9 (21%) patients–5 (17%) in the combination group and 4 (27%) in the monotherapy group ($P = .46$)–with 4 cases of grade 3 neurotoxicity (2 motor neuropathy, 1 seizure, and 1 altered mental status), which were all transient with full recovery. Neurotoxicity was not associated with presence or absence of CNS disease status at diagnosis ($P = .39$) or at relapse ($P = .83$), number of nelarabine cycles ($P = .26$), nelarabine dosing schedule (650 mg/m^2 days 1-5 vs 1500 mg/m^2 days 1, 3, and 5; $P = .27$), or type of CNS adjuvant therapy (IT vs IT + radiation vs no CNS therapy; $P = .60$). The only AEs that were more common in adults than in children were infections and grade 3-4 thrombocytopenia (58% vs 11%; $P = .002$ and 65% vs 33%; $P = .036$, respectively).

Three patients (aged 17, 32, and 61 years) died within 30 days of nelarabine therapy, 2 of whom were treated with nelarabine monotherapy and 1 with NECTAR. In these patients, nelarabine was given as third-line (2 patients) or fourth-line (1 patient) therapy, and none of them had achieved CR at any point during their treatment course (primary refractory disease). Each patient died with active disease and concomitant infection. Overall, during study follow-up, 24 (54%) patients died; the majority (n = 19, 79%) due to R/R disease with the remainder because of transplant-related complications (n = 3; 2 due to graft-versus-host disease, 1 due to veno-occlusive disease), infection (n = 1), and sudden cardiac death of unknown cause (n = 1).

Table 2. Adverse events

AEs among evaluated patients	All patients		Nelarabine combination therapy		Nelarabine monotherapy	
	All	Grade 3/4	All	Grade 3/4	All	Grade 3/4
Hematological toxicities						
Anemia	36 (82)	25 (57)	26 (90)	22 (79)	10 (67)	3 (20)*
Thrombocytopenia	32 (73)	23 (52)	24 (83)	19 (66)	8 (53)	4 (27)*
Neutropenia	30 (68)	29 (66)	22 (76)	22 (76)	8 (53)	7 (47)
Neurotoxicity	9 (21)	4 (9)	5 (17)	2 (7)	4 (27)	2 (13)
Sensory peripheral neuropathy	3 (7)	0	2 (7)	0 (0)	1 (7)	0 (0)
AIDP/motor neuropathy	2 (5)	2 (5)	2 (7)	2 (7)	0 (0)	0 (0)
Altered mental status	1 (2)	1 (2)	0 (0)	0 (0)	1 (7)	1 (7)
Seizure	2 (5)	1 (2)	1 (3)	0 (0)	1 (7)	1 (7)
Vertigo	1 (2)	0	0	0 (0)	1 (7)	0 (0)
Infections	17 (39)	16 (36)	13 (45)	12 (41)	4 (27)	4 (27)
Others						
Venous thrombosis	2 (4)	2 (4)	1 (3)	1 (3)	1 (7)	1 (7)
Gastrointestinal bleed	1 (2)	1 (2)	1 (3)	1 (3)	0	0
Perforated appendicitis	1 (2)	1 (2)	1 (3)	1 (3)	0	0
Elevated liver enzymes/bilirubin	2 (2)	0	2 (7)	0	0	0
Gastritis	1 (2)	0	1 (3)	0	0	0
Vomiting	1 (2)	0	1 (3)	0	0	0
Diarrhea	1 (2)	0	1 (3)	0	0	0

AIDP, acute inflammatory demyelinating polyneuropathy.
*P value < .05 for comparison between groups.

