Pilot Study of Nelarabine in Combination With Intensive Chemotherapy in High-Risk T-Cell Acute Lymphoblastic Leukemia: A Report From the Children's Oncology Group

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Submitted November 23, 2011; accepted May 8, 2012; published online ahead of print at www.jco.org on June 25, 2012.

Supported by Grants No. CA98543, CA29139, and CA086011 from XXXX and by GlaxoSmithKline, which provided nelarabine for this study.

Presented at the 48th Annual Meeting of the American Society of Hematology, Orlando, FL, December 9-12, 2006, and the 44th Annual Meeting of the American Society of Clinical Oncology, Chicago, IL, May 30-June 3, 2008.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Clinical Trials repository link available on JCO.org.

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0732-183X/12/3022-2753/\$20.00

DOI: 10.1200/JCO.2011.40.8724

ABSTRACT

Purpose

Children's Oncology Group study AALL00P2 was designed to assess the feasibility and safety of adding nelarabine to a BFM 86-based chemotherapy regimen in children with newly diagnosed T-cell acute lymphoblastic leukemia (T-ALL).

Patients and Methods

In stage one of the study, eight patients with a slow early response (SER) by prednisone poor response (PPR; $\geq 1,000$ peripheral blood blasts on day 8 of prednisone prephase) received chemotherapy plus six courses of nelarabine 400 mg/m² once per day; four patients with SER by high minimal residual disease (MRD; $\geq 1\%$ at day 36 of induction) received chemotherapy plus five courses of nelarabine; 16 patients with a rapid early response (RER) received chemotherapy without nelarabine. In stage two, all patients received six 5-day courses of nelarabine at 650 mg/m² once per day (10 SER patients [one by MRD, nine by PPR]) or 400 mg/m² once per day (38 RER patients; 12 SER patients [three by MRD, nine by PPR]).

Results

The only significant difference in toxicities was decreased neutropenic infections in patients treated with nelarabine (42% with v 81% without nelarabine). Five-year event-free survival (EFS) rates were 73% for 11 stage one SER patients and 67% for 22 stage two SER patients treated with nelarabine versus 69% for 16 stage one RER patients treated without nelarabine and 74% for 38 stage two RER patients treated with nelarabine. Five-year EFS for all patients receiving nelarabine ($n = 70$) was 73% versus 69% for those treated without nelarabine ($n = 16$).

Conclusion

Addition of nelarabine to a BFM 86-based chemotherapy regimen was well tolerated and produced encouraging results in pediatric patients with T-ALL, particularly those with a SER, who have historically fared poorly.

J Clin Oncol 30:2753-2759. © 2012 by American Society of Clinical Oncology

INTRODUCTION

Historically, children with T-cell acute lymphoblastic leukemia (T-ALL) have had inferior outcomes compared with children with B-precursor ALL. Various intensive combination chemotherapy regimens have significantly improved event-free survival (EFS) for patients with T-ALL.¹⁻¹¹ However, children with T-ALL with poor initial responses to chemotherapy, based on response to a 7-day prednisone prephase or elevated minimal residual disease (MRD) levels at the end of induction therapy, have fared poorly, with long-term EFS less than 50%.^{1,7,12-17} Some investigators recommend allogeneic stem-cell transplantation (SCT) in first remission (CR1) for such higher-risk patients.^{12,13}

Nelarabine is a water-soluble prodrug of araG (9-B-arabinofuranosylguanine), a synthetic deoxyguanosine derivative resistant to cleavage by endogenous purine nucleoside phosphorylase. It is cytotoxic to T lymphoblasts at micromolar concentrations. Cytotoxicity is mediated by the accumulation of araG nucleotides, especially araGTP, which accumulates preferentially in T cells rather than B cells, resulting in inhibition of ribonucleotide reductase and inhibition of DNA synthesis.¹⁸⁻²⁰ This differential cytotoxicity has created interest in treating T-cell malignancies with nelarabine.

