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Pediatric-Like Acute Lymphoblastic Leukemia Therapy in Adults With Lymphoblastic Lymphoma: The GRAALL-LYSA LL03 Study

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ABSTRACT

Purpose

This study evaluated the efficacy of pediatric-like acute lymphoblastic leukemia (ALL) therapy in adults with lymphoblastic lymphoma (LL).

Patients and Methods

This was a prospective phase II study in adults 18 to 59 years old with previously untreated LL. Patients were treated with an adapted pediatric-like ALL protocol, which included a corticosteroid prephase, a five-drug induction reinforced by sequential cyclophosphamide administration, dose-dense consolidation, late intensification, CNS prophylaxis, and a 2-year maintenance phase. Treatment response was assessed by computed tomography and optional positron emission tomography. Allogeneic hematopoietic stem cell transplant was offered to selected patients in first complete remission (CR) or unconfirmed CR.

Results

The study enrolled 148 patients (131 with T-lineage LL [T-LL] and 17 with B-lineage LL [B-LL]). A total of 119 patients with T-LL (90.8%) and 13 with B-LL (76.5%) reached CR/unconfirmed CR, including 26 with T-LL and two with B-LL who needed a second induction salvage course. Relapse occurred in 34 patients with T-LL and four with B-LL. In patients with T-LL, 3-year event-free survival was 63.3% (95% CI, 54.2% to 71.0%), disease-free survival was 72.4% (95% CI, 63.0% to 79.7%), and overall survival was 69.2% (95% CI, 60.0% to 76.7%). Multivariate analysis identified serum lactate dehydrogenase level and the *NOTCH1/FBXW7/RAS/PTEN* oncogene (a four-gene oncogenetic classifier) status but not positron emission tomography or hematopoietic stem cell transplant as independent prognostic factors for outcome in T-LL.

Conclusion

In adults with LL, an intensive pediatric-like ALL treatment protocol was associated with a good response rate and outcome. In patients with T-LL, the four-gene oncogenetic classifier and lactate dehydrogenase level were independent prognostic indicators.

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INTRODUCTION

Lymphoblastic lymphoma (LL) is a rare and aggressive form of non-Hodgkin lymphoma (NHL) that most often affects young men.¹ In the current WHO classification, LL is grouped with acute lymphoblastic leukemia (ALL), although it is arbitrarily differentiated from ALL by the presence of less than 20% marrow blasts. Most cases of LL (> 80%) are T-lineage (T-LL); the rest are B-lineage (B-LL). At presentation, most patients with LL have advanced disease with

multiorgan involvement, including mediastinal masses. Patients with LL may also have bone marrow involvement (< 20% of cases) and CNS involvement (5% to 10% of cases).² Management of patients with LL is often difficult because of the aggressiveness of the disease and frequent mediastinal enlargement, which require urgent diagnosis and treatment.

Until recently, adult patients with LL were treated according to conventional NHL or ALL protocols.^{1,3} Response rates of 55% to 79% have been reported with NHL protocols, but overall

survival (OS) has been unsatisfactory because of frequent relapse, often related to spread of the disease to the CNS.⁴ In a retrospective analysis of 92 patients with LL who were included in the French LNH-87/93 trials, 5-year event-free survival (EFS) was only 22% and 5-year OS only 32%.⁵ Better results have been obtained using ALL protocols, with response rates of 55% to 100% and improved long-term survival.⁴

Although ALL-like intensive therapy is now considered the best option for treating adult LL, it is not yet standardized. The roles of mediastinal irradiation in patients with a high tumor burden, cranial irradiation as part of CNS prophylaxis, and autologous or allogeneic hematopoietic stem cell transplantation (HSCT) as consolidation therapy for high-risk patients continue to be debated.^{1,3,4} Several reports have shown that younger adults with ALL benefit from pediatric-like treatment protocols,⁶ but whether these protocols might also benefit adult patients with LL has been unclear.

We report here the results of the LL03 phase II study, which was conducted by the Group for Research on Adult ALL (GRAALL) and the Lymphoma Study Association (LYSA). Adult patients with LL were prospectively treated with a pediatric-like regimen adapted from the GRAALL protocol, previously shown to provide good responses in adult ALL.⁷ The study examined outcome of the treatment and investigated potential prognostic factors, including oncogenetic markers, as well as the influence of [¹⁸F]fluorodeoxyglucose positron emission tomography (PET) and allogeneic HSCT.

