Pediatric T-Acute Lymphoblastic Leukemia and T-Lymphoblastic Lymphoma (Study T2008-002 NECTAR)

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Abbreviation Key:

ALL	acute lymphoblastic leukemia
ALT	alanine amino transferase
CLIA	Clinical Laboratory Improvement Amendments
CNS	central nervous system
COG	Children's Oncology Group
CPM	cyclophosphamide
CR	complete response
CRp	complete response with incomplete platelet recovery
CSF	cerebrospinal fluid
CTCAE	Common Terminology Criteria for Adverse Events
DL	dose level
DLT	dose-limiting toxicity
EFS	event-free survival
ETOP	etoposide
FDA	United States Food and Drug Administration
G-CSF	granulocyte-colony stimulating factor
GFR	glomerular filtration rate
Gr	grade
GTP	guanosine triphosphate
HSCT	hematopoietic stem cell transplant or hematopoietic stem cell transplantation
ITCC	Innovative Therapies for Childhood Cancer
IV	intravenous
LBL	lymphoblastic lymphoma
MMA	methylmalonic acid
MRD	minimal residual disease

MTD	maximum tolerated dose
N/A	not available
NCT	National Cancer Institute clinicaltrials.gov identifier
NE	not evaluable
NECTAR	**N**elarabine Etoposide **C**yclophosphamide in **T**-cell **A**cute **R**elapse
NEL	nelarabine
NR	non-response or no response
PCP/PJP	*Pneumocystis carinii/Pneumocystis jiroveci* pneumonia
PD	progressive disease
POETIC	Pediatric Oncology Experimental Therapeutics Investigators' consortium
PR	partial response
RP2D	recommended phase II dose
SAE	serious adverse events
SD	stable disease
SOS	sinusoidal obstruction syndrome
TACL	Therapeutic Advances for Childhood Leukemia/Lymphoma
T-ALL	T-cell acute lymphoblastic leukemia
UKALL	United Kingdom Acute Lymphoblastic Leukemia
T-LBL	T-cell lymphoblastic lymphoma
ULN	upper limit of normal
VOD	veno-occlusive disease

Abstract

Children with relapse of T-cell acute lymphoblastic leukemia (T-ALL) or lymphoblastic lymphoma (T-LBL) have a dismal prognosis, largely due to difficulty attaining second remission. We hypothesized that adding etoposide and cyclophosphamide to the nucleoside analogue nelarabine could improve response rates over single agent nelarabine for relapsed T-ALL and T-LBL. This phase I dose-escalation trial's primary objective was to evaluate the dose and safety of nelarabine given in combination with etoposide at 100 mg/m^2/day and cyclophosphamide at 330-400 mg/m^2/day, each for 5 consecutive days in children with either T-ALL (13 patients) or T-LBL (10 patients). Twenty-three patients were treated at 3 dose levels; 21 were evaluable for dose limiting toxicities (DLT) and response. The recommended phase 2 doses (RP2D) for this regimen, when given daily x 5 every 3 weeks, were nelarabine 650 mg/m^2/day, etoposide 100 mg/m^2/day, and cyclophosphamide 400 mg/m^2/day. DLTs included peripheral motor and sensory neuropathies. An expansion cohort to evaluate responses at the RP2D was terminated early due to slow accrual. The overall best response rate was 38% (8/21), with 4/12 (33%) responses in the T-ALL cohort and 4/9 (44%) responses in the T-LBL cohort. These response rates are comparable to those seen with single agent nelarabine in this setting. These data suggest that the addition of cyclophosphamide and etoposide to nelarabine does not increase the incidence of neurologic toxicities or the response rate beyond that obtained with single-agent nelarabine in children with first relapse of T-ALL and T-LBL.

