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Successful Outcomes of Newly Diagnosed T Lymphoblastic Lymphoma: Results From Children's Oncology Group AALL0434

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abstract

PURPOSE The Children's Oncology Group (COG) protocol AALL0434 evaluated the safety and efficacy of multiagent chemotherapy with Capizzi-based methotrexate/pegaspargase (C-MTX) in patients with newly diagnosed pediatric T-cell lymphoblastic lymphoma (T-LL) and gained preliminary data using nelarabine in high-risk patients.

PATIENTS AND METHODS The trial enrolled 299 patients, age 1-31 years. High-risk (HR) patients had ≥ 1% minimal detectable disease (MDD) in the bone marrow at diagnosis or received prior steroid treatment. Induction failure was defined as failure to achieve a partial response (PR) by the end of the 4-week induction. All patients received the augmented Berlin-Frankfurt-Muenster (ABFM) C-MTX regimen. HR patients were randomly assigned to receive or not receive 6 5-day courses of nelarabine incorporated into ABFM. Patients with induction failure were nonrandomly assigned to ABFM C-MTX plus nelarabine. No patients received prophylactic cranial radiation; however, patients with CNS3 disease (CSF WBC ≥ 5/μL with blasts or cranial nerve palsies, brain/eye involvement, or hypothalamic syndrome) were ineligible.

RESULTS At end-induction, 98.8% of evaluable participants had at least a PR. The 4-year event-free survival (EFS) and overall survival (OS) were 84.7% ± 2.3% and 89.0% ± 2.0%. The 4-year disease-free survival (DFS) from end-induction was 85.9% ± 2.6%. There was no difference in DFS observed between the HR and standard-risk groups ($P = .29$) or by treatment regimen ($P = .55$). Disease stage, tumor response, and MDD at diagnosis did not demonstrate thresholds that resulted in differences in EFS. Nelarabine did not show an advantage for HR patients. CNS relapse occurred in only 4 patients.

CONCLUSION COG AALL0434 produced excellent outcomes in one of the largest trials ever conducted for patients with newly diagnosed T-LL. The COG ABFM regimen with C-MTX provided excellent EFS and OS without cranial radiation.

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INTRODUCTION

Lymphoblastic lymphoma makes up approximately 20% of childhood non-Hodgkin lymphoma. More than 80% of patients have a precursor T-cell immunophenotype (T-cell lymphoblastic lymphoma, T-LL).[1] Identifying prognostic factors has been challenging, because age, sex, race, or cytogenetic abnormalities have not been found to be prognostically significant.[2-7] However, modern treatments have resulted in event-free survival (EFS) spanning 80%-90% for high-stage patients (III-IV).[8-12] Salvage rates are dismal for relapsed patients.[13]

Prior studies have reported that the amount of minimally detectable disease (MDD) in the bone marrow measured by flow cytometry at diagnosis is prognostically important.[7,14] Our previous trial (A5971; ClinicalTrials.gov identifier: NCT00004228) found that patients with ≥ 1% MDD had an inferior outcome compared with patients with < 1% MDD.

Nelarabine is a water-soluble prodrug of ara-G, a synthetic deoxyguanosine derivative that is resistant to cleavage by endogenous purine nucleoside phosphorylase and is cytotoxic to T-lymphoblasts.[15] Initial studies have demonstrated that it is highly active in T-cell leukemia/lymphoma and can be combined safely with chemotherapy in newly diagnosed pediatric T-cell acute lymphoblastic leukemia (T-ALL).[16-18] We therefore sought to explore whether the addition of nelarabine could improve outcomes in a high-risk (HR) T-LL group.

Recent studies have demonstrated that leukemia-based therapy is an effective strategy in the treatment of T-LL.[8-10,12] Two different methotrexate (MTX) intensification strategies are used commonly: high-dose

ASSOCIATED CONTENT

Appendix

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objectives

Children, adolescents, and young adults with newly diagnosed T-cell lymphoblastic lymphoma (T-LL) were enrolled in AALL0434 to evaluate the Children's Oncology Group augmented Berlin-Frankfurt-Muenster regimen using Capizzi-style methotrexate (MTX) plus pegaspargase rather than high-dose MTX. A high-risk T-LL subpopulation was also randomly assigned to receive the regimen with or without nelarabine.

Knowledge Generated

Using this regimen, which did not require cranial radiation, the overall survival and disease-free survival rates were comparable or superior to expected. Furthermore, the treatment-related mortality rate was low, and no patient developed a secondary malignancy. High-risk patients had comparable outcomes to standard-risk patients regardless of the use of nelarabine, suggesting that pegaspargase contained within Capizzi-style MTX was an important component of the therapy.

Relevance

This regimen can therefore provide the backbone to build future therapies for T-LL to further improve outcomes while minimizing treatment-related sequelae.

MTX with leucovorin rescue (HD-MTX), and Capizzi-style MTX, escalating intravenous MTX without leucovorin rescue plus pegaspargase (C-MTX).[15,19] Recent T-LL trials have used modifications of ALL-BFM-90 with HD-MTX instead of C-MTX, which typically results in 2 fewer doses of pegaspargase.

Children's Oncology Group (COG) AALL0434 was a phase III trial developed for children, adolescents, and young adults 1-30.99 years old with T-ALL. The trial featured a 2 × 2 pseudo-factorial randomization for patients with T-ALL using the COG augmented Berlin-Frankfurt-Muenster (ABFM) regimen comparing C-MTX versus HD-MTX in patients with intermediate and high-risk T-ALL also randomly assigned to receive or not receive nelarabine.[15,19,20] Results of the T-ALL population showed that C-MTX had a superior disease-free survival (DFS) and overall survival (OS) to HD-MTX.[20,21] The addition of nelarabine further improved the DFS.[21] The previous COG T-LL study (A5971) failed to demonstrate that HD-MTX improved the outcome for these patients. Furthermore, the Pediatric Oncology Group demonstrated that L-asparaginase was important in T-cell malignancies,[22] Thus, we wished to examine whether the C-MTX ABFM regimen, which includes a total of 7 doses of pegaspargase, would be efficacious for pediatric T-LL, compared with 5 doses of pegaspargase for HD-MTX.