PATIENTS AND METHODS

Study Design

This single-arm, phase II study was conducted between 2004 and 2012 at 58 centers in France and Belgium (ClinicalTrials.gov registry no. NCT00195871). The primary objective was to evaluate the efficacy of pediatric-like ALL therapy in adults age 18 to 59 years with newly diagnosed, previously untreated LL, as assessed by EFS. Secondary objectives were to determine response rate, disease-free survival (DFS), OS, and progression/relapse rate; and to identify prognostic factors, including early response to therapy (assessed by computerized tomography [CT] and PET scans) and oncogenetic markers, in patients with T-LL. The study was performed in accordance to the Declaration of Helsinki and local laws. The protocol was approved by the Comité de Protection des Personnes Nord-ouest I in France and the independent ethics committees of each institution in Belgium. All patients provided written informed consent.

Patients

Adults 18 to 59 years of age with diffuse, previously untreated LL at any stage, diagnosed according to WHO 2008 criteria,⁸ were considered for enrollment. Patients had to be able to submit to regular monitoring and could not have a contraindication to anthracyclines, general or visceral contraindications to intensive treatment, infection with HIV, previous treatment with chemotherapy, lymphoblastic blast crisis of chronic myeloid leukemia, or malignant tumors except for basal cell carcinoma or carcinoma in situ of the cervix. Women of childbearing age had to have a negative pregnancy test.

Baseline Assessments

At enrollment, a biopsy of the tumor mass and a sternal or iliac bone marrow aspirate and/or trephine were performed in all patients, whenever possible. When present, a sample of pleural or peritoneal fluid was collected.

The disease was staged according to the Ann Arbor system.⁹ Whenever possible, immunophenotypic, cytogenetic, and molecular status was determined from diagnostic cells or tissue. In T-LL cases, gene screening included *NOTCH1/FBXW7* (N/F) mutations, *N/K-RAS* mutations, *PTEN* alterations, and T-cell receptor (TCR) gene rearrangements.¹⁰⁻¹² Only samples with $\geq 50\%$ infiltration by pathologic cells were considered interpretable for oncogenetic status. As described previously,¹¹ patients with T-LL were defined as having a favorable four-gene oncogenetic classifier if they had an N/F mutation in the absence of *RAS* or *PTEN* abnormalities; all other patients were defined as having an unfavorable four-gene classifier. Immunophenotype was classified according to the European Group for the Immunologic Classification of Leukaemias.¹³ Performance status was assessed using the Eastern Cooperative Oncology Group criteria (ECOG-PS).¹⁴ All patients had a thoraco-abdominal-pelvic CT scan with IV injection of iodine and optional gallium scan or 18-deoxyglucose PET scan; a complete and differential blood count; standard blood biochemistry analyses, including lactate dehydrogenase (LDH) and β -2 microglobulin levels; standard immunohematology, hemostasis, and virology serology; and human leukocyte antigen (HLA) typing.

Treatment

All patients received an adapted GRAALL protocol consisting of a corticosteroid prephase, a five-drug induction with sequential administration of cyclophosphamide (hyperC sequence), dose-dense consolidation, late intensification, CNS prophylaxis with intrathecal chemotherapy and cranial irradiation, and a 2-year maintenance phase (Data Supplement).⁷ Allogeneic HSCT was offered in first complete remission (CR) or unconfirmed complete remission (CRu) to patients with high-risk disease who had an HLA sibling-matched donor or who had a fully matched unrelated donor (ie, 10 of 10 HLA matched). Patients were considered to have high-risk disease if they had clinical or cytologic CSF CNS involvement or required a second induction salvage course to reach CR or CRu.

Assessment During and After Treatment

Early sensitivity to chemotherapy was assessed locally on day 8 of induction therapy. Treatment response was determined by CT scan and using Cheson criteria.¹⁵ After completion of the study, histologic findings were centrally reviewed by LYSA pathologists for approximately 70% of the patients. Survival measures are defined in the Data Supplement.

Study Size Calculation

The targeted study size was 120 patients. This was estimated to provide 20% precision (maximal 95% CI width) in the EFS and given a 20% dropout rate.

Statistical Analysis

Statistical analysis was performed using SAS version 9.3 (SAS Institute, Cary, NC). Analyses were performed in the full analysis set, defined as all patients with LL who received treatment. *P* values less than 0.05 were considered to be statistically significant. EFS, DFS, and OS were estimated by the Kaplan-Meier method. DFS was estimated from patients who experienced CR or CRu following induction or salvage therapy. A Cox model was used for estimation of hazard ratios (HRs). Candidate prognostic factors for survival measures (Data Supplement) were first assessed by univariate analysis using a log-rank test. Multivariate analysis was performed with the following cofactors: age, Ann Arbor stage, LDH, ECOG-PS, and all factors with *P* < .10 in the univariate analysis. Factors were excluded from the multivariate analyses if greater than 10% of the values were missing. The proportional hazard assumption was confirmed graphically and by an interaction test between time and each independent variable in the Cox models.