In a phase I study of nelarabine in 93 children and adults with refractory T-ALL or T-cell non-Hodgkin's lymphoma, there were seven complete and four partial responses among 26 pediatric

patients.²¹ Responses were observed at all dose levels (5 to 75 mg/kg once per day for 5 days). One half of pediatric patients and 85% of adults experienced reversible neurotoxicity. More severe neurotoxicity was noted at the higher dose levels. The only child treated with 75 mg/kg developed neurotoxicity including seizures, ascending paralysis, and coma beginning 12 days after starting nelarabine. The patient achieved complete remission but developed progressive leukemia and died 3 months after nelarabine therapy without recovery from the majority of the neurotoxicity. Approximately 40% of adults treated with nelarabine 40 mg/kg experienced reversible neurotoxicity (somnolence, confusion, malaise, and ataxia).²¹

A pediatric phase II trial of nelarabine (Pediatric Oncology Group P9673) accrued 153 patients with T-ALL or T-cell non-Hodgkin's lymphoma from June 1997 to July 2002.²² First-relapse patients had a complete response rate of approximately 50%, and 23% of patients with second or subsequent relapses achieved a complete

response. Grades 3 and 4 neurologic events, including those attributed to nelarabine and those attributed to disease or other causes, occurred in 18% of patients. Grades 3 and 4 CNS toxicities (seizure or somnolence) occurred in 12% of patients; 9% of patients had grade 3 or 4 peripheral neurotoxicity (including weakness or Guillain-Barre syndrome). One patient with a history of seizures experienced grade 5 CNS toxicity of status epilepticus without recovery on day 4 of nelarabine.²²

On the basis of these promising data, nelarabine was deemed an attractive agent to test in patients with newly diagnosed T-ALL, but there were significant concerns about the potential for serious neurotoxicity. Children's Oncology Group (COG) protocol AALL00P2 was a two-stage pilot study to assess the feasibility and safety of adding nelarabine to an intensive modified BFM (Berlin-Frankfurt-Münster) 86 regimen in children with newly diagnosed higher-risk T-ALL.¹

Table 1. Protocol Design: Children's Oncology Group ALL00P2

Protocol	Dosage	Timing
Prephase, week 0		
IT methotrexate	Age adjusted	Week 0
Prednisone	60 mg/m ² per day PO	Days 1-7
Induction, weeks 1-9		
Vincristine	1.5 mg/m ² IV once per week	Weeks 1-4
Prednisone	60 mg/m ² per day PO	Weeks 1-2
Daunorubicin	40 mg/m ² IV once per week	Weeks 1-4
E coli asparaginase	10,000 units/m ² IM	Days 12, 15, 18, 22, 24, 27, 30, 33
Cyclophosphamide	1 g/m ² IV	Days 36, 50
Cytarabine	75 mg/m ² IV	Days 36-39, 43-46, 50-53, 57-60
Mercaptopurine	60 mg/m ² PO	Days 36-63
IT methotrexate	Age adjusted	Days 1, 43, 57
Consolidation, weeks 10-19		
Mercaptopurine	25 mg/m ² PO	Days 1-56
Methotrexate with leucovorin rescue	5 g/m ² IV	Days 8, 22, 36, 50
IT methotrexate	Age adjusted	Days 8, 22, 36, 50
Reinduction, weeks 20-29		
Dexamethasone	10 mg/m ² PO	Days 1-21, age < 13 years; days 1-7, 15-21, age ≥ 13 years
Vincristine	1.5 mg/m ² IV once per week	Days 1, 8, 15
Doxorubicin	25 mg/m ² IV once per week	Days 1, 8, 15
Peg asparaginase	2,500 units/m ² IM	Day 4
Cyclophosphamide	1 g/m ² IV	Day 36
Cytarabine	75 mg/m ² IV	Days 36-39, 43-46
Thioguanine	60 mg/m ² PO	Days 36-49
IT methotrexate	Age adjusted	Days 36, 43
Maintenance, weeks 30-101		
Vincristine	1.5 mg/m ² IV	Day 1, every 8 weeks
Dexamethasone	6 mg/m ² PO	Days 1-5, every 8 weeks
Mercaptopurine	75 mg/m ² PO once per day	Every 8 weeks
Methotrexate	20 mg/m ² PO once per week	Days 1, 8, 15, 22, 36, 43, 50, every 8 weeks
Nelarabine dosing		
SER peripheral blood blast > 1,000, day 7		
Stage one	400 mg/m ² IV	Days 29-33 in induction, reinduction, and first four courses of maintenance
Stage two	650 mg/m ² IV	Days 29-33 in induction, reinduction and first four courses of maintenance
SER MRD > 1%, day 36		
Stage one	400 mg/m ² IV	Days 29-33 in reinduction and first four courses of maintenance
Stage two	400 mg/m ² IV	Days 29-33 in induction
Stage two	650 mg/m ² IV	Days 29-33 in reinduction and first four courses of maintenance
RER		
Stage two	400 mg/m ² IV	Days 29-33 in induction, reinduction and first four courses of maintenance