PATIENTS AND METHODS

Patient Population

Enrollment of patients with T-ALL began in January 2007, with the addition of T-LL enrollment in September 2010. Study accrual was completed in July 2014. All patients fulfilled the diagnosis for T-LL using institutional standards on the basis of WHO criteria. The diagnosis was confirmed by central review (S.L.P., R.R.M.). Patients with Murphy stage II-IV disease were eligible. Subjects with Down syndrome were ineligible; patients found to have the Philadelphia chromosome were not eligible for postinduction therapy in this study. Risk assignment was not based on cytogenetics,[2-4] genomic alterations,[5,6] or the early T-precursor phenotype.[7]

MDD status was achieved using flow cytometry of bone marrow specimens obtained at diagnosis, analyzed at the University of Washington (B.L.W.) using established methodologies.[23] Before receiving systemic therapy, CSF examination established the CNS disease status; CNS1 (no blasts in the CSF), CNS2 (CSF WBC $<$ 5/μL with blasts), and CNS3 (CSF WBC $\geq$ 5/μL with blasts or cranial nerve palsies, brain/eye involvement, or hypothalamic syndrome).[19,24] Patients with T-LL with CNS3 disease or gross involvement of the testes were ineligible to participate. Our previous study, A5971, only had 12 patients of 266 with CNS disease at presentation and no patients with testicular disease. Given the low number of expected patients, the patients were not eligible for enrollment.

AALL0434 was approved by the National Cancer Institute, Cancer Therapy Evaluation Program, US Food and Drug Administration, and Pediatric Central Institutional Review Board (IRB), and by IRBs at each participating center. In accordance with the Declaration of Helsinki, informed consent/assent was obtained before study entry.

Study Design

The treatment assignments for participants with T-LL in AALL0434 were based on their risk status established at diagnosis (Data Supplement). High-risk (HR) patients were defined as patients with $\geq$ 1% MDD in the bone marrow or who had received steroid pretreatment for $>$ 48 hours before diagnosis, potentially masking the extent of bone marrow disease. All others were designated standard risk (SR).

All SR patients with T-LL received the COG ABFM regimen, arm A. Patients assigned to the HR category were randomly assigned to receive arm A or the same regimen with 6 5-day courses of nelarabine (arm B).[20] The study used 2 consents, one for induction and a second for the postinduction therapy, when the HR patients were randomly assigned their treatment (Appendix Table A1, online only).[15]

Arm A began with a 28-day, prednisone-based, 4-drug induction, followed by an ABFM consolidation phase (Table A1). This was followed by an 8-week interim maintenance (IM) phase, where patients received C-MTX with escalating doses of intravenous MTX without leucovorin plus 2 doses of pegaspargase, vincristine (5 doses), and intrathecal MTX (2 doses). After completion of IM, patients received a single delayed intensification (DI) phase. Details of pegaspargase dosing were not captured for these patients. All patients then received maintenance therapy for 2 years after the start of IM, (Table A1). No patient received cranial radiation therapy (CRT).

Patients assigned to arm B received therapy identical to arm A, with the addition of nelarabine. Nelarabine was administered as 5-day courses (consolidation, days 1-5 and 29-33, in DI, days 29-33, and 3 courses in maintenance on days 29-33 of the first 3 cycles; Table A1).

Treatment-related adverse events were graded using Common Terminology Criteria for Adverse Events version 4. Toxicities associated with nelarabine, including CNS toxicity, peripheral neuropathy, and rhabdomyolysis, were monitored with immediate notification of the study chair.

Disease Evaluation

Disease evaluations were performed at the end of induction, consolidation, and at the end of therapy, using the radiologic imaging modalities to stage the disease at diagnosis. Additional radiologic monitoring was not anticipated to affect the ultimate number of patients with progressive disease and was not required. Responses were determined by the treating institution, and nuclear imaging was not required for evaluation. The following were used to classify responses at the end of the 4-week induction:

- Complete response (CR): disappearance of all evidence of disease.
- Complete response unconfirmed (CRu): a lymph node mass $>$ 1.5 cm that regressed by $>$ 75% in sum of the products of the greatest perpendicular diameters (SPD), or any lesions that had decreased by $>$ 75%.
- Partial response (PR): a $>$ 50% decrease in the SPD of disease and no new lesions.
- No response (NR): failure to qualify for a PR and no new lesions.
- Progressive disease (PrD): $>$ 25% increase in the SPD or appearance of new lesion(s) with the first measurement at the end of induction.
- Induction failure (IF) was defined as NR or PrD at the day-29 evaluation.

Patients deemed to have NR were nonrandomly assigned to arm B (C-MTX plus nelarabine) to begin consolidation therapy as soon as possible without waiting until day 36 or count recovery. Patients with PrD after induction were removed from protocol therapy. Evaluations of persistent masses did not require additional imaging. Relapse was defined as any recurrence of disease.

Statistical Analysis

EFS was defined as time from study enrollment (first consent) to first event (IF, induction death, relapse, second malignant neoplasm, remission death) or date of last contact for those who were event free. DFS was defined as time from postinduction random assignment (second consent) to first event or date of last contact for those who were disease-free. OS was defined as time from study enrollment to death or date of last contact for those who were alive. OS for the randomly assigned cohorts was defined as time from postinduction random assignment to death or date of last of contact for those who were alive.

The patients with T-LL were stratified and analyzed separately from analyses for the patients with ALL. As expected when the study was amended to include the patients with T-LL, there was insufficient power for any formal comparison of outcomes between randomized regimens (± nelarabine). Outcomes of the randomly assigned cohort are descriptive in nature only.

Data current as of June 30th, 2018 are included in this report. Survival rates were estimated by using the method of Kaplan-Meier with standard errors of Peto et al.[25,26] Survival rates and hazard ratios are presented as number (95% CI). Two-sided log-rank tests were used for comparison of survival curves. Proportions were compared between groups using a χ^2 test or Fisher's exact test. A $P < .05$ was considered significant for all comparisons. All analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC). Graphics were generated with R Version 2.13.1.[27]

RESULTS

Participants

AALL0434 enrolled 299 patients with T-LL (2010-2014). Seventeen were subsequently deemed ineligible/unevaluable, leaving 282 patients who were evaluable for induction (Appendix Table A2, online only), including 95 SR and 180 HR patients, 3 patients with IF, and 4 unknowns (Fig 1). Of these, 82 SR patients, 121 HR patients and 2 patients defined as IF continued on postinduction therapy. Reasons for the 77 patients coming off protocol therapy at the end of induction are summarized in Table A3 (online only). The design of the study required a second consent at the end of induction, which included the random assignment of the HR patients to nelarabine. Sixty-one percent of these 77 patients refused additional protocol therapy.