Introduction

T-cell acute lymphoblastic leukemia (T-ALL) comprises approximately 15% of ALL in children and 25% of ALL in adults.[1] Although children with T-ALL and T lymphoblastic lymphoma (T-LBL) historically fared more poorly than their B-lineage counterparts[2,3] recent treatment approaches have led to event-free survival (EFS) in newly diagnosed childhood T-ALL and T-LBL that is similar to those for children with B-lineage ALL/LBL.[4-10] However, recurrence of childhood T-ALL or T-LBL carries a dismal prognosis, with long-term survival of less than 25%[11-13] and, despite multiple clinical trials, little progress has been made over the past three decades in altering this outcome.

A significant challenge in the management of relapsed T-ALL and T-LBL is attaining second remission, a prerequisite for potentially curative therapies such as allogeneic hematopoietic stem cell transplantation (HSCT). While the majority of children with relapsed B-ALL respond to standard cytotoxic chemotherapy with or without newer immunotherapeutic approaches, fewer than a quarter of children with relapsed T-ALL attain second remission.[13] Thus, new therapeutic approaches to remission reinduction in children with recurrent T-ALL and T-LBL represent an important unmet need.

Nelarabine (NEL), a prodrug of the deoxyguanosine analogue 9-h-D-arabinofuranosylguanine (ara-G), is efficacious for the treatment of acute T-cell malignancies. Nelarabine is demethylated by adenosine deaminase to form ara-G, after which deoxyguanosine kinase and deoxycytidine kinase sequentially phosphorylate ara-G to form ara-GTP.[14,15] The selective cytotoxicity of nelarabine for T-cells is related to higher levels of deoxyribonucleoside phosphorylating activity and lower levels of deoxyribonucleotide dephosphorylating activity in malignant T-cells compared to malignant B-cells, leading to greater intracellular accumulation of deoxyribonucleosides and related analogues and thus greater cellular toxicity.[16]

A phase I trial of nelarabine in adults and children with resistant T-ALL or T-LBL produced an overall response rate (CR+PR) in T-ALL/T-LBL of 54% after 1-2 courses and 7 of 26 (27%) CRs in pediatric T-ALL/T-LBL patients.[17] The dose-limiting toxicity was neurotoxicity, with transient somnolence, malaise, and fatigue most commonly reported. In a pediatric phase II trial of nelarabine as a single agent in relapsed childhood T-ALL, significant neurotoxicity was seen at the initial dose of 1.2 g/m^2 daily for 5 consecutive days every 3 weeks, leading to a final recommended dose of 650 mg/m^2 daily for 5 days in patients with bone marrow relapse and 400 mg/m^2 daily for 5 days in patients with extramedullary relapse.[18] Nelarabine was approved by the US FDA in 2005 for treatment of patients with relapsed or refractory T-cell ALL/LBL after at least two prior regimens, based on its ability to induce complete responses in this highly refractory patient population.[19] The efficacy of single-agent nelarabine in children and young adults with relapsed or refractory T-

ALL/T-LBL was confirmed in a phase 4 study, with an overall response rate of 39% and CR rate of 35.7%.[20]

Given that cytotoxic agents are rarely optimally effective as single agents, we hypothesized that combining nelarabine with additional cytotoxic chemotherapy agents could enhance its efficacy. Based on earlier observations that the combination of cyclophosphamide and etoposide was safe and effective in relapsed ALL[13,21] and that other nucleoside analogues such as clofarabine could be safely combined with cyclophosphamide and etoposide, [22,23] we conducted a phase I trial to evaluate the safety and preliminary efficacy of a regimen (NECTAR) combining nelarabine (NEL) with cyclophosphamide (CPM) and etoposide (ETOP) in children with first relapse of T-ALL and T-LBL.

Methods

T2008-002 was an investigator-initiated phase I dose-escalation study of the combination of concurrently administered NEL, ETOP and CPM, with a cohort expansion at the recommended phase II dose (RP2D). The trial was conducted as a collaboration among the Therapeutic Advances in Childhood Leukemia & Lymphoma (TACL), Innovative Therapies for Children with Cancer (ITCC), and Pediatric Oncology Experimental Therapeutics Investigators (POETIC) consortia.

