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RESEARCH ARTICLE

Nelarabine as salvage therapy and bridge to allogeneic stem cell transplant in 118 adult patients with relapsed/refractory T-cell acute lymphoblastic leukemia/lymphoma. A CAMPUS ALL study

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Abstract

The outcome of relapsed or refractory (R/R) T-cell acute lymphoblastic leukemia/lymphoma (T-ALL/T-LBL) in adults is poor, with less than 20% of patients surviving at 5 years. Nelarabine is the only drug specifically approved for R/R T-ALL/T-LBL, but the information to support its use is based on limited available data. The aim of this observational phase four study was to provide recent additional data on the efficacy and safety of nelarabine in adults with R/R T-ALL/T-LBL and to evaluate the feasibility and outcome of allogeneic hematopoietic stem cell transplant (SCT) after salvage with nelarabine therapy. The primary endpoints were overall response rate (ORR) and overall survival (OS). Additional endpoints were safety, SCT rate and post-SCT OS. Between May 2007 and November 2018, 118 patients received nelarabine salvage therapy at 27 Italian hematology sites. The median age was 37 years (range 18-74 years), 73% were male, 77 had a diagnosis of T-ALL and 41 of T-LBL, and 65/118 (55%) had received more than two lines of therapy. The median number of nelarabine cycles was two (range 1-4); 43/118 (36%) patients had complete remission (CR), 16 had partial remission (14%) and 59 (50%) were refractory, with an ORR of 50%. The probability of OS, from the first dose of nelarabine, was 37% at 1 year with a median survival of 8 months. The OS at 1 year was significantly better for the 47 patients (40%) who underwent SCT after nelarabine salvage therapy (58% vs 22%, log-rank $P < .001$). The probability of OS at 2 and 5 years from SCT was 46% and 38%, respectively. Seventy-five patients (64%) experienced one or more drug-related adverse events (AE). Grade III-IV neurologic toxicities were observed in 9/118 (8%) of cases and thrombocytopenia or/and neutropenia (grade III-IV) were reported in 41% and 43% of cases, respectively. In conclusion, this is one of the largest cohorts of adult patients with R/R T-ALL/T-LBL treated in real life with nelarabine. Taking into account the poor prognosis of this patient population, nelarabine represents an effective option with an ORR of 50% and a CR rate of 36%. In addition, 40% of cases following nelarabine salvage therapy could undergo SCT with an expected OS at 2 and 5 years of 46% and 38%, respectively. The safety profile of nelarabine was acceptable with only 8% of cases showing grade III-IV neurological AE.

1 | INTRODUCTION

Continuous improvements have been achieved in the management and outcomes of adult patients with acute lymphoblastic leukemia (ALL) in recent years following adoption of pediatric-like regimens and targeted therapies. Nonetheless, the occurrence of relapse or resistance to treatment in patients with T-cell acute lymphoblastic leukemia/lymphoma (T-ALL/T-LBL) continues to represent a clinical challenge.[1-4] In adults, T-ALL/T-LBL accounts for approximately 15% of acute lymphoproliferative disorders, and the overall outcome of relapsed/refractory (R/R) T-ALL/T-LBL is poor, with less than 20% of the patients surviving at 5 years.[1,2,4-6] There are only few controlled trials in this setting and the standard of care is not yet established.[2,7]

Nelarabine is a deoxyguanosine analog (water-soluble prodrug of ara-G), which is resistant to degradation by the purine nucleoside phosphorylase and toxic to T lymphocytes leading to inhibition of DNA synthesis. Nelarabine is the only drug that has been specifically approved (as an orphan drug) for the treatment of patients with R/R T-ALL/T-LBL. However, the information to support its Food and Drug Administration (FDA) approval and indication of use are based on the

limited available data.[7-11] Recently, this drug has also been used in combination with chemotherapy in the frontline setting with encouraging results in the pediatric, but not adult, patient population.[12,13]

The aim of this observational phase four study (called "CAMPUS-ALL" study) was to provide recent additional data on the efficacy and safety of nelarabine used in real life in adult patients with R/R T-ALL/T-LBL, and to evaluate the feasibility and outcome of allogeneic hematopoietic stem cell transplantation (SCT) after nelarabine salvage therapy.