Table 1 summarizes characteristics of the patients who continued postinduction therapy on protocol by risk-group assignment. Staging information was not submitted for 77 patients, and stage was given as indeterminate for 11 patients. Fifty-seven (47%) of the HR patients were classified as HR solely because of prior steroid exposure, despite having an MDD at diagnosis of $< 1\%$ in the bone marrow. Twenty-one (17%) of the HR patients who received steroids before enrollment still had an MDD $\geq 1\%$, and 38 (31%) who did not receive steroid pretreatment were HR because they had MDD $\geq 1\%$.

Outcomes Defined by Risk Groups and Early Response

At the end of induction (EOI), 98.8% of all eligible, evaluable patients achieved at least a partial response (30.8% CR, 34.0% CRu, 34.0% PR). Median follow-up was 4.9 years. The 4-year EFS and OS for the whole cohort (including those who did not continue protocol therapy postinduction) was 84.7% ± 2.3% and 89.0% ± 2.0%, respectively (Fig 2A). Four-year DFS from the end of induction for all patients who continued with postinduction therapy in the study was 85.9 ± 2.6% (Fig 2B). The 2 patients with T-LL IF assigned to C-MTX plus nelarabine completed therapy and were event free.

There were 10 events within the SR group and 23 events in the HR group (11 in arm A and 12 in arm B; Table A4, online only). There were 3 remission deaths in the SR group and 2 in the HR group (1 in each arm). Progressive disease after induction occurred in 5 patients; 3 of these patients had a PR and 2 had CRu at the EOI. Relapse occurred in 5 SR and 17 HR patients (7 in arm A and 10 in arm B). Four patients had CNS relapses. Four-year DFS was 85.0% ± 3.4% for SR patients compared with 87.4% ± 4.0% for HR patients ($P = .2866$; Fig 3A). There was no significant difference in DFS when comparing SR versus HR arm A vs HR arm B cohorts (Appendix Fig A1, online only). Furthermore, patients with MDD levels in the bone marrow at diagnosis of $<$ 1% had an EFS 82.4% ± 3.1% compared with 89.5% ± 3.3% for those with an MDD $\geq 1\%$ ($P = .3084$; Fig 3B).

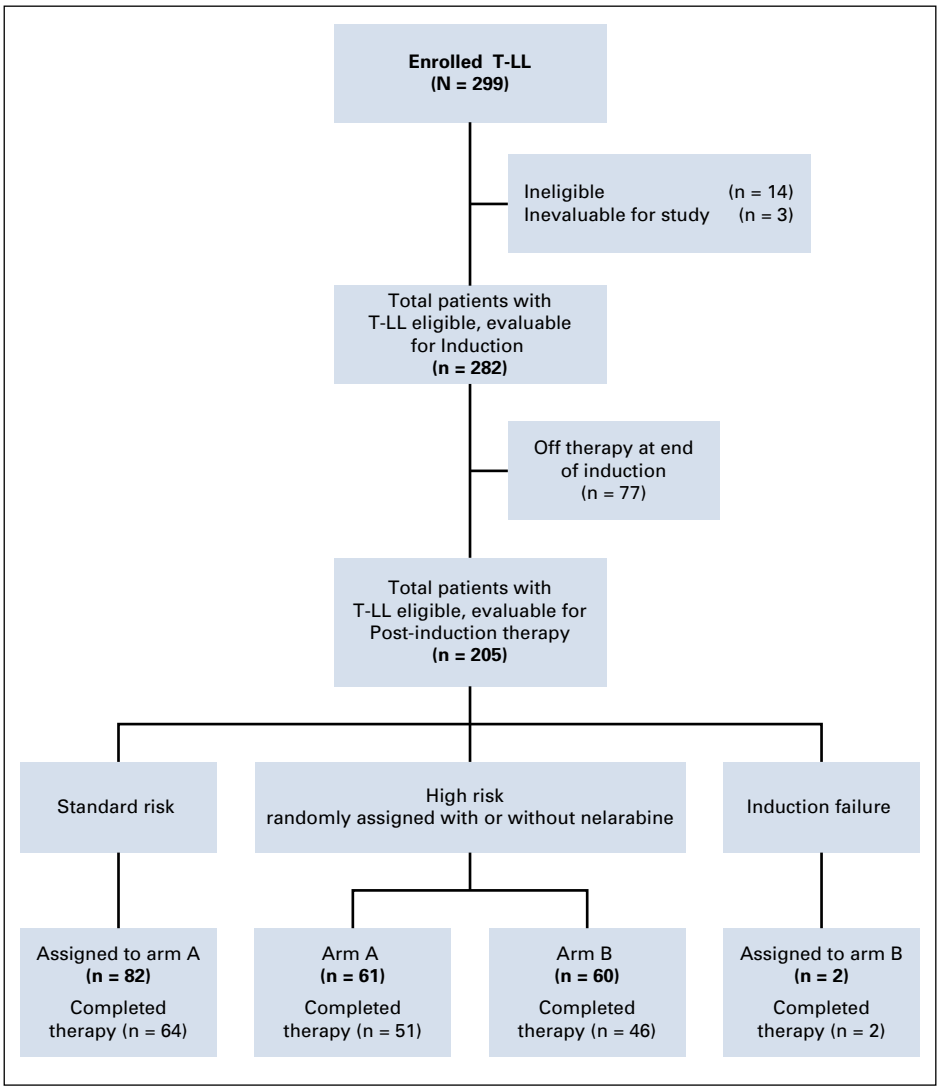

FIG 1. CONSORT diagram. Arm A, Capizzi-based methotrexate/pegaspargase, Arm B: Capizzi-based methotrexate/pegaspargase plus nelarabine; T-LL, T-cell non-Hodgkin lymphoma.