Response

Twenty-four (55%) patients achieved CR as best response to nelarabine-based therapy. Patient responses and number of cycles are shown in Table 3. MRD response was evaluated by multiparameter flow cytometry in 22 patients who achieved CR, with 16 patients (73%) achieving a negative MRD response. The CR rates were 62% and 40% among the combination and monotherapy groups (P = .21), respectively, with MRD-negative CR rates of 77% and 60% (P = .59). Within each age group, 12 patients (67%) in the pediatric group and 12 patients (46%) in the adult group achieved CR (P = .23). Of note, CR rate among patients with ETP ALL/LBL vs non-ETP ALL/LBL was numerically lower but not statistically different between groups (43% vs 75%; P = .13).

Twenty-one out of the 24 patients (88%) who achieved CR proceeded directly with alloSCT. The remaining 3 patients who achieved CR were treated with alloSCT before nelarabine treatment, 2 of whom received a donor lymphocyte infusion(s) after CR achievement. Of the 3 patients not consolidated with an alloSCT post nelarabine, 2 progressed shortly after treatment and the third was lost to follow-up.

An additional 5 patients were treated with alloSCT: 3 in the combination group, including 2 who achieved CR after subsequent salvage therapy and 1 who received sequential transplant with active disease, and 2 in the monotherapy group, both of whom achieved CR with additional salvage therapy before alloSCT. Overall, alloSCT consolidation post nelarabine treatment was pursued in 19 (66%) and 7 (47%) patients in the nelarabine combination group vs monotherapy group, respectively (P = .33). The clinical course of treated patients is shown in Figure 2. There were no differences between the combination and monotherapy groups regarding conditioning intensity, use of total body irradiation (TBI) during conditioning regimen, or donor origin Table 3.

Survival

The median OS for the entire cohort was 12.9 months (95% CI, 7-not reached [NR]; Figure 3A) with 12- and 24-month OS of 52.4% (95% CI, 36-67) and 37.6% (95% CI, 22-53), respectively. The OS was higher in the combination group than in the monotherapy group (24-month OS of 52.9% [95% CI, 32-70] vs 8% [95% CI, 1-30], respectively; P = .0026; Figure 4A). In a landmark analysis at 30 days, the higher OS persisted (24-month OS 54.7% [95% CI, 33-72] vs 9.4% [95% CI, 1-34], respectively; P = .006; Figure 4B). In a predefined subgroup analysis of NECTAR vs monotherapy group, excluding patients who received other combination regimens, patients in the NECTAR group (n = 23) had higher OS than those in the monotherapy group (24-month OS of 44.3% [95% CI, 22-65] vs 8.2% [95% CI, 1-31]; P = .026; supplemental Figure 1A). This was also demonstrated in a 30-day landmark analysis (supplemental Figure 1B). In survival analysis evaluating all patients who proceeded with transplant (n = 26), patients in the combination group (n = 19) had higher OS than patients in the monotherapy group (n = 7) (24-month OS 70.9% [95% CI, 43-87] vs 16.7% [95% CI, 1-52], respectively; P = .0021; Figure 4C).

Table 3. Treatment characteristics and responses

Characteristics (n, %)	All patients (n = 44)	Nelarabine combination therapy (n = 29)	Nelarabine monotherapy (n = 15)	*P* value
Best achieved response				.29
CR	24 (54)	18 (62)	6 (40)	
PR	2 (5)	1 (3)	1 (7)	
SD/PD	18 (41)	10 (35)	8 (53)	
Negative MRD*	16/22 (73)	13/17 (76.5)	3/5 (60)	.59
Number of cycles to best response				.65
1	29 (65)	18 (62)	11 (73)	
2	13 (30)	9 (31)	4 (27)	
3	2 (5)	2 (7)	0	
Total number of nelarabine cycles				>.99
1	25 (57)	16 (55)	9 (60)	
2	16 (36)	11 (38)	5 (33)	
3	1 (2)	1 (3.5)	0	
4	2 (5)	1 (3.5)	1 (7)	
AlloSCT post nelarabine treatment	26 (59)	19 (66)	7 (47)	.33
Conditioning regimen (MAC)	23 (88)	16 (84)	7 (100)	.54
TBI in conditioning regimen	23 (88)	17 (89)	6 (86)	>.99
Donor origin				.36
Matched related donor	8 (31)	4 (21)	4 (57)	
Matched unrelated donor	11 (42)	9 (47)	2 (29)	
Mismatched unrelated donor	3 (12)	3 (16)	0 (0)	
Other (haploidentical or umbilical cord)	4 (15)	3 (16)	1 (14)	
Second AlloSCT post nelarabine treatment†	2 (29)	1 (25)	1 (33)	>.99
DLI post nelarabine treatment†	3 (43)	2 (50)	1 (33)	>.99