RESULTS

Patients

Between 2004 and 2012, 155 patients were recruited. Data were missing for one patient. On histologic review, two patients were reclassified as having diffuse large B-cell NHL, one with NHL of unknown type, and three with thymoma. Of the remaining 148 patients, 131 had T-LL and 17 had B-LL (Table 1). All patients had less than 20% marrow blasts. Most patients with T-LL were male (80.2%), whereas B-LL patients included nearly equal numbers of men (52.9%) and women (47.1%). Ages were similar for both subtypes (median, 37 years for B-LL and 33 years for T-LL). Most patients were asymptomatic or completely ambulatory (ECOG-PS 0 or 1), even though most had advanced disseminated disease (Ann Arbor stage 4). Most patients with T-LL had mediastinal involvement (94.7%) and about one-half had serous involvement (53.4%), but few had nonserous extranodal involvement (22.9%), whereas most patients with B-LL had nonserous extranodal involvement (58.8%) but not mediastinal (23.5%) or serous (17.6%) involvement. Approximately one-quarter of the patients in both groups had medullary involvement (25.0% B-LL, 26.6% T-LL). Few

patients had CNS involvement (11.8% B-LL, 4.6% T-LL), and few or no blasts were detected by cytology in the peripheral blood of patients in either group (median, 0.0% [range, 0.0% to 0.1%] for B-LL and 0.0% [range, 0.0% to 1.5%] for T-LL).

Response to Therapy

All 17 patients with B-LL and 125 of the patients with T-LL completed the study according to protocol. One patient with T-LL received HSCT not according to protocol, one received radiotherapy not according to protocol, and three partial responders received consolidation treatment without salvage treatment.

T-LL. Of the 131 patients with T-LL, 119 (90.8%) attained CR or CRu after induction or salvage treatment (Fig 1). Thirty patients (25.2%) needed a salvage course, and 34 (26.0%) relapsed (median follow-up, 35.7 months). Of the 34 patients who relapsed, seven had received salvage therapy to reach CR or CRu, and 14 had mediastinal relapse. At 3 years, EFS was estimated at 63.3% (95% CI, 54.2% to 71.0%; median follow-up, 30.3 months), DFS at 72.4% (95% CI, 63.0% to 79.7%; median follow-up, 57.7 months), and OS at 69.2% (95% CI, 60.0% to 76.7%; median follow-up, 35.7 months) (Fig 2). Overall, 88 patients with T-LL attained first complete remission, one attained second complete remission, two relapsed, and 40 died.

B-LL. Of the 17 patients with B-LL, 13 (76.5%) attained CR or CRu after induction or salvage treatment (Fig 1). Four patients needed a salvage course and four relapsed. Of the four patients who relapsed, none had received salvage therapy to reach CR or CRu. At 3 years, EFS, DFS, and OS were not estimated for B-LL because of the low number of patients. Overall, 10 patients with B-LL attained first complete remission, one attained stable disease, and six died.

Deaths, grade 3/4 adverse events, and serious adverse events. A total of 40 patients died during the study: five died because of induction toxicity, three because of allograft toxicity, one for an unknown reason, and 31 because of relapse or progression (Data Supplement). Grade 3/4 adverse events and the numbers of patient experiencing serious adverse events are summarized in the Data Supplement.

Prognostic Factors in T-LL

Because few patients had B-LL, prognostic analysis was only performed in patients with T-LL.

Oncogenetic factors. Fifty-four patients had diagnostic material with at least 50% infiltration (fresh or cryopreserved pleural or pericardial samples [$n = 7$] or tissue biopsies [$n = 47$]). The clinical characteristics, EFS, DFS, and OS for these patients did not differ significantly from the overall group (data not shown). *N/F* mutations were found in 51.9% (27 of 52) of the patients. *RAS/PTEN* alterations were found in 27.1% (13 of 48 patients). In univariate analysis, the presence of a high-risk genetic profile, as assessed by our four-gene oncogenetic classifier,¹¹ was associated with shorter EFS, DFS, and OS (Fig 2; Data Supplement). After adjustment for age, LDH level, Ann Arbor stage, and ECOG-PS, the four-gene oncogenetic classifier was confirmed to be an independent prognostic indicator for EFS (HR, 20.5 [95% CI, 2.6 to 164.1]; $P = 0.0045$), DFS (HR, 12.6 [95% CI, 1.5 to 104.8]; $P = .019$), and OS (HR, 17.0 [95% CI, 2.1 to 136.8]; $P = .0078$) (Table 2).