Patient eligibility

Eligible patients were between 1 and 21 years at enrollment with first relapse or initial induction failure of T-ALL or T-LBL, and either >25% blasts in the bone marrow (T-ALL) or extramedullary involvement of non-sanctuary sites such as lymph node or mediastinum (T-LBL). Patients with an isolated extramedullary relapse or with frank leukemic involvement of the central nervous system (i.e., CNS3 status) were not eligible. T-LBL patients were included because while this patient population is rare, the potential benefit of a nelarabine-based regimen was considered, yet a separate study was deemed infeasible. Recognizing that meaningful statistical sub-set analysis would be unlikely, the hope was to obtain descriptive data about any potential activity of this combination for patients with relapsed T-LBL while assessing toxicity within a study.

Other eligibility criteria included Lansky/Karnofsky performance score ≥50%, recovery from acute toxic effects of prior therapy and lack of evidence of active infection. Patients had to be ≥7 days from prior cytotoxic therapy (including intrathecal methotrexate), with the exceptions of (1) maintenance-type ALL therapy, for which there was no washout period, and 2) hydroxyurea, which was permitted until 24 hours prior to the first dose of study chemotherapy. At least 6 weeks must have elapsed since nitrosoureas, and at least 12 weeks must have elapsed since craniospinal, hemipelvic or other radiation therapy to >25% of the bone marrow containing spaces. Prior nelarabine was allowed, but the prior combination of nelarabine/cyclophosphamide/etoposide was not allowed. Prior HSCT was not

allowed. Other eligibility requirements included: adequate renal function defined as serum creatinine ≤1.5x upper limit of normal (ULN) for age, or a calculated creatinine clearance or radioisotope GFR ≥70 mL/min/1.73m^2; normal cardiac function defined as shortening fraction of ≥27% by echocardiogram or ejection fraction ≥45% by gated radionuclide study; adequate pulmonary function defined as evidence of no dyspnea at rest, no exercise intolerance, and a pulse oximetry ≥94% at sea level (≥ 90% at altitude ≥ 5000 feet); adequate liver function defined as total bilirubin ≤1.5x ULN for age (or conjugated (direct) serum bilirubin ≤ULN for age) and ALT ≤ 5xULN of normal for age. Additional exclusion criteria included patients with Down syndrome, pre-existing Grade (Gr) ≥2 peripheral motor or sensory neurotoxicity, prior seizure disorder requiring anti-convulsant therapy, or a history of prior veno-occlusive disease (VOD)/sinusoidal obstruction syndrome (SOS) or findings consistent with a diagnosis of VOD/SOS.

This clinical trial was registered at www.clinicaltrials.gov (NCT00981799). Local institutional review board approval was required prior to patient enrollment. Procedures followed were in accordance with the Helsinki Declaration. Written informed consent from patients ≥18 years or from parents/legal guardians of children age <18 years was obtained (with assent as appropriate) according to local institutional policies.

Study design and treatment

The primary objective of the study was to establish the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) of nelarabine in combination with escalating doses of cyclophosphamide and a fixed dose of etoposide. The primary endpoint was the occurrence of dose-limiting toxicity (DLT) during course 1 of therapy. Secondary endpoints included response (all subjects), ability to proceed to HSCT within 20 weeks from study entry for patients achieving CR2 (all subjects), and minimal residual disease (MRD) levels at the end of each course of therapy for T-ALL patients who attained CR2.

A course consisted of nelarabine at an assigned dose of 480-650 mg/m^2/day intravenously (IV) over 60 minutes, followed by etoposide 100 mg/m^2/day IV over 2 hours, followed by cyclophosphamide at an assigned dose of 330-400 mg/m^2/day IV over 30-60 minutes, each for 5 consecutive days. Intrathecal methotrexate (age-based dosing) was administered no less than 7 days prior to or at least 21 days following the start of a course. A standard 3+3 dose-escalation design[24] was followed. The first dose level (DL1) was nelarabine administered at 480 mg/m^2/day (75% of the single-agent dose on a daily x 5 schedule) and cyclophosphamide at 330 mg/m^2/day, DL2 was nelarabine administered at 650 mg/m^2/day and cyclophosphamide at 330 mg/m^2/day, and DL3 was nelarabine administered at 650 mg/m^2/day and cyclophosphamide at 400 mg/m^2/day. Nelarabine was provided and distributed by GlaxoSmithKline. Dose escalation beyond DL3 were not planned. Intra-patient dose escalation was not allowed. A subject enrolled in the trial who