2 | PATIENTS AND METHODS

In this multicenter observational phase four study, 118 consecutive patients were included. The inclusion criteria were: age 18 years or more, diagnosis of R/R T-ALL/T-LBL and treatment with at least one complete course of nelarabine at the standard approved dose (schedule 1500 mg/m^2 per day on days 1, 3 and 5, every 21 days). Data were retrospectively collected in 27 Italian hematology centers, from all patients treated with nelarabine as salvage therapy between May 2007 and November 2018. The patients' clinical, cytogenetic and molecular data were collected in a proper case report form (CRF) and entered in a specific database. This observational study was approved by the Ethical Committee of Udine University Hospital in Italy and was performed in agreement with the Declaration of Helsinki.

All patients had a refractory or relapsed T-ALL/T-LBL defined according to the Cheson criteria.[14]

The primary endpoints of this study were the overall response rate (ORR) and overall survival (OS) of patients after nelarabine therapy. Additional endpoints were safety, SCT rate and post-SCT OS and event-free survival (EFS).

The ORR was defined as the proportion of patients who obtained a partial (PR) or complete response (CR) to therapy. The response criteria were defined according to the standard criteria as reported in the Gökbuget's pivotal study.[15]

Complete response was defined as no evidence of leukemic blasts in the bone marrow (BM) (<5%). If present, all extramedullary manifestations had to be resolved. Extramedullary disease was assessed via CT-scan or PET-scan.

Partial response was defined as a BM blast count ≥5% and <25% or, in patients with extramedullary involvement, a reduction of the disease burden by at least 50%.

Non-response (NR or refractory) was defined as a persistence of BM blast count ≥25%, a less than 50% reduction of extramedullary disease or the appearance of new lesions.

Relapse was defined as the reappearance of disease either as unequivocal blasts in the BM (≥5%), in the central nervous system (CNS), or at extramedullary sites after a prior CR achievement.

Safety was evaluated and graded according to the Common Terminology Criteria for Adverse Events v3.0 (CTCAE).

The population characteristics were analyzed with descriptive statistics, and the Fisher's exact test was used to examine the differences between frequencies. Survival was estimated using the Kaplan-Meyer method and the differences between groups were compared with the log-rank test. Overall survival after nelarabine therapy was calculated from the date of the first nelarabine dose to the date of the last follow-up for live patients, or to the date of death of any cause. Post-transplant EFS was calculated from the date of hematopoietic stem cell transplant to the date of relapse or death of any cause. The follow-up of the entire population was updated on 31 December 2019. Univariate and multivariate analyses were carried out using the Cox regression method. Statistical significance level in all cases was considered with a *P* value less than .05. Data were analyzed with the MedCalc software, version 12.5.0.0 (MedCalc Software bvba, Belgium).

3 | RESULTS

3.1 | Patients' characteristics and nelarabine therapy

The patients' characteristics are summarized in Table 1. Median age at nelarabine therapy was 37 years (range 18-74 years), 73% of patients were male. Seventy-seven (65%) had a diagnosis of T-ALL and 41 (35%) of T-LBL; 43% (51/118) had a refractory disease and 57%

TABLE 1 Patients' characteristics (118 cases)

Age (years) at diagnosis	
Mean ± SD	36.9 ± 13.4
Median (range)	36 (10-73)
Age (years) at nelarabine therapy	
Mean ± SD	38.1 ± 13.2
Median (range)	37 (18-74)
Diagnosis	
T-ALL	77/118 (65%)
T-LBL	41/118 (35%)
Phenotype	
Early / MatureT	86/118 (73%)
Thymic	32/118 (27%)
Previous lines of therapy	
1	53/118 (45%)
2	47/118 (40%)
≥3	18/118 (15%)
Disease status prior to nelarabine treatment	
Relapsed	67/118 (57%)
Refractory	51/118 (43%)
Time from diagnosis to nelarabine treatment	
Median - months (range)	11 (1-145)
Number of nelarabine cycles / patient	
Median (range)	2 (1-4)
Number of total nelarabine cycles	210

(67/118) had relapsed after a median time from diagnosis of 11 months (range 4-145). Of these 67 cases, 37 (55%) relapsed earlier than 1 year from the diagnosis. Sixty-five patients (55%) had received two or more prior chemotherapy lines, and these patients' first lines of chemotherapy were heterogeneous according to the different national protocols adopted between 2007 and 2018 and included the NILG 10/07 protocol, LAL0904, LAL1913, LAL1308, LAL1104 GIMEMA (Gruppo Italiano Malattie Ematologiche) protocols and Hyper-CVAD scheme. Only two patients had a central nervous system involvement at the start of nelarabine therapy.