TABLE 1. Patient Characteristics Receiving Postinduction Therapy

Characteristic	Total Patients (N = 282)[a]	SR, C-MTX (n = 82)	HR, C-MTX Randomly Assigned (n = 61)	HR, C-MTX + Nel Randomly Assigned (n = 60)	HR, C-MTX + Nel Induction Failure (n = 2)
Age, years, (mean + SD)	11.2 ± 5.9	11.3 ± 6.0	10.0 ± 5.8	10.6 ± 5.6	8.0 ± 2.6
Sex					
Male	195 (69.2)	54 (65.9)	40 (65.6)	44 (73.3)	2 (100)
Female	87 (30.8)	28 (34.1)	21 (34.4)	16 (26.7)	0
Murphy stage					
2	17 (6.0)	4 (4.9)	4 (6.6)	4 (6.6)	0
3	138 (49.0)	51 (62.2)	31 (50.8)	33 (55.0)	1 (50)
4	39 (13.8)	3 (3.7)	15 (24.6)	13 (21.7)	0
Unknown	88 (31.2)	24 (29.2)	11 (18.0)	10 (16.7)	1 (50)
Pretreatment MDD, %					
< 0.10	134 (47.5)	66 (80.5)	27 (44.3)	24 (40.0)	2 (100)
0.10-0.99	32 (11.4)	16 (19.5)	3 (4.9)	3 (5.0)	0
≥ 1.0	80 (28.4)	0	31 (50.8)	28 (46.7)	0
Unknown	36 (12.8)	0	0	5 (8.3)[b]	0
Tumor response					
CR	78 (27.6)	26 (31.7)	17 (27.9)	18 (30.0)	0
CRu	86 (30.5)	29 (35.4)	19 (31.1)	25 (41.7)	0
PR	86 (30.5)	27 (32.9)	25 (41.0)	17 (28.3)	0
NR	2 (0.7)	0	0	0	2 (100)
PD	1 (0.4)	0	0	0	0
Unknown	29 (10.3)	0	0	0	0

NOTE. Data are presented as No. (%) unless otherwise noted.

Abbreviations: C-MTX, Capizzi-based methotrexate/pegaspargase; CR, complete response; CRu, complete response unconfirmed; HR, high risk; MDD, minimal detectable disease; Nel, nelarabine; NR, no response; PD, progressive disease; PR, partial response; SD, standard deviation; SR, standard risk.

[a]Total patients include 77 who are off therapy at the end of induction.

[b]Assigned to HR group because of prior steroid exposure.

EFS for different ages (patients < 10 years, 82.6% ± 3.6%; 10-16 years, 86.1% ± 3.5%, *v* > 16 years old, 86.4% ± 5.2%; *P* = .4360), stages (stage II, 88.9% ± 7.7%; III, 87.6% ± 2.9%; IV, 95.4% ± 3.3%; *P* = .197), or responses (CR, 92.2% ± 3.3%; CRu, 84.4% ± 4.1%; PR, 81.0% ± 4.5%; *P* = .217) were not significantly different (Appendix Fig A2, online only).

Comparison of the 2 HR treatment arms did not demonstrate a significant difference in DFS (ie, C-MTX, 85.1% ± 4.8%; and C-MTX plus nelarabine, 85.0% ± 4.9%; *P* = .834; Fig 4). There was also no difference in DFS (82.7% ± 6.3%, 83.3% ± 6.0%) or OS (87.8% ± 5.3%, 85.7% ± 5.6%) when comparing the C-MTX and C-MTX plus nelarabine arms for those patients with prior steroid exposure (*P* = .954 and *P* = .761), respectively. Finally, DFS comparison of MDD < 1% versus ≥ 1% for the subset of HR patients also was not significantly different (Appendix Fig A3, online only). Thus, HR assignment because of steroid exposure or MDD ≥ 1 had comparable DFS and OS outcomes.

Toxicities

There were only 5 nonrelapse deaths. In the SR group there were 3 deaths (fungal infection during consolidation [n = 1]; unknown causes during DI [n = 1]; hemophagocytic lymphohistiocytosis [n = 1]). In the HR group there were 2 deaths (arm-A patient from pancreatitis during maintenance therapy [n = 1]; arm-B patient from cerebral edema attributed to pegaspargase during DI, 34 days from the last dose of nelarabine [n = 1]). One benign tumor was observed with no other secondary malignancies.

Targeted neurotoxicity reporting was performed because of prior experience with nelarabine.[17,28,29] There was no significant difference in grade 1-4 CNS toxicity in HR patients randomly assigned to either C-MTX or CMTX plus nelarabine (*P* = .06; Table 2). However, for peripheral motor and sensory neuropathy, patients receiving nelarabine had a significantly higher rate of grade 1-3 toxicity, (*P* = .03 and