Table 1. Patient Demographic and Clinical Characteristics

Characteristic	B-LL (N = 17)	T-LL (N = 131)
Sex, no. (%)		
Male	9 (52.9)	105 (80.2)
Female	8 (47.1)	26 (19.8)
Age, years		
Mean \pm SD	38.3 \pm 14.9	35.0 \pm 12.1
Median	37	33
Range	19–58	18–59
ECOG-PS, no. (%)		
0	7 (41.2)	56 (42.7)
1	6 (35.3)	57 (43.5)
2	2 (11.8)	16 (12.2)
3	2 (11.8)	1 (0.8)
4	0 (0.0)	1 (0.8)
CNS involvement, n/N (%)	2/17 (11.8)	6/131 (4.6)
Mediastinal involvement, n/N (%)	4/17 (23.5)	124/131 (94.7)
Nonserous extranodal involvement, n/N (%)	10/17 (58.8)	30/131 (22.9)
Serous involvement, n/N (%)	3/17 (17.6)	70/131 (53.4)
Ann Arbor stage, no. (%) [*]		
1	1 (5.9)	14 (10.8)
2	3 (17.6)	22 (16.9)
3	0 (0.0)	15 (11.5)
4	13 (76.5)	79 (60.8)
Medullary involvement, n/N (%)	4/16 (25.0)	34/128 (26.6)
Peripheral blood blasts, % [†]		
Median	0.0	0.0
Interquartile range	0.0	0.0
Range	0.0–0.1	0.0–1.5
LDH concentration, no. (%) [*]		
Normal range	9 (52.9)	38 (29.2)
1.1–1.9 \times normal limit	4 (23.5)	47 (36.2)
2.0–3.9 \times normal limit	2 (11.8)	38 (29.2)
4.0–9.9 \times normal limit	2 (11.8)	7 (5.4)

Abbreviations: B-LL, B-type lymphoblastic leukemia; ECOG-PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; T-LL, T-type lymphoblastic leukemia.

^{*}N = 130 patients with T-LL.

[†]N = 127 patients with T-LL.