DLI, donor lymphocyte infusion; MAC, myeloablative conditioning; PD, progressive disease; RIC, reduced intensity conditioning; SD, stable disease.
*MRD was evaluated by multicolor flow cytometry, with a threshold of 0.01%, and was available in 22/24 patients who achieved CR.
†Among 7 patients (4, in nelarabine combination group; 3, in the monotherapy) who received alloSCT before nelarabine treatment.

When stratified by age groups, the OS was comparable between various age groups (12-month OS of 57.7% [95% CI, 31-77], 47.6% [95% CI, 23-36], and 52.5% [95% CI, 12-82] in patients aged <18 years, 18 to 39 years, and ≥40 years, respectively; $P = .55$; supplemental Figure 2). In addition, there was no difference in OS by the presence of *Notch* mutation at diagnosis, T-ALL vs T-LBL at diagnosis, or lines of therapy (second-line vs higher; supplemental Figures 3-5, respectively). Patients with ETP ALL/LBL at diagnosis had similar survival rates with non-ETP ALL/LBL (24-month OS of 68.1% [95% CI, 35-87] vs 41.7% [95% CI, 15-66], respectively; $P = .53$; supplemental Figure 6,). CNS involvement, at either diagnosis or relapse, did not affect OS (12-month OS 67.7% [95% CI, 35-87] vs 47% [95% CI, 27-64]; $P = .1$ and 75% [95% CI, 32-93] vs 54% [95% CI, 35-70], respectively; $P = .22$).

The median RFS among patients who achieved CR was not reached, with 24-month estimated RFS of 60.5% (95% CI, 36-78; Figure 3B). All relapses following CR occurred in the first year. The median RFS was higher in the combination group than in the monotherapy group, with borderline statistical significance (NR [95% CI, 9.6-NR] vs 7.6 months [95% CI, 4.3-NR]; $P = .07$) and 24-month RFS of 68.8% (95% CI, 41-86) vs 26.7% (95% CI, 1-69), respectively. The RFS was similar between the pediatric and adult groups (12-month RFS of 60% [95% CI, 25-83] vs 60.6% [95% CI, 26-83]; $P = .99$).

In a univariate Cox regression analysis of nelarabine combination therapy vs monotherapy (hazard ratio [HR], 0.3; 95% CI, 0.13-0.69; $P = .004$), alloSCT post-nelarabine (HR, 0.17; 95% CI, 0.06-0.48; $P < .001$) and bone marrow involvement at relapse (HR, 0.36; 95% CI, 0.14-0.94; $P = .037$) were associated with improved OS. Age, other initial disease characteristics including CNS involvement either at diagnosis or at relapse, number of prior lines of therapy, alloSCT before nelarabine treatment, and duration between first treatment and nelarabine treatment were not associated with OS (supplemental Table 1). In a multivariate Cox regression model, both nelarabine combination therapy and alloSCT post nelarabine retained their predictive value (HR, 0.41; 95% CI, 0.17-0.96; $P = .04$ and HR, 0.25; 95% CI, 0.09-0.7; $P = .008$).