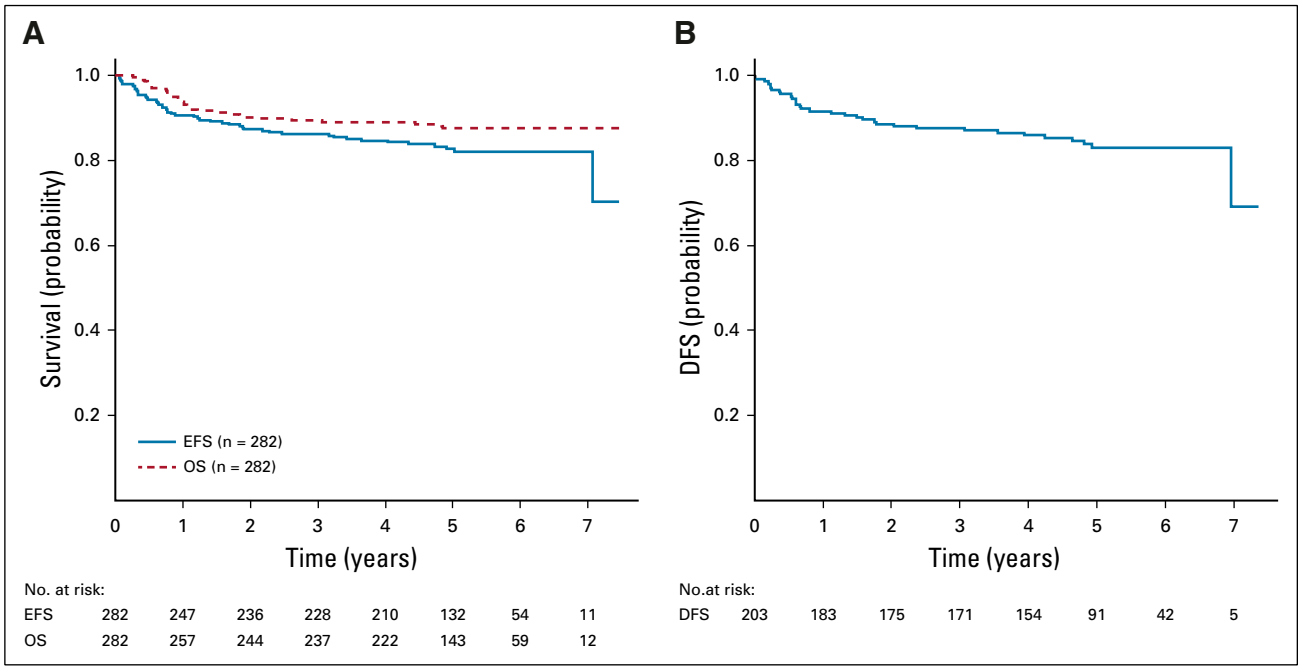

FIG 2. (A) Event-free survival (EFS) and overall survival (OS) curves. Four-year EFS and OS for all patients with T-cell non-Hodgkin lymphoma were 84.7% ± 2.3% and 89.0% ± 2.0% (n = 282), respectively. (B) Overall disease-free survival (DFS) from the end of induction; 4-year DFS was 85.9% ± 2.6% (n = 203).

.005). Neither group experienced grade 4 sensory toxicity, but 3 patients in arm A and 5 patients in arm B experienced grade 3 toxicity. There were no differences in either peripheral motor or sensory neuropathy within age groups. (Appendix Tables A5 and A6).

No other nelarabine-associated toxicities were observed in patients with T-LL, including rhabdomyolysis. There were no significant differences in infection risk between the patients who received nelarabine versus those who did not (P = .857).

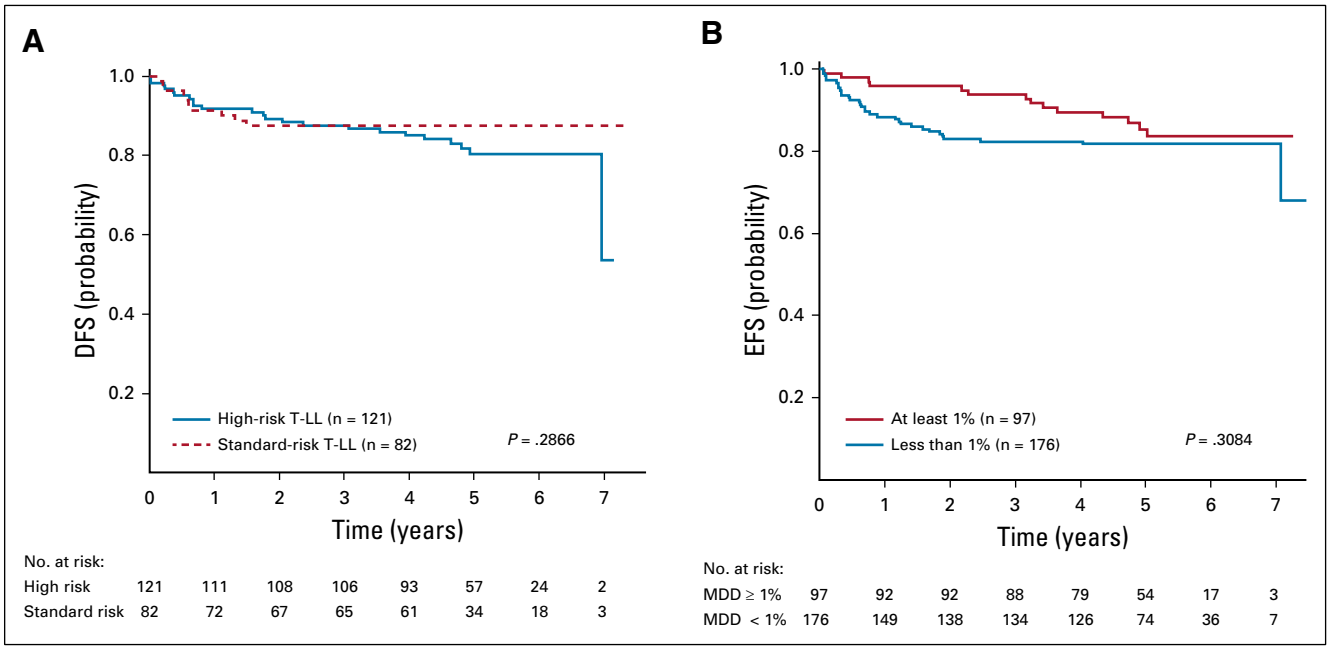

FIG 3. (A) Disease-free survival (DFS) for high-risk versus standard-risk groups; 4-year DFS was 85.0% ± 3.4% (n = 121) versus 87.4% ± 4.0% (n = 82; P = .2866). (B) Event-free survival (EFS) for minimal detectable disease (MDD) < 1% versus MDD ≥ 1% detected in the bone marrow at diagnosis: 4-year EFS, 82.4% ± 3.1% (n = 176) versus 89.5% ± 3.3% (n = 97; P = .3084). T-LL, T-cell non-Hodgkin lymphoma.