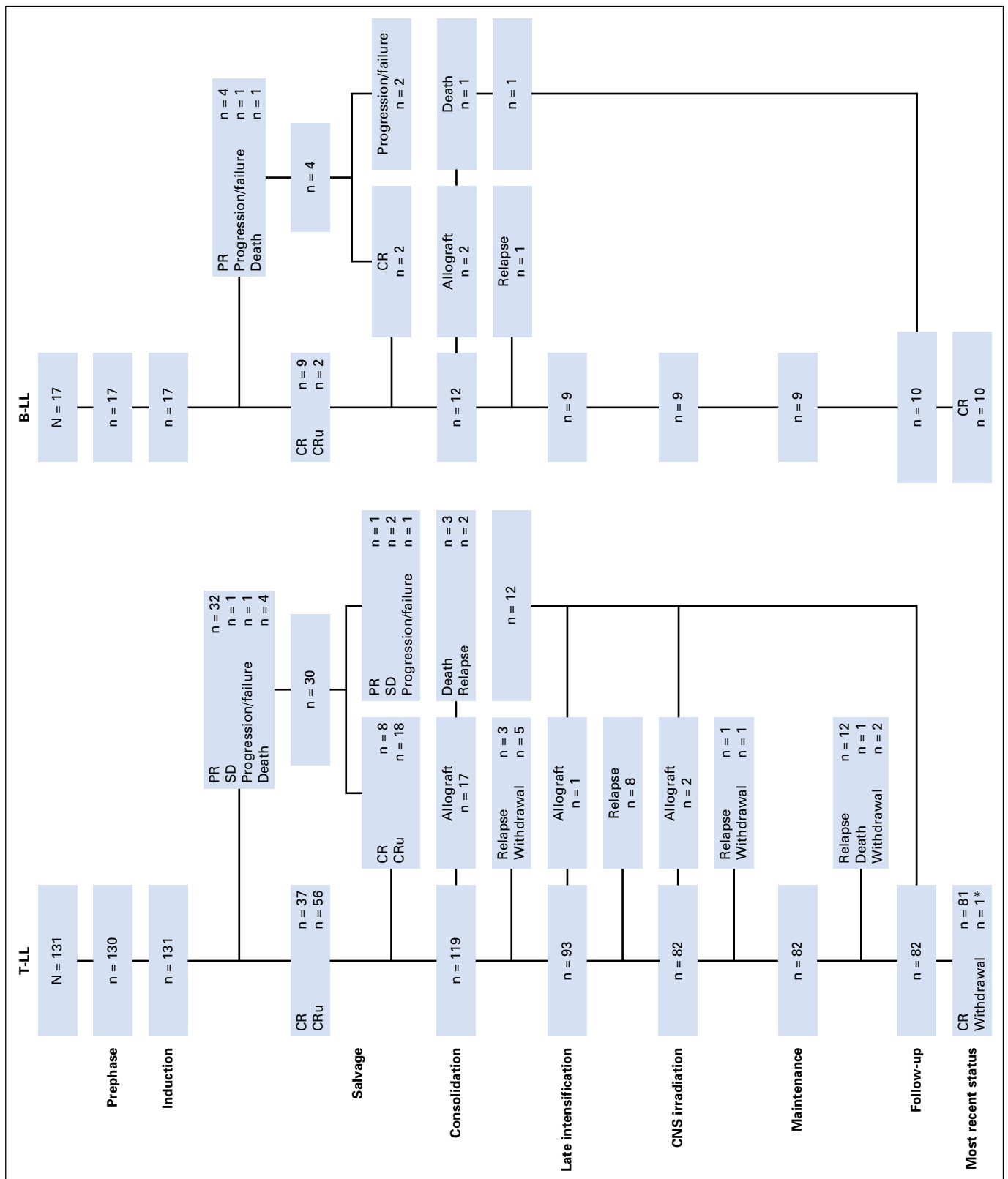


Fig 1. Flow of patients and treatment response. Treatment response was assessed using Cheson criteria.¹⁵ B-LL, B-lineage lymphoblastic lymphoma; CR, complete remission; CRu, unconfirmed complete remission; PR, partial remission; SD, stable disease; T-LL, T-lineage lymphoblastic lymphoma. (*) This patient attained complete remission after another lymphoma.

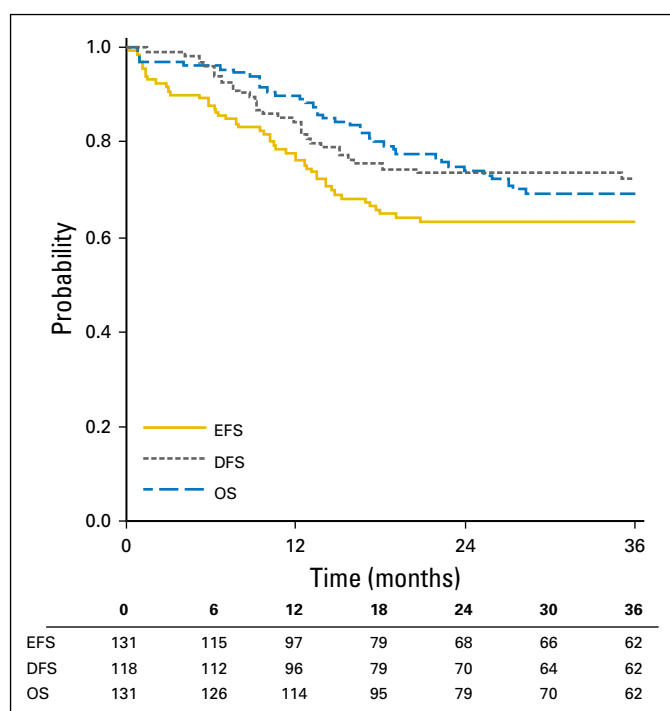


Fig 2. Event-free survival (EFS), disease-free survival (DFS), and overall survival (OS) patient data.

TCR gene rearrangement. The absence of TCR γ gene rearrangement has been reported to predict a poor prognosis in pediatric T-ALL¹⁶ and T-LL.¹² After exclusion of cases with thymoma, following a review of histologic data, six of 54 patients were TCR γ -negative and 10 of 53 were TCR β -negative. However, neither subgroup had inferior EFS, DFS, or OS (Data Supplement).

18-deoxyglucose PET scan. 18-deoxyglucose PET scans were available at the end of induction for 68 patients with T-LL and eight patients with B-LL. PET scans were positive for 23 patients with T-LL (33.8%) and three patients with B-LL (37.5%). Use of PET scan at the end of induction did not influence the ability to predict EFS, DFS, OS, or mediastinal relapse in patients with T-LL (Table 3), although PET findings at the end of induction correlated with status determined by CT scan (Data Supplement).

HSCT. Of 25 patients with T-LL who were eligible for HSCT (ie, high-risk patients), 17 were transplanted and eight were not. HRs for EFS, DFS, and OS were not significantly different in patients receiving allogeneic HSCT compared with patients not receiving it (Table 3).