Discussion

Nelarabine is approved as a single agent based on the results of previous studies which showed CR rates of 27% to 55%[16] and 31%[17] in pediatric and adult patients, respectively. In an effort to increase the number of patients with relapsed T-ALL/LBL who benefit

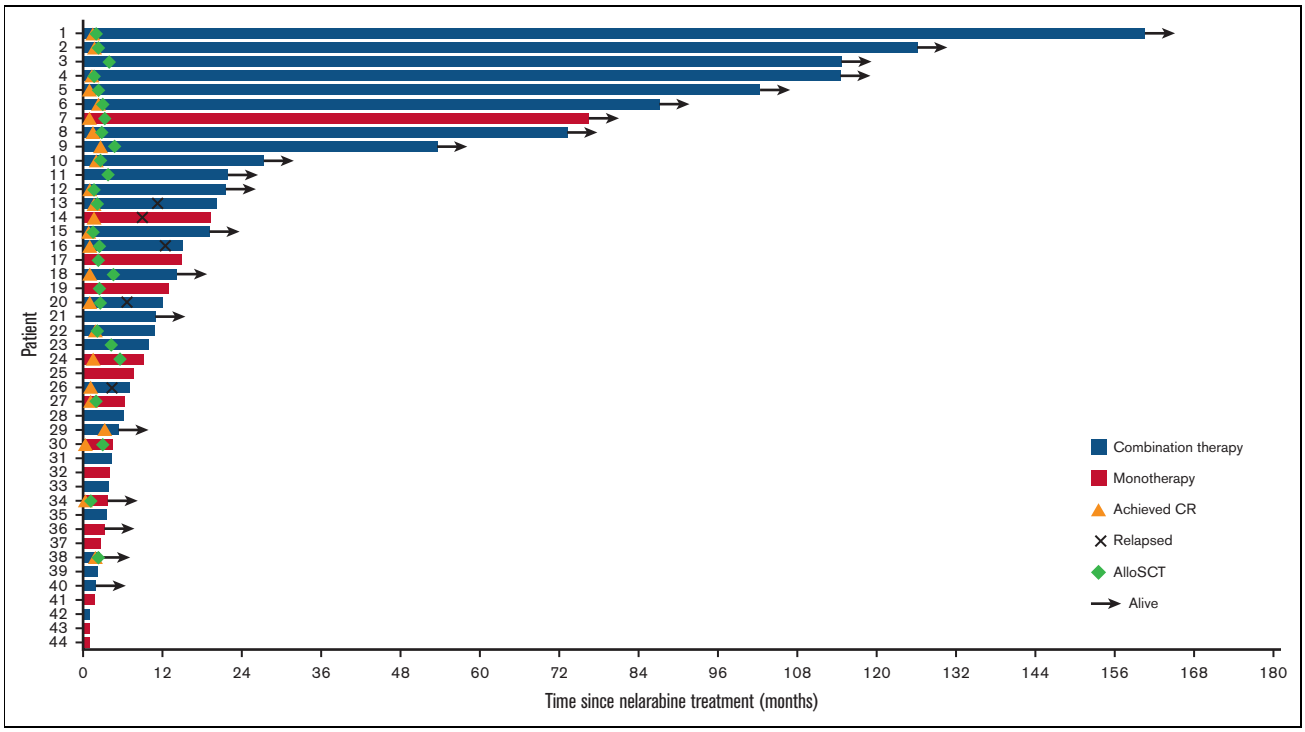

Figure 2. Remission duration of 44 patients treated with nelarabine-based therapy.