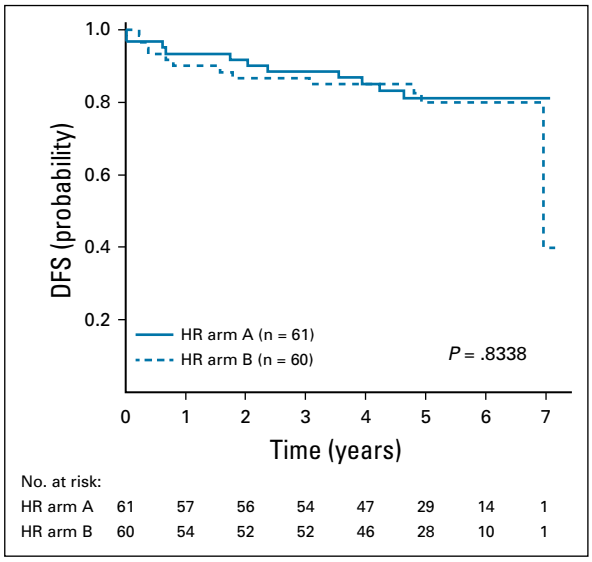

FIG 4. Disease-free survival (DFS) for high-risk (HR) patients by randomly assigned arm: no nelarabine (arm A) versus nelarabine (arm B); 4-year DFS was 85.1% ± 4.8% (n = 61) versus 85.0% ± 4.9% (n = 60; *P* = .8338), respectively.

DISCUSSION

AALL0434 assembled one of the largest prospective studies for pediatric patients with T-LL and provided excellent DFS and OS outcomes. The use of C-MTX is in contrast to recent studies that have used HD-MTX and CRT, which are both associated with significant toxicity.[30-35]

TABLE 2. Summary of Toxicities

Toxicity	No Nelarabine	Nelarabine	*P*
No. of patients	61	60	
Neurologic (grade 1-4)			
Central neurologic toxicities[a]	6	12	.058
Peripheral motor neuropathy	14	23	.033
Peripheral sensory neuropathy	13	26	.005
Rhabdomyolysis related (grade 3-4)			
Alanine aminotransferase elevation	24	24	.471
CPK elevation	1	1	.748
Generalized muscle weakness	1	1	.748
Myalgia	0	2	.244
Myositis	0	1	.496
Infection (grade 3-4)	25	19	.857

Abbreviation: CPK, creatine phosphokinase.

[a]Central neurologic toxicities include: agitation, anxiety, blurred vision, depressed level of consciousness, dizziness, encephalopathy, memory impairment, other nervous system disorders, optic nerve disorder, seizure, somnolence, and tremor.

Nelarabine failed to demonstrate a difference in outcome despite the reported success in T-ALL but was not powered to detect a benefit. However, given previous reports of activity in T-LL with nelarabine, it is likely that this agent is active. The addition of nelarabine into this leukemia protocol backbone for T-LL was safe, with only a modest increase in peripheral sensory neuropathy. Given the acceptable toxicity profile, and the compelling evidence that nelarabine is active in T-ALL, using nelarabine for future trials should be considered, particularly if larger studies could clarify its role.

Risk categories were assigned based on the MDD at diagnosis, which was shown to be associated with a worse outcome in COG A5971.[7] Despite these previous findings, there was no difference in outcome when comparing the HR to SR subjects who were assigned the same C-MTX therapy. This finding is also in contrast to other published reports that MDD is of prognostic importance.[14] Hence, it appears that the C-MTX ABFM therapy may have negated the prognostic impact of MDD. In A5971, MDD was assessed using a BFM backbone containing HD-MTX. Although 2 different preparations were used for each trial (L-asparaginase for A5971 and pegaspargase for ALL0434), the asparaginase exposure of C-MTX in AALL0434 was approximately 30% greater than the HD-MTX in A5971.[7,36] Given the superior outcome of patients with T-ALL receiving C-MTX compared with HD-MTX on AALL0434,[20] C-MTX may have improved the outcome of the HR T-LL population.

Risk factors correlating with recurrence in T-LL have been difficult to identify.[14,37-39] This problem is especially important, given the dismal outcome of relapsed patients.[13,40] We were unable to identify any significant differences in outcome when examining variables previously associated with inferior prognosis. Thus, continued efforts are needed to identify new prognostic factors in T-LL that can be used in future trials evaluating novel agents.

Overall, this study represents one of the largest prospective trials for the treatment of newly diagnosed pediatric T-LL with outcomes that are either comparable or superior to other trials for this disease.[9,12,36-38,41-43] Previous trials with higher EFS have included cranial radiation for high-stage patients irrespective of their CNS status.[8] Cranial radiation is associated with a panoply of long-term toxicities in childhood cancer survivors.[44-46] This trial demonstrated that the COG ABFM C-MTX regimen can achieve a low CNS recurrence rate (1.97%) without prophylactic CRT. However, because patients with CNS3 with T-LL were excluded from this trial, we cannot comment on its role for these patients. Despite this limitation, the observed toxicities of this treatment regimen were relatively low, with 1 benign tumor to date and a nonrelapse mortality rate of only 1.8%. The outstanding outcomes achieved from this trial provide the basis on which future therapies can be built.

AFFILIATIONS

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EQUAL CONTRIBUTION

T.G.G. and C.M.B. contributed equally as senior authors.

PRIOR PRESENTATION

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Successful Outcomes of Newly Diagnosed T Lymphoblastic Lymphoma: Results From Children's Oncology Group AALL0434

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APPENDIX

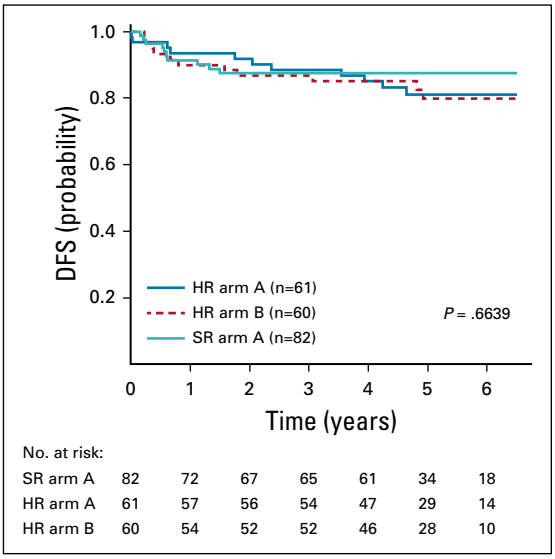

FIG A1. Disease-free survival (DFS) comparison of standard-risk (SR) versus high-risk (HR) arm A versus HR arm B.