Other factors. Multivariate analysis showed that LDH level (normal or elevated) was an independent prognostic indicator for EFS (HR, 2.8 [95% CI, 1.3 to 5.9]; $P = .010$) and OS (HR, 3.4 [95% CI, 1.3 to 8.7]; $P = .012$) (Data Supplement). In addition, ECOG-PS score (≥ 3 v ≤ 2) was an independent prognostic factor for DFS (HR, 0.1 [95% CI, 0.0 to 0.7]) and OS (HR, 0.1 [95% CI, 0.0 to 0.6]), although only two of the 118 patients included in the analysis had an elevated ECOG-PS score (≥ 3). Interestingly, the need for a salvage course to reach CR or CRu was not associated with shorter DFS in patients with CR or CRu.

DISCUSSION

This study confirms that a pediatric-like ALL therapy improves outcome in adults with LL. The study also supports an independent prognostic value of the four-gene oncogenetic classifier status at diagnosis in patients with T-LL.

With 148 patients enrolled over 8 years, this phase II study is one of the largest conducted to date in adults with LL. Treatment in this study was based on the GRAALL protocol for ALL,⁷ although it

Table 2. Significant Independent Prognostic Indicators of Survival As Determined by Multivariate Analysis

Variable	EFS				DFS			OS		
	No.	No. of Events	aHR* (95% CI)	P	No. of Events	aHR* (95% CI)	P	No. of Events	aHR* (95% CI)	P
Four-gene oncogenetic classifier†				.0045			.0187			.0078
Favorable	19	1	1		1	1		1	1	
Unfavorable	30	16	20.5 (2.6 to 164.1)		10	12.6 (1.5 to 104.8)		14	17.0 (2.1 to 136.8)	
Total	49	17			11			15		
LDH level‡				.010			.221			.0119
Normal	38	8	1		8	1		5	1	
Elevated	91	39	2.8 (1.3 to 5.9)		23	1.7 (0.7 to 3.8)		32	3.4 (1.3 to 8.7)	
Total	129	47			31			37		
ECOG-PS§				.084			.012			.010
≥ 3	2	2	1		2	1		2	1	
≤ 2	129	45	0.3 (0.1 to 1.2)		116	0.1 (0.0 to 0.7)		129	0.1 (0.0 to 0.6)	
Total	131	147			118			131		

Abbreviations: aHR, adjusted hazard ratio; CR, complete response; CRu, unconfirmed complete response; ECOG-PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; OS, overall survival.

*Adjusted hazard ratios were determined by multivariate Cox regression analysis.

†T-LL patients were defined as having a favorable *NOTCH1/FBXW7/RAS/PTEN* 4-gene oncogenetic classifier if they had an *NOTCH1/FBXW7* mutation in the absence of *RAS* or *PTEN* abnormalities. Multivariate analysis was adjusted for age, LDH level and ECOG-PS score.

‡Normal range was determined independently by each laboratory. Multivariate Cox regression analysis was adjusted for age, Ann Arbor stage, and ECOG-PS score.

§Adjusted for Ann Arbor stage, LDH level, and ECOG-PS score.

Table 3. Univariate Analysis of Survival According to PET Scan Findings at the End of Induction and According to the Use of HSCT in Patients With T-LL

Stratification Criterion	No.	Events Before 3 Years	Value (95% CI)	P
PET scan*				.1532
EFS				
Total	68	21		
Negative	42	12	72.7% (56.9 to 83.5)	
Positive	23	9	59.7% (36.7 to 76.7)	
DFS				.9236
Total	64	15		
Negative	45	11	74.8% (59.0 to 85.2)	
Positive	19	4	72.5% (39.9 to 89.4)	
OS				.7845
Total	68	15		
Negative	45	11	73.4% (56.9 to 84.4)	
Positive	23	4	79.3% (53.1 to 91.9)	
Survival without mediastinal relapse				.1876
Total	14	7		
Negative	10	4	50.0% (13.7 to 78.5)	
Positive	4	3	25.0% (0.9 to 66.5)	
HSCT†				
EFS				.5061
Total	25	7		
HSCT	17	4	HR, 1	
No HSCT	8	3	HR, 0.602 (0.135 to 2.690)	
DFS				.7303
Total	25	8		
HSCT	17	5	HR, 1	
No HSCT	8	3	HR, 0.776 (0.184 to 3.278)	
OS				.3718
Total	25	6		
HSCT	17	3	HR, 1	
No HSCT	8	3	HR, 0.482 (0.097 to 2.39118)	

Abbreviations: DFS, disease-free survival; EFS, event-free survival; HR, hazard ratio; HSCT, hematopoietic stem-cell transplantation; OS, overall survival; PET, positron emission tomography; T-LL, T-type lymphoblastic leukemia.