The median number of nelarabine cycles was two (range 1-4). A total of 210 nelarabine cycles have been delivered with 55% of patients receiving two or more cycles. The median time between diagnosis and nelarabine therapy was 11 months (range 1-145 months). All patients were evaluable for response and 43/118 (36%) achieved a CR, 16/118 (14%) a PR, and 59/118 (50%) were NR. The ORR (CR + PR) was 50% (Table 2A). The median cycles of nelarabine to best response was two (range 1-3). A factor affecting nelarabine response was disease status (relapsed ORR 61% vs refractory ORR 35%; P = .008) while there were no significant differences in nelarabine response according to age (≤40 or > 40 years), diagnosis (T-ALL vs T-LBL), phenotype (early or mature vs thymic) or number of previous treatment lines (1 vs ≥2) (Table 2A).

The main adverse events (AEs) are reported in Table 2B. Seventy-five patients (64%) experienced one or more drug-related AEs. Neurologic toxicities of any grade were observed in 16/118 (14%) cases. In detail, neurological toxicity of grade III-IV were observed in 9/118 (8%) patients (one complete paraplegia, one encephalopathy, seven peripheral neuropathies); mild neurologic AEs (grade I-II) were reported in 7/118 (6%) cases, including headache, paresthesia and peripheral neuropathy. Thrombocytopenia or/and neutropenia (grade III-IV) were reported in 42% and 45% of cases, respectively. Hepatic toxicity (grade II) was observed in only 4/118 only (3%). No deaths due to neurologic toxicity were reported. There were three cases of AE-related deaths (two septic shocks and one aspergillosis), with an overall treatment-related mortality of 2.5% (3/118).

TABLE 2 (A) Response rate and pre-nelarabine factors affecting response, (B) Most common adverse events

(A) Response to nelarabine		
Complete remission (CR)	43/118 (36%)	
Partial remission (PR)	16/118 (14%)	
No response (NR)	59/118 (50%)	
Factors affecting nelarabine response Factor	**% ORR (CR + PR)**	***P****
Age		.71
18-40 y	20/63 (48)	
>40 y	29/55 (33)	
Diagnosis		.43
T-ALL	41/77 (53%)	
T-LBL	18/41 (44%)	
Phenotype		.83
Early T/Mature	17/32 (53)	
Thymic	42/86 (49)	
Previous lines of therapy		.19
1 line	31/54 (57)	
2 or more lines	28/64 (44)	
Disease status before nelarabine		.008
Relapsed	41/67 (61)	
Refractory	18/51 (35)	
(B) Toxicity and grade	**Number of cases (%)**	
Hematologic toxicity (CTCAE grade III-IV)	59/118 (50%)	
Neutropenia (Grade III-IV)	53/118 (45%)	
Thrombocytopenia (Grade III-IV)	50/118 (42%)	
Extra-hematologic toxicity (any grade)	38/118 (32%)	
Grade I-II	14/118 (12%)	
Grade III	15/118 (13%)	
Grade IV	9/118 (8%)	
Type of extra-hematologic toxicity (any grade)		
Neurologic toxicity	16/118 (14%)	
Infections	13/118 (11%)	
Others	9/118 (8%)	
Neurologic toxicity grade III-IV	9/118 (8%)	
Adverse events-related deaths	3/118 (3%)	

*Fisher's exact test.