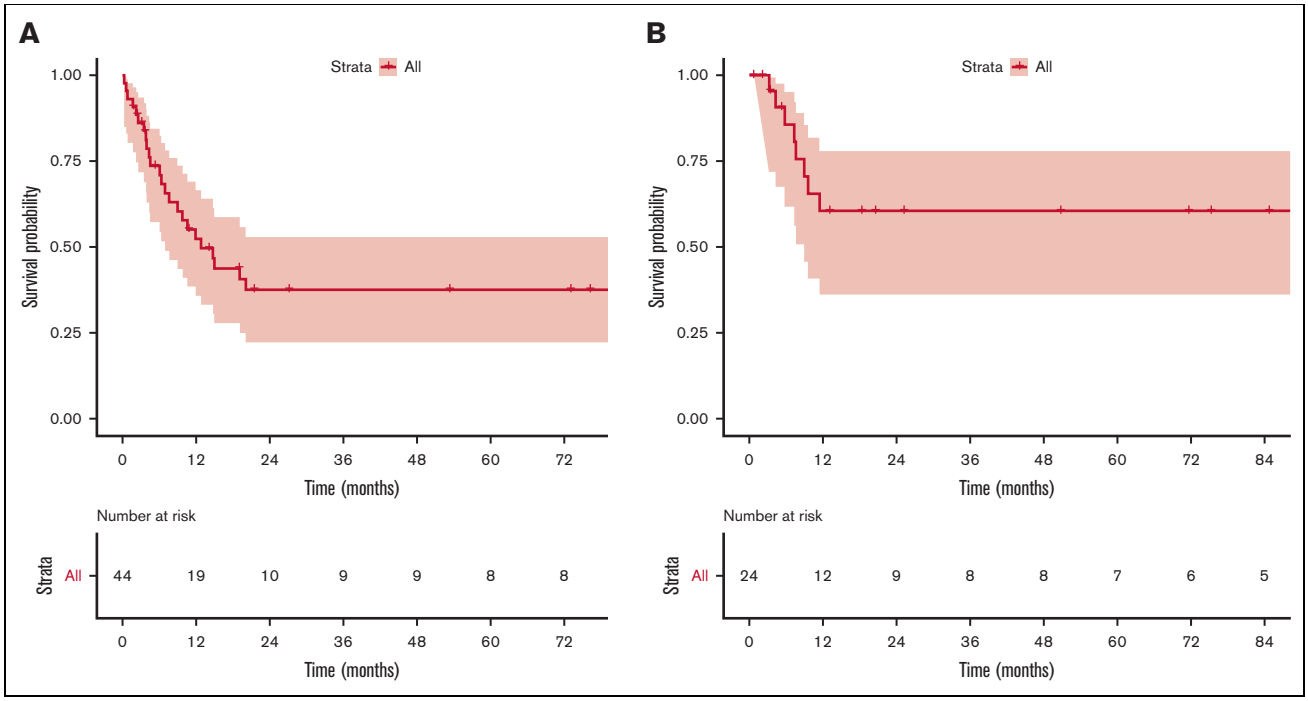

Figure 3. Outcomes of all patients treated with nelarabine-based therapy. (A) OS. (B) RFS.