NOTE. All patients received cranial radiation (CNS involvement, 18 Gy; no CNS involvement, 12.6 Gy) at the end of reinduction before maintenance therapy. Abbreviations: IM, intramuscular; IT, intrathecal; IV, intravenous; MRD, minimal residual disease; PO, orally; RER, rapid early responder; SER, slow early responder.

PATIENTS AND METHODS

Patients

Eligible patients were age 1 to 22 years with newly diagnosed T-ALL ($> 25\%$ marrow blasts or $WBC \geq 25,000/\mu L$ with $\geq 50\%$ blasts). Patients were required to have adequate hepatic (bilirubin ≤ 1.5 mg/dL; ALT $< 5\times$ the upper limit of normal) and renal function (creatinine normal for age or creatinine clearance ≥ 60 mL/min/1.73 m²), and performance status scores $\geq 50\%$. High-risk patients were defined as patients having slow early response (SER) based on either a prednisone poor response (PPR; $\geq 1,000$ peripheral blood blasts on prednisone prephase day 8) or MRD $\geq 1\%$ at induction therapy day 36. Other patients were considered to have rapid early response (RER). In AALL00P2 stage two, eligibility was limited to patients 1.00 to 21.99 years of age with newly diagnosed T-ALL meeting National Cancer Institute high-risk criteria with $WBC \geq 50,000/\mu L$ and/or age ≥ 10 years. Patients with pre-existing grade 2 or higher neuropathy were ineligible unless the neuropathy was the result of leukemic infiltration. Pregnant or lactating women were ineligible. Patients could not have had prior therapy other than intrathecal cytarabine or emergency mediastinal irradiation, in patients with severe respiratory distress. Patients receiving chronic steroid treatment were not eligible. Those who received corticosteroids within 48 hours of study entry were eligible provided that results of a physical examination and complete blood count with differential performed immediately before beginning corticosteroids were known.

Patients and/or their legal guardians provided written informed consent consistent with federal, state, and local institutional requirements. The protocol was also approved by the institutional review board at participating COG institutions and performed in accordance with assurances filed with and approved by the Department of Health and Human Services.

Treatment Plan

AALL00P2 was a feasibility pilot to determine the toxicity of adding nelarabine to an intensive multiagent chemotherapy backbone for patients

with T-ALL. Toxicities were graded according to National Cancer Institute Common Toxicity Criteria version 3.0. Because of concerns about CNS toxicity, three specific toxicities were targeted for intensive data collection: peripheral neuropathy, central neurotoxicity, and seizures. The chemotherapy backbone (Table 1) consisted of a modified BFM 86 backbone with a prephase of 1 week of oral prednisone and intrathecal methotrexate on day 1.¹ All patients received cranial radiation (CNS involvement, 18 Gy in 10 fractions; no CNS involvement, 12.6 Gy in seven fractions) at the end of reinduction before maintenance therapy.