received any prescribed therapy was considered evaluable for toxicity and response; a subject who did not receive at least 85% of the required dose of protocol for any reason other than toxicity or intolerability of the regimen, and who did not experience toxicity, was not counted for purposes of dose-escalation, and was replaced.

Responding patients without DLT during or following the first course were eligible to receive a second course; a maximum of 2 courses were allowed. Disease assessment was performed following each course.

An expansion of the MTD cohort was planned for a total of 20 patients with T-ALL treated at the MTD who were evaluable for response.

Supportive care measures

Filgrastim (G-CSF) 5 micrograms/kg/day administered IV or subcutaneously began on Day 6 and ended when the absolute neutrophil count (ANC) was >1000/μl for two consecutive days. All patients were recommended to receive prophylaxis for *Pneumocystis carinii/jiroveci (PCP/PJP*); anti-bacterial, and anti-fungal prophylaxis during periods of neutropenia. Management of febrile neutropenia followed local institution guidelines.

Toxicity evaluation

Toxicities were graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 which was in place at the time of protocol approval, with modified grading for sensory and motor neuropathy. DLT was defined as any of the following events that were attributed as possibly, probably or definitely related to the treatment regimen: bone marrow aplasia (defined as failure to recover a peripheral ANC >500/μl and platelet count >20,000/μl) in the absence of persistent leukemia or lymphoma) >42 days from Day 1 of Course 1; ≥Gr 2 neurologic toxicity; development of VOD/SOS, defined as (a) conjugated serum bilirubin >1.4 mg/dL, and (b) unexplained weight gain greater than 10% of baseline weight or ascites, and (c) hepatomegaly or right upper quadrant pain without another explanation, or (d) reversal of portal vein flow on ultrasound, or (e) pathological confirmation of VOD/SOS on liver biopsy; any Gr3 or 4 non-hematologic toxicities excluding infection, fever with or without neutropenia, fatigue, electrolyte abnormalities, hyperglycemia, hypoglycemia, nausea or vomiting controlled with standard supportive care measures, GGT elevation, hypoalbuminemia, hemorrhage or bleeding, elevation in hepatic transaminases or alkaline phosphatase that returned to ≤Gr2 within 14 days of first occurrence, Gr3 elevation in amylase, lipase, or total bilirubin that was asymptomatic and returning to ≤Gr2 within 7 days of first occurrence, Gr3 rash that returned to ≤Gr 2 within 7 days. Initial DLT attributions performed by the investigator were reviewed and subject to adjudication by a toxicity review committee consisting of the study chair, co-chair, and statistician, in conjunction with the treating investigator.

Response criteria

For T-ALL patients, CR2 was defined as no evidence of circulating blasts or extramedullary disease, a bone marrow with <5% blasts, and recovery of peripheral counts (platelets ≥75,000/μl and ANC ≥750/μl)); CR2p was defined as no evidence of circulating blasts or extramedullary disease, a bone marrow with <5% blasts, and an ANC ≥750/μl with platelets <75,000/μl); partial remission (PR) was defined as complete disappearance of circulating blasts, appearance of normal hematopoietic progenitor cells, and either a bone marrow with ≥5% and ≤25% blasts with recovery of peripheral counts (platelets ≥75,000//μl and ANC ≥750/μl) or a bone marrow with <5% blasts that does not qualify for CR or CRp (i.e., platelets <20,000/μl and ANC <750/μl). Progressive disease (PD) was defined as an increase of at least 25% of the absolute number of blasts in either bone marrow or peripheral blood, development of extramedullary disease, or other laboratory or clinical evidence of progression. No response (NR) was defined as failure to qualify for CR, CRp, or PR, and also included PD. Response criteria for T-LBL patients were based on those used in adult NHL.[25]