3.2 | Allogeneic stem cell transplantation

A total of 47/118 (40%) patients underwent SCT after nelarabine salvage therapy. The median age at SCT was 36 years (range 20-64 years) and the median time between nelarabine therapy and SCT was 2.5 months (range 1-6 months). Twenty-eight of the 47 patients (60%) were transplanted in CR and four (8%) in PR, while 15 (32%) received SCT in the setting of R/R disease. A matched unrelated donor transplant (MUD-SCT) was performed in 18/47 cases (38%), a matched sibling donor transplant (MRD-SCT) in 17 (36%) and a haploidentical donor transplant (haplo-SCT) in 12 (26%). Twenty-seven patients who achieved cytologic response (CR or PR) after nelarabine therapy didn't undergo SCT for a variety of reasons (age, performance status, loss of response, no donor available).The transplanted patients received a variety of SCT preparative regimens according to the available protocols at the time of transplant. However, the most used conditioning regimens were TBI-based (total body irradiation + cyclophosphamide or fludarabine) in 20 cases (43%) and TBF (thiotepa, busulfan, fludarabine) in 16 cases (34%). The prevalent source of stem cells was peripheral blood, in 27 cases (55%). The median follow-up after SCT was 13 months (range 3-114 months) and the 2-year transplant-related mortality was 13% (6/47) and the relapse rate 46%.

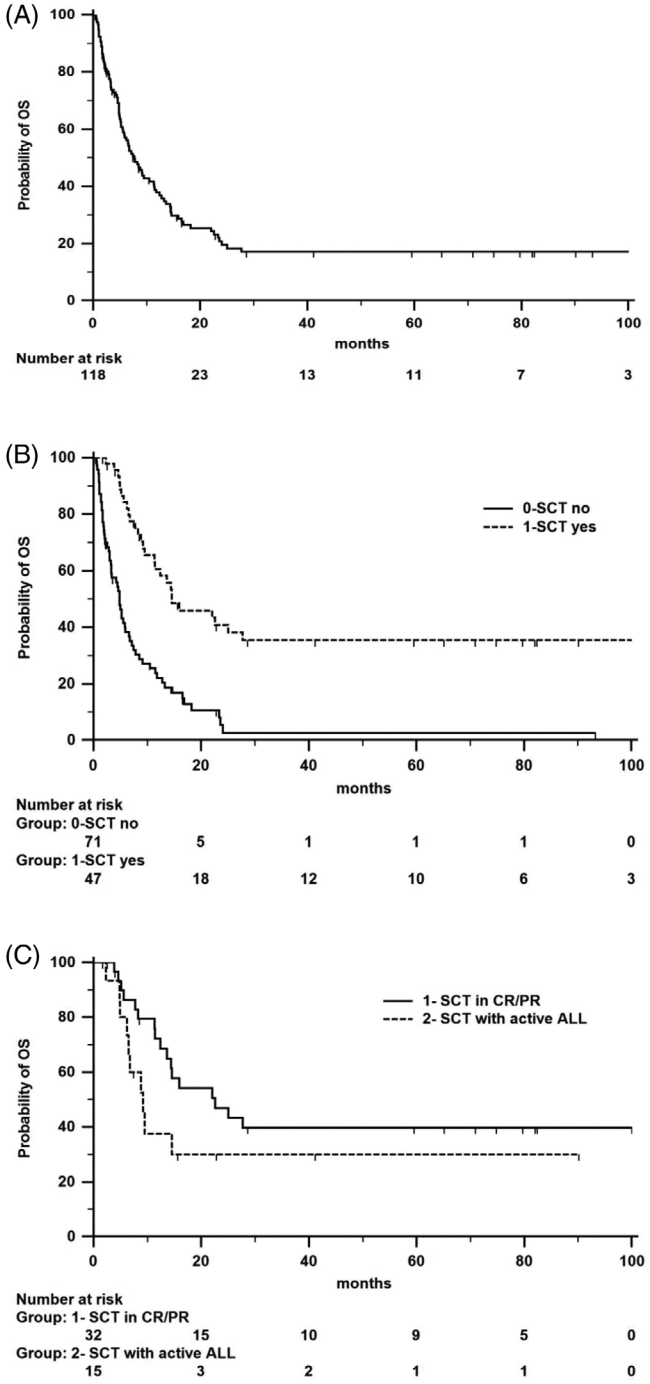

FIGURE 1 A, OS of the whole population (118 cases): 38% at 1 year and 18% at 5 years. Median survival 8 months. B, OS after nelarabine therapy according to SCT. Median OS: 14.5 (SCT) vs 4.8 months (no SCT); 1-year OS 54% vs 22% ($P < .001$). C, OS after SCT according to disease status at transplant. Median survival of 32 responders to nelarabine and allo-transplanted = 22.5 months and 5 years probability of OS = 40%

3.3 | Survival

The probability of OS from the first dose of nelarabine for the entire population was 37% at 1 year and 18% at 5 years, with a median survival of 8 months (Figure 1A).