During AALL00P2 stage one, SER patients were assigned nonrandomly to receive six 5-day courses of nelarabine 400 mg/m² for those with a PPR and five 5-day courses if they were SER only on the basis of MRD. After 10 patients had been assigned to the nelarabine regimen in stage one, and all had completed at least 3 months of therapy, study accrual was halted temporarily, and toxicities were reviewed. On the basis of predefined criteria, no major toxicities were noted, and stage two of the study was opened.

In stage two, all RER patients received six 5-day courses of nelarabine 400 mg/m². The first 10 SER patients received nelarabine 650 mg/m². After 10 SER patients were enrolled, the 650 mg/m² dose level was closed to enrollment for interim analysis of toxicities; both RER and SER patients continued to be enrolled on the 400 mg/m² regimen.

MRD Detection

Bone marrow specimens were submitted to a central reference laboratory (Johns Hopkins Hospital, Baltimore, MD; M.J.B.) at initial diagnosis and at the end of induction to determine MRD by four-color fluorescence flow cytometry using a limited panel of antibodies conjugated to fluorescein isothiocyanate/phycoerythrin/peridinin chlorophyll-protein/allophycocyanin, as follows: CD4/CD1a/CD8/CD5, CD7/CD10/CD3/CD5, CD99/CD7/CD45/CD5, and TdT/CD34/CD45/cytoplasmic CD3. All patient cases studied were CD5 and cCD3 positive at initial diagnosis. A minimum of 500,000 cells were assayed, an acquisition gate was set on CD5 or cCD3 to enrich for T cells, and phenotypically aberrant populations were identified based on the previously

Fig 1. CONSORT diagram for 92 patients enrolled onto AALL00P2. MRD, minimal residual disease; PPR, prednisone poor response; RER, rapid early response; SER, slow early response.

described principle that they were found in portions of dual-parameter displays determined to be devoid of cells when the antibody panels were tested on a series of normal individuals.²³ MRD was not studied at later time points.

Statistical Analysis

Results are based on analysis of data current as of June 30, 2010. All data analyses were performed using SAS software (SAS Institute, Cary) and R software (<http://www.r-project.org>). The Kaplan-Meier method²⁴ was used to obtain EFS estimates, and SEs of estimates were obtained using the method of Peto et al.²⁵ Time to event was calculated as the time from study entry to first event (relapse, secondary malignancy, or death) or date of last contact. The log-rank test was used to compare survivor functions. Fisher's exact test was used to compare rates. Attribution for toxicity was assessed by individual investigators for its relationship to nelarabine.

RESULTS

Patient Characteristics

Between April 2001 and October 2005, 92 patients (88 eligible; 28 in stage one and 60 in stage two) were enrolled (Fig 1). Ineligibility was because of inadequate consent,¹ use of a second investigational agent,¹ and major data submission deficiencies.² On audit, it was discovered that two RER patients had been erroneously assigned to SER treatments arms; they were considered evaluable for toxicity but not evaluable for outcome.

Patient characteristics are described in Table 2. Extramedullary disease was present at diagnosis in eight patients; six had CNS involvement, one had testicular leukemia, and one had both CNS and testicular leukemia. Overall, 95% of patients had high-risk age/WBC features, and 69% had initial WBC $\geq$ 50,000/microliter.

Toxicities Associated With Nelarabine and Intensive Chemotherapy

Toxicities are summarized in Table 3. Therapy caused significant myelosuppression, but the toxicity was acceptable in all treatments. Ninety percent of patients who received nelarabine had grade 3 or 4 myelosuppression versus 100% of patients treated without nelarabine ($P = .342$). Grade 3 or 4 neutropenia with infection occurred in only 42% of patients receiving nelarabine versus 81% of patients not receiving nelarabine ($P = .005$; Table 3). The most common grades 3 and 4 GI toxicity was AST/ALT elevation: 44% with nelarabine treatment and 56% without nelarabine ($P = .420$). There were no significant differences in toxicities when RER patients were compared with SER patients (Table 3).