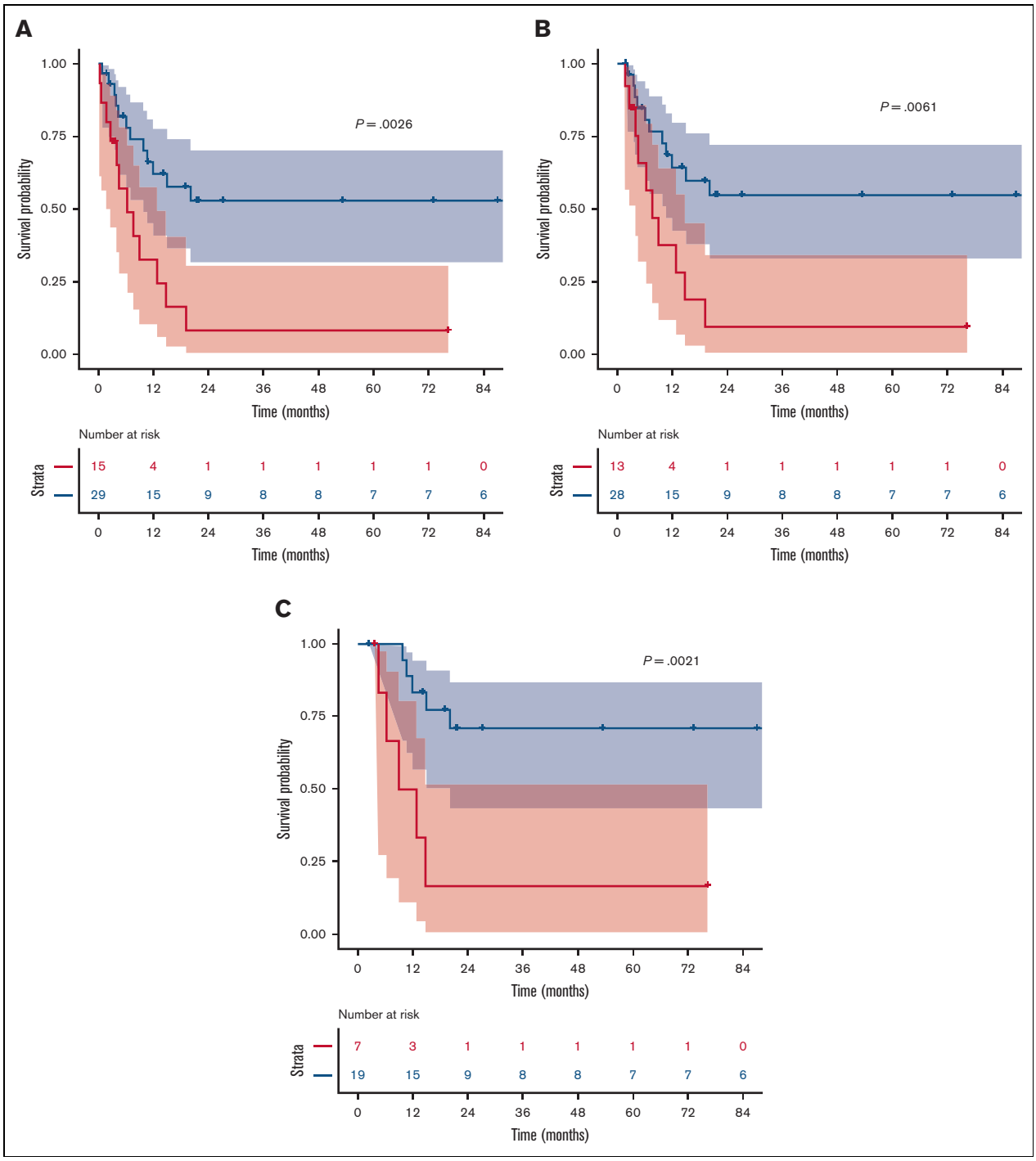

Figure 4. Patients' survival stratified by therapy type (combination therapy vs monotherapy). (A) OS without landmark analysis. (B) OS with landmark analysis at 30 days. (C) OS among patients who underwent transplantation.

from nelarabine salvage therapy, combination regimens, primarily adding cyclophosphamide and etoposide have been developed, which have reported CR rates of 35% to 71% in children[19,20] and 60%[21] in adults. However, there remains limited knowledge about the relative benefits and toxicities of nelarabine monotherapy vs combination therapy for the treatment of R/R T-ALL/LBL.

To the best of our knowledge, here we have reported on the largest series (n = 44) of children and adults with R/R T-ALL/LBL treated with nelarabine alone or in combination with other chemotherapy agents. We show that nelarabine therapy can induce CR in a significant proportion of patients (55%, n = 24) with comparable rates between children and adults and that the majority of

responding patients (88%, n = 21 of responders) are able to be bridged successfully to alloSCT. This resulted in an encouraging median OS of 12.8 months (95% CI, 6.9-NR) in the entire cohort.