The OS at 1 year was significantly better for the 47 patients who underwent SCT after nelarabine salvage treatment (58% vs 22%, $P < .001$) (Figure 1B). The probability of OS at 2 and 5 years from transplant was 46% and 38%, respectively (Figure 1B). The post SCT probability of EFS at 2 and 5 years was 35% and 35%, respectively. The 18 cases that received a MUD-SCT had a better OS (5-year OS = 56%) compared with haplo-SCT (5-year OS = 26%) and with MRD-SCT (5-year OS = 28%).

Remarkably, the median survival of the 32 cases that underwent SCT while in CR or PR after nelarabine treatment was 22.5 months, with a 5-year probability of OS of 40% (Figure 1C).

4 | DISCUSSION

Adult patients with R/R T-ALL/T-LBL continue to have limited therapeutic options and a particularly poor prognosis.[2,5,6] In recent years, several biological studies have demonstrated a high genetic heterogeneity of these diseases; however, they have also enabled identification of druggable genetic alterations and potentially targetable pathways.[15-17] Novel potential therapeutic approaches for patients with R/R T-ALL/T-LBL, including gamma-secretase inhibitors, BCL-2 inhibitors, mTor inhibitors, and monoclonal antibodies (such as daratumumab) have demonstrated promising preliminary results. However, none of these agents have received approval for clinical use.[1,5,18,19] Stem cell transplant remains the sole potentially curative option for these patients, but there is limited information regarding the feasibility and outcomes of SCT in the adult R/R T-ALL/T-LBL population.[20] The most recent and extensive analysis on this population was the multicenter retrospective cohort study performed by Hamilton et al. (2017), which included 208 adult patients with T-ALL (median age, 37 years) who underwent SCT between 2000 and 2014.

The majority of patients underwent the transplantations in CR1 (43%), while 39% (80/208) were in CR2 or greater and 18% (38/208) had R/R disease. There were no details regarding the treatment used as a bridge to transplant in CR2 or greater and in the R/R population. One-quarter of the cases underwent an alternative donor SCT using a mismatched umbilical cord blood or a haploidentical donor. With a median follow-up of 38 months, the 5-year OS reported was 34% for the entire patient population but, in patients with R/R disease, the 5-year OS was only 14%.[21]

Nelarabine was granted accelerated approval as an orphan drug by the U.S. FDA in 2005 for the treatment of R/R T-ALL/T-LBL in adults and children. The approval was based on two multicenter, non-randomized, open-label, single-arm trials (one including 84 pediatric and the other including 39 adult patients) that proved the efficacy of nelarabine monotherapy.[9,10] The registration study on adults (CALGB 19801 study) included only 39 patients with R/R T-ALL. The patients were treated with nelarabine at the dose of 1500 mg/m^2 on days 1, 3, and 5. The CR rate was 31% and the 1-year OS rate was 28%. As reported in the early phase trials, the most relevant toxicity was represented by reversible neurological events. In the CALGB 19801 registration study, for example, this was reported in 38% of patients (14%

grade three and 8% grade four).[10] Moreover, the CALGB 19801 study did not assess patients who underwent SCT.[10]

Given the paucity of data in the adult patient population, the FDA recommended appropriate post-marketing clinical trials to support and validate the accelerated approval of this drug.

Since FDA approval of nelarabine for R/R T-ALL/T-LBL, our study with 118 patients (including 47 who underwent SCT) and a German phase two trial with 126 patients (including 36 who underwent SCT) are the largest studies conducted in a post-marketing context to evaluate the the safety and efficacy of nelarabine as a single drug in adult patients with R/R T-ALL/T-LBL.[15] These two large studies used identical evaluation criteria of response and identical schedule of nelarabine therapy. The median ages of the patients treated (all R/R) were also similar in both studies. As reported in Table 3, a higher percentage of relapsed cases were included in our study (57% vs 36%). The total number of nelarabine cycles was 210 in 118 patients in the CAMPUS-ALL Italian study and 201 in 126 patients in the German study. The performance of nelarabine was comparable in the two studies, with a CR rate of 36% and a PR rate of 14% in the present observational study (ORR 50%), and 36% and 10%, respectively in the German phase two study (ORR 46%).