Neurotoxicity

Grade 3 or 4 peripheral neuropathy occurred in 15% of patients who received nelarabine and in no patients who did not receive nelarabine ($P = .203$). Paradoxically, central neurotoxicity, excluding seizures, occurred in 4% of patients (three of 72) treated with nelarabine versus 25% of patients treated without nelarabine (four of 16 RER patients; $P = .019$). Four patients (6%) treated with nelarabine had five seizure episodes versus none occurring in those treated without nelarabine (P not significant). No seizures occurred in conjunction with nelarabine administration. Two occurred with CNS hemorrhage during asparaginase therapy, before any nelarabine, and one with intravenous cytarabine therapy in combination with starting paroxetine. One seizure occurred after a dose of intrathecal methotexate not in association with nelarabine. The fifth seizure episode was described

Table 2. Characteristics of Eligible Patients Enrolled Onto ALL00P2 (n = 88)

Characteristic	No Nelarabine	Nelarabine	Total
Sex			
Male	10	52	62
Female	6	20	26
Congenital abnormality			
Unknown	3	7	10
None	12	63	75
Other (not Down syndrome)	1	2	3
CNS status			
1	11	48	59
2	5	17	22
3	0	7	7
Testicular			
Unknown	0	1	1
No	10	49	59
Yes	0	2	2
NA	6	20	26
Age at diagnosis, years			
< 10	9	34	43
$\geq$ 10	7	38	45
Initial WBC, /μL			
< 50,000	8	19	27
$\geq$ 50,000	8	53	61
NCI risk group			
Standard	3	1	4
High	13	71	84
Induction response			
RER	16	38	54
MRD+	0	8	8
PPR	0	26	26
Age, years			
Minimum	4.32	1.62	1.62
First quartile	5.04	5.60	5.44
Median	8.71	10.34	10.17
Third quartile	12.44	14.01	13.86
Maximum	18.18	20.79	20.79
WBC, /1,000			
Minimum	2.10	1.60	1.60
First quartile	7.75	47.20	29.40
Median	57.25	118.30	107.25
Third quartile	167.15	259.50	238.20
Maximum	334.00	820.00	820.00

Abbreviations: MRD, minimal residual disease; NCI, National Cancer Institute; RER, rapid early responder; SER, slow early responder.

as staring spells with stiff hands, which were not associated with nelarabine use and resolved completely.

Five patients treated with nelarabine experienced additional neurologic adverse events: one patient had a Guillan-Barre-like syndrome that occurred 2 weeks after nelarabine, which had partially resolved at the time of his removal from protocol therapy; one patient developed somnolence, lethargy, and decreased oral intake after cranial irradiation and nelarabine, which resolved completely and was possibly related to nelarabine; one patient experienced pseudotumor cerebri after cranial irradiation and nelarabine (additional nelarabine doses were held); and one patient developed sensory neuropathy and mild motor weakness associated with vincristine, not nelarabine, that was exacerbated during a viral illness. A full neurologic evaluation including magnetic resonance imaging of brain and spine, lumbar puncture,

Table 3. Toxicities in Patients in ALL00P2

Selected Toxicity	No Nelarabine (n = 16)		Nelarabine (n = 72)		P	RER (n = 54)		SER (n = 34)		P
	No.	%	No.	%		No.	%	No.	%	
Neutropenia with infection	13	81.25	30	41.67	.0053	28	51.85	15	44.12	.5176
AST/ALT	9	56.25	32	44.44	.420	25	46.30	16	47.06	1.00
Hgb, neutropenia, platelets	16	100.00	65	90.28	.3417	50	92.59	31	91.18	1.00
Pancreatitis	1	6.25	5	6.94	1.00	3	5.56	3	8.82	.6726
Neurotoxicity (pooled)	4	25.00	15	20.83	.7413	10	18.52	9	26.47	.4306
Central neurotoxicity	4	25.00	3	4.17	.0189	4	7.41	3	8.82	1.00
Peripheral neuropathy	0	0.00	11	15.28	.2034	6	11.11	5	14.71	.7434
Seizures	0	0.00	4	5.56	1.00	0	0.00	4	11.76	.0199

Abbreviation: Hgb, hemoglobin.

electromyography, and nerve conduction studies revealed only mild nerve conduction abnormalities, consistent with vincristine toxicity. These symptoms resolved completely.