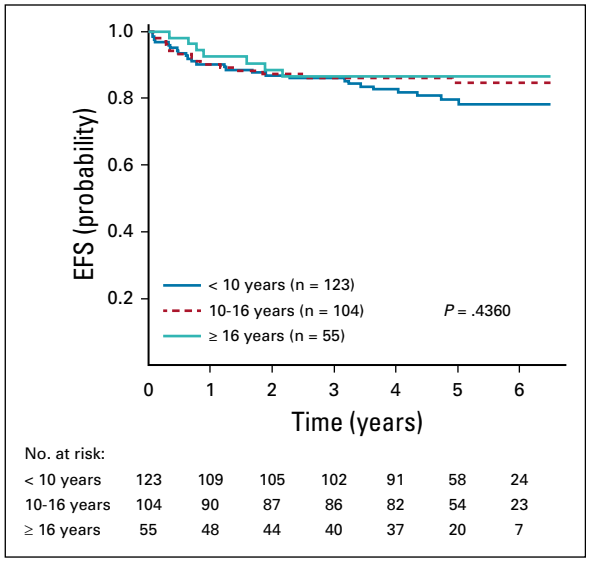

FIG A2. Event-free survival (EFS) comparing age groups, < 10 years (n = 123), 10-16 years (n = 104), ≥ 16 years (n = 55; *P* = .4360).

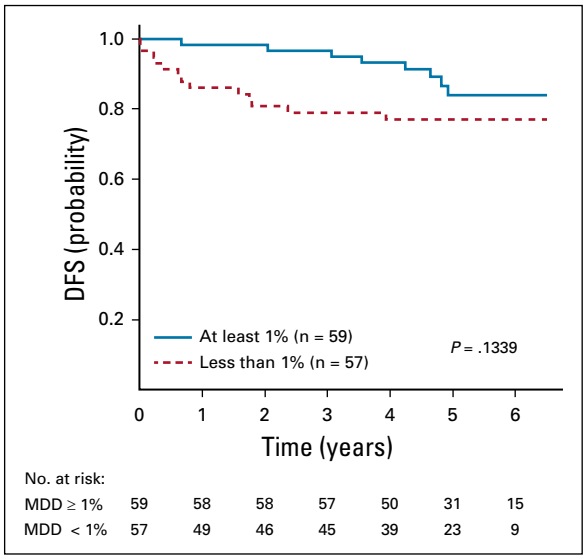

FIG A3. Disease-free survival (DFS) comparison of minimal detectable disease (MDD) $< 1\%$ versus $\geq 1\%$ for the subset of high-risk (HR) patients is given below.

TABLE A1. Two-Stage Consenting Process and Details of Therapies

First Stage Consent: Induction – All Arms			
Induction	**Drug**	**Dose**	**Schedule**
	IT cytarabine	Age adjusted[a]	At diagnostic lumber puncture OR day 1
	Vincristine	1.5 mg/m^2 (2 mg maximum)	Days 1, 8, 15, 22
	Prednisone	30 mg/m^2/dose twice a day	Days 1-28
	Daunorubicin	25 mg/m^2	Days 1, 8, 15, 22
	Pegaspargase	2,500 units/m^2	Day 4, 5, or 6
	IT-MTX	Age adjusted[a]	Days 8, 29

Second Stage Consent: Risk Stratification and Post Induction Randomizations to Arms A, and B[b]						
Consolidation		**Courses Without Nelarabine (Arms A)**			**Courses with Nelarabine (Arms B)**	
	Drug	**Dose**	**Schedule**	**Drug**	**Dose**	**Schedule**
	Cyclophosphamide	1,000 mg/m^2	Days 1, 29	Cyclophosphamide	1,000 mg/m^2	Days 8, 50
	Cytarabine	75 mg/m^2	Days 1-4, 8-11, 29-32, 36-39	Cytarabine	75 mg/m^2	Days 8-11, 15-18, 50-53, 57-60
	Mercaptopurine	60 mg/m^2	Days 1-14, 29-42	Mercaptopurine	60 mg/m^2	Days 8-21, 50-63
	Vincristine	1.5 mg/m^2 (2 mg maximum)	Days 15, 22, 43, 50	Vincristine	1.5 mg/m^2 (2 mg maximum)	Days 22, 29, 64, 71
	Pegaspargase	2,500 units/m^2	Days 15, 43	Pegaspargase	2,500 units/m^2	Days 22, 64
	IT-MTX	Age adjusted[a]	Days 8, 15, 22, 29 (high risk); Days 1, 8 (CNS3);Days 1, 8, 15, 22 (all others)	IT-MTX	Age adjusted[a]	Days 15, 22, 57, 64 (omit day 22 for CNS3)
				Nelarabine	650 mg/m^2	Days 1-5, 43-47
Interim maintenance	**Drug**	**Dose**	**Schedule**			
C-MTX (Arms A, B)	Vincristine	1.5 mg/m^2 (2 mg maximum)	Every 10 days × 5 doses/days 1, 11, 21, 31, 41			
	IV-MTX[c]	100 mg/m^2	Every 10 days × 5 doses/days 1, 11, 21, 31, 41			
	Pegasparagase	2,500 units/m^2	Days 2, 22			
	IT-MTX	Age adjusted[a]	Days 1, 31			

(continued on following page)

TABLE A1. Two-Stage Consenting Process and Details of Therapies (continued)