*Survival rates were estimated by Kaplan-Meier analysis and *P* values were determined by log-rank test.

†Hazard ratios and *P* values were determined by a Cox model using time-dependent explanatory variables.

was reinforced by inclusion of a hyperC sequence during induction. The protocol did not include mediastinal irradiation because Hoelzer¹⁷ et al showed that 50% of patients with T-LL that received it had mediastinal relapse and because it was not considered a required, validated option.

The general outcome was good: CR or CRu was attained in 90.8% of patients with T-LL and 76.5% of those with B-LL. Only one-quarter of the patients relapsed or progressed (23% with B-LL, 26% with T-LL) after a median follow-up of 3 years. In patients with T-LL, at 3 years, EFS was estimated at 63%, DFS at 72%, and OS at 69%. This compares with other studies using ALL-like intensive chemotherapy regimens in similar patients, which have reported CR rates of 91% to 93% and 5-year DFS of 62% to 77%.¹⁷⁻¹⁹

To date, consistent prognostic factors have not been reported for adults with LL.⁴ The serum LDH level is reported to be a predictor of response to chemotherapy in childhood ALL.²⁰ This has also been observed in some adult LL studies²¹⁻²³ but not in others.^{19,24} In the current study, LDH level was an independent prognostic indicator for EFS and OS. Other factors reported to be of prognostic value in adult LL include ECOG-PS,²⁵ Ann Arbor

stage,^{23,26} bone marrow involvement,²⁷ and CNS involvement at presentation.¹⁹ We did not find Ann Arbor stage, bone marrow involvement, or CNS involvement to be predictive of outcome. ECOG-PS was a significant predictor of outcome, although only two of 118 patients included in the analysis had an elevated score (≥ 3). These results suggest that intensive pediatric-like ALL-like therapy may reduce the prognostic impact of features associated with systemic diffusion of LL.

Analysis of 141 adult diagnostic T-ALL samples collected from patients in the LALA-94 trial and the GRAALL-2003 trial revealed that the presence of *N/F* mutations was an independent predictor of a better prognosis.¹⁰ Further analysis of 212 GRAALL samples showed that *N/F* mutation was an independent predictor of better outcome only in the absence of *RAS* or *PTEN* abnormalities (favorable four-gene oncogenetic classifier), whereas all other profiles (unfavorable four-gene classifier) were predictive of a worse outcome (Fig 3).¹¹ This four-gene oncogenetic classifier and, to a lesser extent, bone marrow minimal residual disease remained the only two factors associated with relapse incidence in patients with T-ALL in the GRAALL trial.²⁸ The fact that the same four-gene