One patient experienced mild motor neuropathy after vincristine, which increased after steroids and on day 3 of a 5-day course of nelarabine. The last two doses of nelarabine were held, and symptoms resolved. The patient later developed weakness and fatigue after cranial irradiation, before additional doses of nelarabine. Brain magnetic resonance imaging revealed mild leukoencephalopathy. No additional nelarabine was administered.

Outcomes

Five-year EFS was 73% for 11 stage one SER patients and 67% for 22 stage two SER patients treated with nelarabine versus 69% for 16 stage one RER patients treated without nelarabine. Five-year EFS was 74% for 38 stage two RER patients treated with nelarabine. Five-year EFS was 69% (SE, 12%) for patients (n = 16; all RER) treated without nelarabine versus 73% (SE, 11%) for all patients (n = 70) receiving nelarabine ($P = .6459$; Fig 2). There was no significant difference in EFS between SER patients at higher risk based on PPR (n = 25) or high levels of end induction MRD alone (n = 7; 69%) and those experiencing RER (n = 38; 74%; $P = .2393$; Fig A1).

There were 23 events that occurred among study patients. One patient assigned to a nelarabine arm experienced progressive disease

before receiving nelarabine. There were 19 relapses: isolated bone marrow in eight patients, isolated CNS in four patients, testis in one patient, CNS and bone marrow in three patients, CNS and testis in one patient, and unspecified in two patients. Three patients relapsed during consolidation; 11 patients relapsed during weeks 43 to 74 of maintenance, and two patients relapsed after completing therapy (at 4 months and 2.9 years, respectively). Three patients relapsed 4 months to 7 years after going off protocol therapy for SCT, toxicity, or protocol violation. Two patients who received nelarabine (400 mg/m²) developed acute myeloid leukemia (22 and 17 months from diagnosis, respectively). One patient treated without nelarabine developed a low-grade mucoepidermoid carcinoma of the parotid gland.

DISCUSSION

Overall, 75% to 80% of children with T-ALL are cured with contemporary chemotherapy regimens.^{1-11,13} However, the salvage rate is extremely poor for patients who relapse.^{26,27} Thus, to improve survival for children with T-ALL, it is essential to identify effective agents that can be incorporated into first-line chemotherapy regimens.

The most powerful predictor of poor outcome in T-ALL is a poor early chemotherapy response, which some groups have used to allocate patients to SCT in CR1.¹²⁻¹⁷ The BFM group found that patients with T-ALL with a PPR and/or no response by day 33 of therapy had 5-year disease-free survival of 35% in the BFM 90 trial and 51% in the BFM 95 trial, when treated with chemotherapy alone. Disease-free survival of this patient subset was 50% in BFM 90 and 73% in BFM 95, if patients underwent SCT in CR1.¹² In a recent analysis of the AIEOP-BFM-ALL (Associazione Italiana Ematologia Oncologia Pediatrica-BFM-Acute Lymphoblastic Leukemia) 2000 study, a lower relapse rate was noted in patients with MRD high-risk T-ALL undergoing allogeneic SCT in CR1 (13 of 55 relapses) versus 23 of 42 relapses in those treated with chemotherapy alone.¹³ Despite these findings, there is no general consensus regarding the effectiveness of SCT in this setting.

Measurement of MRD response has provided significant prognostic information in T-ALL. Willemse et al¹⁴ measured MRD at the end of induction (week 5) and start of consolidation (week 13) in patients with T-ALL and correlated MRD results with relapse-free survival (RFS). Low-risk patients with no measurable MRD at both weeks 5 and 13 had 5-year RFS of 100%. In contrast, high-risk patients

Fig 2. Kaplan-Meier event-free survival curves for patients receiving versus not receiving nelarabine in ALL00P2.