Importantly, we found that numerically more patients receiving nelarabine combination therapy achieved CR than those receiving nelarabine monotherapy (62% vs 40%), although the results were not significant ($P = .21$). Patients receiving combination therapy did have statistically significantly higher OS than those receiving monotherapy (24 months OS 52.9% vs 8.2%; $P = .0026$) and in a multivariate regression model, both nelarabine combination therapy and alloSCT were associated with improved OS (HR, 0.41; 95% CI, 0.17-0.96; $P = .04$ and HR, 0.25; 95% CI, 0.09-0.7; $P = .008$, respectively), suggesting that nelarabine combination therapy is associated with better outcomes for R/R T-ALL/LBL, independent from alloSCT. Furthermore, NECTAR, the most common regimen in the nelarabine combination group (n = 23), was also associated with improved OS vs nelarabine monotherapy (24 months OS 44.3% vs 8.2%; $P = .026$).

In addition to being associated with better outcomes, we show that nelarabine combination therapy is well tolerated and associated with a toxicity profile comparable to monotherapy. Notably, the rate of neurotoxicity was similar between combination and monotherapy groups (27% vs 17%; $P = .46$). All neurologic toxicities were reversible and no grade 4 neurologic events were recorded in either group. The only notable differences between the combination and monotherapy groups were in grade 3/4 anemia and thrombocytopenia (76% vs 20%; $P < .001$ and 66% vs 27%; $P = .014$, respectively). Rates of grade 3/4 neutropenia and infection were comparable between combination and monotherapy groups (45% vs 27%, respectively; $P = .24$).

Nelarabine therapy was well tolerated by both children and adults. Side effects were comparable between the different age groups, with the exception of higher rates of grade 3-4 thrombocytopenia and infections among adults than in children (65% vs 33%; $P = .036$% and 57.7% vs 11.1%; $P = .002$, respectively). Overall, rates of AEs were similar to those previously reported and were manageable in both age groups. The improved CR and OS rates, without additional severe toxicity observed in our cohort supports the administration of nelarabine in combination therapy for relapsed T-ALL/LBL both in adults and children.

It is important to note that nelarabine is approved as third-line therapy, but the majority (64%, n = 28) of patients in our cohort received nelarabine or a nelarabine combination as a second-line therapy with good outcomes. Given the aggressiveness of relapsed T-ALL/LBL and the lack of other effective, well-tolerated, T-cell-specific salvage treatment options, there is a clear rationale for administering nelarabine earlier in the treatment course. Although we did not see a difference in our cohort between patients who received nelarabine in second vs later lines of therapy, some patients who are refractory to second-line treatment may not have been fit enough to receive third-line therapy and therefore not represented in this cohort. In addition, given the favorable toxicity profile of nelarabine combination therapy, patients may benefit without incurring significant cost in terms of complications, compromise of organ function, or performance status. With potentially higher chance of response and lower likelihood of complications, using nelarabine earlier in treatment may allow more patients to bridge expeditiously to potentially curative alloSCT. The favorable response rates and limited toxicity in our cohort supports the practice of using nelarabine combination therapy in the second-line setting as a bridge to alloSCT.

In fact, a natural extension of this line of reasoning has been taken by several groups who have tested the benefit of adding single-agent nelarabine to first-line therapy. The COG 0434 study randomized children and young adults (aged 1-31 years) with intermediate and high risk T-ALL to receive nelarabine as part of consolidation therapy and showed an improvement in the disease-free survival (88.2% vs 82.1% at 5 years; $P = .01$) and CNS relapse rate (1.3% vs 6.9%; $P = .0001$), but no improvement in OS.[26] In contrast, the addition of nelarabine to the hyper-CVAD regimen in adults (age range 19-78) with newly diagnosed T-ALL/LBL was not associated with improved outcomes.[27,28] Similarly, the UKALL14 trial showed no survival advantage with the addition of nelarabine to standard therapy[29] among adults aged 25 to 65 years, but the dose of nelarabine was markedly reduced compared with COG 0434, which may have influenced the negative outcomes.