Delayed intensification	Drug	Dose	Schedule	Drug	Dose	Schedule
	Vincristine	1.5 mg/m^2 (2 mg maximum)	Days 1, 8, 15, 43, 50	Vincristine	1.5 mg/m^2 (2 mg maximum)	Days 1, 8, 15, 50
	Pegaspargase	2,500 units/m^2/dose	Day 4 or 5 or 6 and 43	Pegaspargase	2,500 units/m^2/dose	Day 4 or 5 or 6 and 50
	Dexamethasone	5 mg/m^2/dose twice a day	Days 1-7, 15-21	Dexamethasone	5 mg/m^2/dose twice a Day	Days 1-7, 15-21
	Doxorubicin	25 mg/m^2/day	Days 1, 8, 15	Doxorubicin	25 mg/m^2/day	Days 1, 8, 15
	Cytarabine	75 mg/m^2/day	Days 29-32, 36-39	Cytarabine	75 mg/m^2/day	Days 36-39, 43-46
	Cyclophosphamide	1,000 mg/m^2	Day 29	Cyclophosphamide	1,000 mg/m^2	Day 36
	Thioguanine	60 mg/m^2/day	Days 29-42 (omit for patients receiving CRT)	Thioguanine	60 mg/m^2/day	Days 36-49 (omit for patients receiving CRT)
	IT-MTX	Age adjusted[a]	Days 1, 29, 36	IT-MTX	Age adjusted[a]	Days 1, 36, 43
				Nelarabine	650 mg/m^2	Days 29-33
Maintenance[d]	**Drug**	**Dose**	**Schedule**	**Drug**	**Dose**	**Schedule**
	Vincristine	1.5 mg/m^2 (2 mg max)	Days 1, 29, 57	Vincristine	1.5 mg/m^2 (2 mg max)	Days 1, 57
	Prednisone	20 mg/m^2/dose twice a day	Days 1-5, 29-33, 57-61	Prednisone	20 mg/m^2/dose twice a day	Days 1-5, 57-61
	Mercaptopurine (oral)	75 mg/m^2/day	Daily/days 1-84	Mercaptopurine (oral)	75 mg/m^2/day	Days 1-28, 36-84
	Methotrexate (oral)	20 mg/m^2/dose	Weekly	Methotrexate (oral)	20 mg/m^2/dose	Days 8, 15, 22, 36, 43, 50, 57, 64, 71, 78/weekly – omitted while taking Nelarabine
	IT-MTX	Age adjusted[a]	Days 1 (and 29 first 4 cycles – low risk only)	IT-MTX	Age adjusted[a]	Day 1
				Nelarabine	650 mg/m^2	Days 29-33 (first 3 cycles)

NOTE. Treatment Arms: A (C-MTX); B (C-MTX + Nelarabine); C (HDMTX); D (HDMTX + Nelarabine)

Abbreviations: C-MTX, Capizzi escalating-dose methotrexate regimen; CNS1, no blasts in the CSF; CNS2, CSF WBC, 5/μL with blasts; CNS3, CSF WBC$5/μL with blasts or cranial nerve palsies, brain/eye involvement, or hypothalamic syndrome; CRT, cranial radiation therapy; HD-MTX, high-dose methotrexate regimen; IT, intrathecal; IT-MTX, intrathecal methotrexate; IV-MTX, intravenous methotrexate; max, maximum; T-ALL, T-cell acute lymphoblastic leukemia.

[a]IT cytarabine: 1 to 1.99 years, 30 mg; 2 to 2.99 years, 50 mg; ≥ 3 years, 70 mg. IT-MTX: 1 to 1.99 years, 8 mg; 2 to 2.99 years, 10 mg; 3 to 8.99 years, 12 mg; ≥ 9 years, 15 mg.

[b]Induction failure (M3 at day 29) begin Arm D consolidation as soon as possible.

[c]IV-MTX: 100 mg/m^2 (dose escalated by 50 mg/m^2 every 10 days for a total of 5 doses, adjusted for toxicity).

[d]Total duration of treatment from start of interim maintenance: female T-ALL, 2 years; male T-ALL, 3 years.

TABLE A2. Patients Ineligible or Inevaluable for Induction Therapy

Status	Cause	No. of Patients	Percentage
Ineligible	Staging information not included	1	5.9
	Misdiagnosis (T-ALL, not T-LL)	9	53.0
	Disease status: CNS3	1	5.9
	Therapy begun before therapy initiation	3	17.6
Inevaluable	No marrow submitted for MDD determination	3	17.6
Total		17	100.0

Abbreviations: CNS3, CSF WBC ≥ 5/μL with blasts or cranial nerve palsies, brain/eye involvement, or hypothalamic syndrome; MDD, minimal detectable disease; T-ALL, T-cell acute lymphoblastic leukemia; T-LL, T-cell non-Hodgkin lymphoma.

TABLE A3. Reasons for Removal From Protocol at the End of Induction

Reason	No. of Patients	Percentage
Physician determines it is in the patient's best interest	8	10.4
Refusal of additional protocol therapy by patient/parent/guardian	47	61.0
Progressive disease	1	1.3
Adverse event/side effects/complications	3	3.9
Withdrawal of consent for any additional data submission	1	1.3
Inevaluable	11	14.3
Transfer to another institution	2	2.6
Drug shortage and protocol deviation	1	1.3
Failed to complete randomization procedure	3	3.9
Total	77	100.0

TABLE A4. T-LL Disease-Free Survival Events for Standard and High Risk

	Standard Risk	High Risk	
Type of Event	**Arm A**	**Arm A**	**Arm B**
Relapse	5	7	10
Progressive disease	2	3	0
Remission death	3	1	1
SMN + benign tumors	0	0	1[a]
Total	10	11	12

NOTE. Sites of relapse: standard risk arm A: original = 3, CNS = 1, other = 1; high risk arm A: original = 2, CNS = 1, bone marrow = 2, other = 2; high risk arm B: original = 6, CNS = 1, bone marrow = 1, bone marrow plus CNS = 1, other = 1.

Abbreviations: SMN, secondary malignant neoplasms; T-LL, T-cell non-Hodgkin lymphoma.

[a]Benign tumor.

TABLE A5. Peripheral Motor Neuropathy

Age Group (years; No. of patients)	No Nelarabine (n = 14)	Nelarabine (n = 23)	*P*
< 10 (n = 57)	5 (35.7)	10 (43.5)	.609
10-16 (n = 42)	5 (35.7)	10 (43.5)	
≥ 16 (n = 22)	4 (28.6)	3 (13.0)	

NOTE. Data presented as No. %.

TABLE A6. Peripheral Sensory Neuropathy

Age Group (years; No. of patients)	No Nelarabine (n = 13)	Nelarabine (n = 26)	*P*
< 10 (n = 57)	3 (23.0)	9 (34.6)	.643
10-16 (n = 42)	5 (38.5)	10 (38.5)	
≥ 16 (n = 22)	5 (38.5)	7 (26.9)	

NOTE. Data presented as No. %.