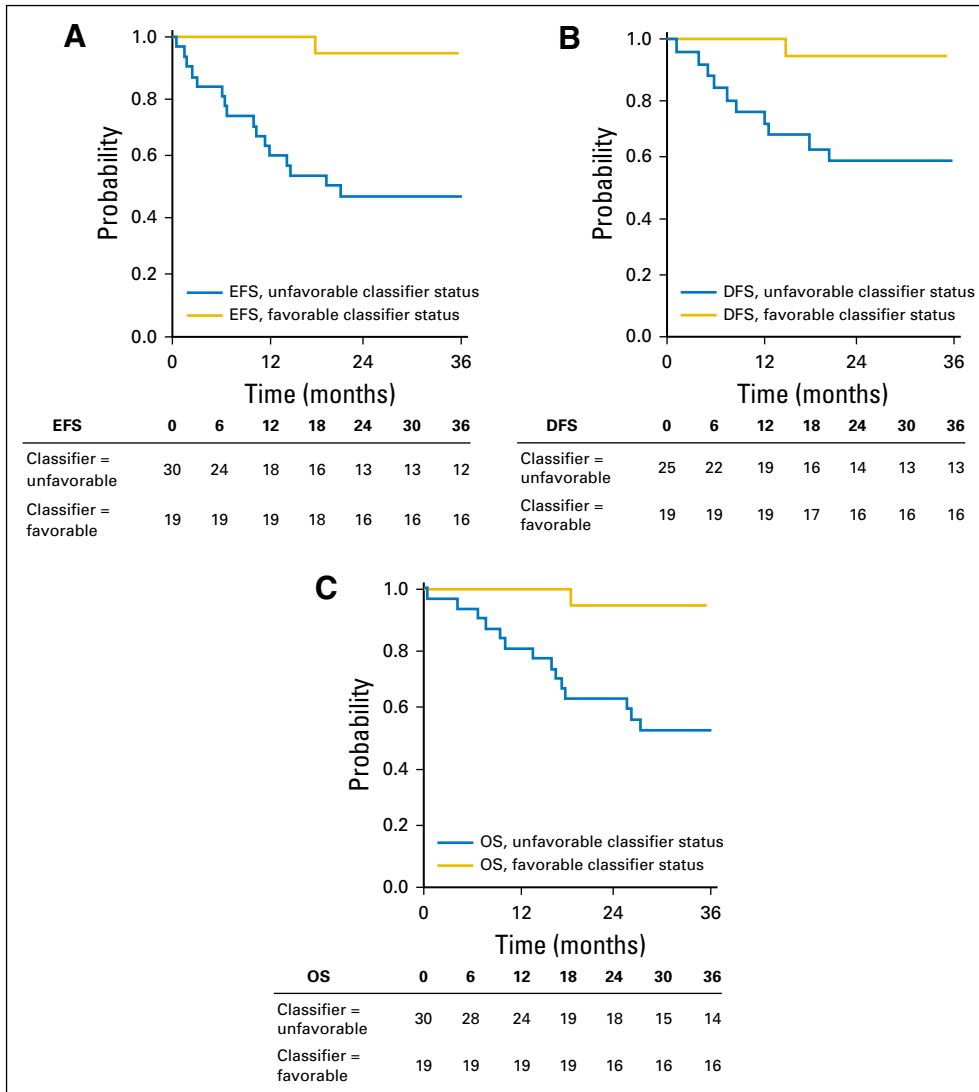


Fig 3. (A) Event-free survival (EFS), (B) disease-free survival (DFS), and (C) overall survival (OS) according to the four-gene oncogenetic classifier. Patients with T-lineage lymphoblastic lymphoma were defined as having a favorable *NOTCH1/FBXW7/RAS/PTEN* four-gene oncogenetics if they had an *N/F* mutation in the absence of *RAS* or *PTEN* abnormalities.

classifier has strong prognostic value in adult T-LL underlines the similarities between T-ALL and T-LL.

The absence of biallelic TCR γ deletion or rearrangement has been shown to predict early treatment failure in pediatric T-ALL.^{16,29} We have also shown that this applies to pediatric patients with T-LL who have mutant *N/F*.¹² Although we did not confirm this in the current study, a review of histologic data identified three cases of thymoma with an absence of biallelic TCR γ rearrangement or deletion, suggesting that TCR rearrangements can be a useful adjunct to histologic review, particularly when DNA diagnostics are already being performed for the four-gene oncogenetic classifier.

In the current study, allogeneic HSCT was offered to patients in CR or CRu who needed a second induction salvage course or who had CNS disease. A retrospective multicenter study of 128 patients with LL treated with autologous or allogeneic stem cell transplant found significantly fewer relapses in patients receiving allogeneic HSCT from an HLA-identical sibling.³⁰ Also, a small randomized trial of the European Group for Blood and Marrow Transplantation and the United Kingdom Lymphoma Group found a

trend for longer DFS but no OS improvement in adult patients with LL receiving allogeneic stem cell transplant compared with those receiving conventional chemotherapy.³¹ In the current study, allogeneic HSCT did not appear to influence outcome, although it was performed in too few patients ($n = 20$) to make definitive conclusions.

We also examined the role of [^{18}F]fluorodeoxyglucose PET in patients with LL. PET is a powerful tool for evaluating responses in lymphomas and other malignancies, and the results correlate with outcome in aggressive NHL and Hodgkin lymphoma.³² In this study, PET was not recommended and was only performed in cases of residual masses. We found that having a PET scan did not improve the ability to predict treatment outcome. Similarly, a recent retrospective analysis of data from the Swedish Lymphoma Registry found that having a [^{18}F]fluorodeoxyglucose PET scan does not predict the risk for relapse in patients with T-LL treated with intensive therapy used for patients with ALL.²⁴ In contrast, in a recent prospective study of 149 patients with T-LL treated according to the German Multicenter Study Group protocol, PET evaluation yielded positive results in 10 of 22 (45%) partial

responders, suggesting that PET can be helpful in making decisions about salvage therapies.³³ Thus, further study is needed to clarify the utility of PET in the treatment of LL.

This study marks a step forward because it provides information on the biology and treatment of adult LL as a distinct entity. We showed that a pediatric ALL-like treatment provides good results in adult patients with LL patients. We also showed that the four-gene oncogenetic classifier is a useful tool for predicting outcome of the treatment in T-LL.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org

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Pediatric-Like Acute Lymphoblastic Leukemia Therapy in Adults With Lymphoblastic Lymphoma: The GRAALL-LYSA LL03 Study

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