Our data, again, demonstrate that alloSCT remains essential for the cure of patients with R/R T-ALL.[17,18,22,30] In fact, the biggest impact on the OS benefit for patients treated with nelarabine combination therapy was the ability to bridge to alloSCT. In the multivariate analysis, both nelarabine combination therapy and alloSCT were predictive for better OS (HR 0.41, 95% CI, 0.17-0.96 and HR 0.25, 95% CI, 0.09-0.7, respectively).

Although nelarabine-based therapies remain an important tool in the treatment of T-ALL/LBL, more therapies are needed. There are still patients who will not respond to nelarabine-based salvage therapy. In addition, increasingly more patients are being exposed to nelarabine in the first-line setting and the use of nelarabine in these patients at relapse has not been well studied. Other treatment strategies that are being explored in R/R T-ALL/LBL include inhibiting antiapoptotic signaling with BCL-2[31-33] or BCL-XL inhibitors,[34] targeting CD38 with daratumumab,[35,36] T-cell directed CAR-T[37,38] therapy, and *NOTCH1* pathway inhibitors.[39] However, nelarabine remains the only approved therapy for R/R T-ALL/LBL, and therefore, optimizing its use represents a very practical approach.

The limitations of this study include the retrospective nature of our cohort and population heterogeneity. In addition, the lack of statistically significant difference in CR and MRD negativity between the combination and monotherapy groups may be associated with the modest number of patients in each subgroup. Yet, these results represent the largest study to date on the administration of nelarabine-based combination regimens in R/R T-ALL/LBL in both pediatric and adult patients.

In conclusion, nelarabine combination therapy is well tolerated and associated with a higher CR and improved OS than nelarabine monotherapy, despite causing higher rates of anemia and thrombocytopenia. The ability to bridge patients to alloSCT is crucial and was associated with marked improvement in OS in patients with R/R T-ALL/LBL.

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Authorship

Contribution: S.S., D.J.D., and M.R.L. designed the research; S.S., Y.K.V., J.D.P., and L.D.W. performed data extraction; S.S. and Y.L. analyzed the data; S.S., D.J.D., and M.R.L. wrote the initial draft. Y.K.V., J.D.P., A.M.B., L.B.S., L.M.V., D.S.N., and R.M.S. reviewed the manuscript and contributed to its final version, and all authors reviewed the final version of the manuscript and agreed to the submission.

Conflict-of-interest disclosure: A.M.B. serves as a consultant for Acceleron, Agios, BMS/Celgene, CTI BioPharma, Gilead, Keros Therapeutics, Novartis, Taiho, and Takeda. L.B.S. has served on advisory boards for Servier, Jazz Pharmaceuticals, and Beam Therapeutics. D.S.N. received research funding from Pharmacyclics; has stock ownership in Madrigal Pharmaceuticals, and is a consultant to the American Society of Hematology Research Collaborative. R.M.S. reports grants and personal fees from AbbVie, Agios, and Novartis; personal fees from Actinium, Argenx, Astellas, AstraZeneca, Biolinerx, Celgene, Daiichi-Sankyo, Elevate, Gemoab, Janssen, Jazz Pharmaceuticals, Macrogenics, Otsuka, Pfizer, Hoffman LaRoche, Stemline, Syndax, Syntrix, Syros, Takeda, and Trovagene; and grants from Arog. D.J.D. has served as a consultant for Amgen, Autolos, Agios, Blueprint, Forty-Seven, Gilead, Incyte, Jazz Pharmaceuticals, Novartis, Pfizer, Servier, and Takeda. He received research funding from AbbVie, Glycomimetics, Novartis, and Blueprint Pharmaceuticals. M.R.L. reports research funding from Novartis and AbbVie and has served on an advisory board for Pfizer. The remaining authors declare no competing financial interests.

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