(those with MRD $\geq 0.1\%$ at both time points) had 5-year RFS of 0%, and those with MRD $\geq 1\%$ at the end of induction had 5-year RFS of 14%. All others were designated intermediate risk and had 5-year RFS of 76%.

The phase I/II experience with nelarabine identified it as a promising agent for patients with T-ALL. However, the occurrence of clinically severe and sometimes fatal CNS toxicity during early trials for patients with relapsed T-ALL made it essential to carefully evaluate the toxicity of nelarabine combined with intensive chemotherapy for those with newly diagnosed T-ALL.

In the current study, we found that five or six 5-day courses of nelarabine 400 or 650 mg/m² could be added safely to BFM 86–based chemotherapy in patients with newly diagnosed T-ALL. Both dose levels were well tolerated, with only one of 72 patients experiencing significant neurotoxicity clearly related to nelarabine (Guillain-Barre-like syndrome). This is a much lower rate of neurotoxicity than seen in the COG P9673 single-agent phase II trial that reported grade 3 or 4 neurologic events in 18% of patients, with 11% having grade 3 or 4 CNS toxicity and 9% grade 3 or 4 peripheral nerve toxicity.²² In AALL00P2, incidence of grades 3 and 4 peripheral nerve toxicity was similar at 15%, but only 4% had grade 3 or 4 CNS toxicity. Patients treated in the phases I and II nelarabine trials had relapsed T-ALL, and many were heavily pretreated with therapy that included repeated cycles of vincristine, high-dose methotrexate, and/or cranial irradiation. The differences in CNS toxicity between AALL00P2 and earlier trials suggest that therapies with significant toxicity in the relapse setting may be better tolerated in newly diagnosed chemotherapy-naïve patients using the moderate phase II suggested dose of 650 mg/m². Interestingly, although the AALL00P2 chemotherapy was myelosuppressive, addition of nelarabine did not lead to increased hematologic or infectious toxicities.

Although AALL00P2 was not powered to determine the efficacy of adding nelarabine to intensive chemotherapy, the results are quite encouraging. SER patients treated with nelarabine at either 400 or 650 mg/m², who were expected to have poor treatment outcomes based on poor early response to induction therapy, had a 5-year EFS rate of 69%, identical to the EFS rate (69%) of RER patients who did not receive nelarabine. RER patients who received nelarabine had a 5-year EFS rate of 74%. The EFS rate for SER patients treated with nelarabine in AALL00P2 compares favorably with that obtained for patients receiving SCT in CR1 in the BFM 90 and 95 protocols (50% to 73%) and is greatly improved over that seen in patients with similar MRD levels in the Willemse et al¹⁴ analysis (14%).¹² In the recently published analysis of the AIEOP-BFM-ALL 2000 study, 7-year EFS for intermediate- and high-risk patients with T-ALL based on high MRD

levels was 81% and 50%, respectively. Intermediate-risk patients were those with MRD positivity at either day 33 or 78 and MRD $< 10^{-3}$ at day 78, and high-risk patients were those with MRD $\geq 10^{-3}$ at day 78.¹³ AALL00P2 did not measure MRD at day 78 but used high MRD levels of $> 1\%$ at day 36. Although the data are not directly comparable, the AALL00P2 high-risk patients would be a mixture of AIEOP-BFM intermediate- and high-risk patients, and albeit based on small numbers, comparable results were achieved without SCT in CR1.

In summary, patients with T-ALL with a poor early treatment response that predicted for poor outcomes in previous trials attained a 5-year EFS rate of 69% with intensive chemotherapy plus nelarabine. There was no increase in CNS or non-CNS toxicities at either the 400 or 650 mg/m² dose level. On the basis of these results, the COG is now conducting a randomized phase III trial of chemotherapy with and without nelarabine (650 mg/m²) in children, adolescents, and young adults with T-ALL, with careful monitoring for neurotoxicity.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: None **Consultant or Advisory Role:** None **Stock Ownership:** None **Honoraria:** None **Research Funding:** Michael J. Borowitz, Becton-Dickinson Biosciences **Expert Testimony:** None **Other Remuneration:** None

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