The transplantation rate after nelarabine salvage therapy was higher in our study (40% vs 29%), probably due to the greater availability of donors in more recent years, and a progressive increase in the upper age limit for transplantation. Additionally, the transplantation-related mortality was low and acceptable in both studies (13% and 11%, respectively). The 1-year OS was better in the current observational study (38% vs 24%), probably due to the higher percentage of patients who underwent allotransplantation and/or improvement in supportive care measures in recent years. The 3-year OS post-SCT was also slightly better in the present study (40% vs 31%).

TABLE 3 Comparison between Campus ALL post-marketing study (2020) and German phase II Study (2011)

Candoni et al Campus ALL Study (2020)	Gökbuget et al Phase II Study (2011) [6]
118 cases	126 cases
T-ALL 65% / T-LBL 35% REF 43% / REL 57%	T-ALL 85% / T-LBL 15% REF 74% / REL 36%
Median age	Median age
37 (18–74)	33 (18-81)
Total N° of nelarabine cycles: 210	Total N° of nelarabine cycles: 201
RESPONSE	RESPONSE
CR 36%	CR 36%
PR 14%	PR 10%
NR 50%	NR 52%
NE 0%	NE 2%
Transplantation rate 40%	Transplantation rate 29%
TRM 13%	TRM 11%
1-year OS 38%	1-year OS 24%
3-year OS in SCT 40%	3-year OS in SCT 31%

Abbreviations: CR, Complete Remission; NE, Not evaluable; NR, Not Responders; PR, Partial Remission; REF, Refractory; REL, Relapsed; SCT, Stem Cell Transplantation; TRM, Transplant-related mortality.

Taken together, the results of these two post-marketing studies are in agreement and support the use of a sequential program that includes nelarabine followed by SCT for adult patients with R/R T-ALL/T-LBL, at least until new, more effective drugs become available.

Particularly patients with responsive disease should be allografted as soon as possible, independently from sibling donor availability. In this regard, it is worthwhile emphasizing that if we consider the outcome of the 32 patients who, in our study, achieved a response to nelarabine (CR or PR) and were then allografted, the median survival was 22.5 months with a 5-year OS probability of 40%.

We confirmed that neurological and hematological toxicities were the most common AEs of nelarabine therapy.[11] However, as in the German study, we observed an acceptable safety profile of nelarabine in the present study, with no deaths due to neurological toxicity. The neurological toxicity was manageable and often reversible, similar to the hematological toxicity.[15] Deaths due to AEs were less than 3% in both studies and were essentially due to infection complications.

Our study has several limitations. In particular, it was an observational and retrospective study, and the available biological data were limited. Therefore, we could not conduct a correlation analysis between specific genetic or molecular characteristics and response to nelarabine treatment. However, this is the most recent and largest cohort of adult patients with R/R T-ALL/T-LBL treated in real-life settings with this drug. Taking into account the poor prognosis of this patient population, nelarabine can be considered an effective therapeutic option with an expected ORR of 50% and a CR rate of 36%, provided SCT is feasible after achieving a response. Indeed, 40% of the patients who received nelarabine salvage therapy and subsequently underwent SCT experienced an OS at 2, 3, and 5 years of 46%, 40%, and 38%, respectively. Overall, the safety profile was acceptable, with 8% of cases experiencing grade III-IV neurological AEs. In conclusion, the results of our study support the usefulness, in the absence of other options, of a sequential program including salvage nelarabine treatment followed by SCT for the management of adult patients with R/R T-ALL/T-LBL.

CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

Anna Candoni conceived, directed and supervised the study, collected and analyzed the data, and wrote the manuscript. Roberto Foà and Giovanni Pizzolo revised the manuscript. Davide Lazzarotto collected and analyzed the data. All authors collected the data, read, revised and approved the final manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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