Optional correlative biology studies available only at TACL institutions included collection of blood and/or bone marrow samples for phospho-flow cytometry, evaluation of mechanisms of nelarabine toxicity, and Mer tyrosine kinase and T-ALL oncogene expression. Preliminary data from studies of nelarabine in adult patients suggest that the neurotoxicity seen is histologically similar to that noted in patients with vitamin B12 deficiency.[26,27] As such, an exploratory aim of this study was to evaluate the vitamin B12 pathway and metabolites, and any possible association of the described neurotoxicity of nelarabine. Measurement of homocysteine, methylmalonic acid (MMA), cystathionine, 2-methylcitric acid, methionine, cysteine, methylglycine, dimethylglycine, serine, glycine and alpha-aminobutyrate, S-adenosylmethionine and S-adenosylhomocysteine levels in blood and CSF pre- and post-treatment for all patients were included as optional correlative studies. In the event of neurotoxicity, additional specimens for the same analytes were collected at the onset of neurotoxicity. These studies were performed in a CLIA-certified laboratory according to standard methods described in the Supplemental Materials.

Results

Twenty-three patients were enrolled between April 2010 and October 2015, including 4 of 20 planned patients with T-ALL in the expansion cohort. Slow accrual during the expansion cohort phase of the study led to early study termination prior to its completion. Characteristics of the study population are summarized in Table 1. Thirteen patients had first relapse of T-ALL, and 10 had first relapse of T-LBL. No patients enrolled due to induction failure. All enrolled patients were deemed eligible and were evaluable for toxicity; 21 patients were evaluable for DLT. Four patients had received prior nelarabine as a single agent. Of two inevaluable patients, one

died early in treatment due to progressive/refractory disease and one proceeded to HSCT before completing a full course of NECTAR. Ten patients received two courses of NECTAR, all having had at least stable disease after Course 1.

Dose level, severe adverse events (SAEs), DLTs and response data are listed in Table 2, and ≥Gr3 non-hematologic adverse events occurring in >5% of patients are listed in Table 3. DLTs are detailed in Table 4. Three patients were enrolled onto DL1 with no DLTs thus the study was escalated to DL2 enrolling 3 patients. One patient experienced DLT (Gr2 peripheral motor neuropathy, Gr3 peripheral sensory neuropathy) and DL2 was expanded to enroll up to 3 additional patients. Two additional patients were enrolled at DL2 with the occurrence of a second DLT (Gr4 hyperbilirubinemia), and the study regressed to DL1. Three additional patients were enrolled onto DL1 (for a total of 6) with no DLTs. The non-neurologic DLT of hyperbilirubinemia at DL2 was subsequently reviewed by the toxicity review committee in the context of additional information provided by the treating physician, who noted that hyperbilirubinemia occurred in the context of concurrent gastrointestinal bleeding not attributed to nelarabine, with a decrease to Gr3 within 8 hours of onset, and thus was subsequently ruled not to be a DLT. That patient discontinued study and was consequently deemed not evaluable for DLT, thus DL2 re-opened to 2 additional patients. This decision was approved by the Data Safety Monitoring Committee overseeing study conduct. With DLT in 1 of 6 evaluable patients on DL2, dosing was escalated to DL3. Six patients enrolled onto DL3 with DLT in one subject (Gr3 peripheral motor neuropathy). Following the evaluation of DL3 results together with a review of the response data amongst all dose levels, it was determined that there was sufficient evidence of response to warrant continuation of the study with the expansion cohort at DL3 as the recommended phase II dose (RP2D). Four patients with T-ALL were enrolled into the expansion cohort prior to eventual closure due to an inadequate rate of accrual over more than 18 months' time, with the occurrence of DLT in one additional subject (Gr3 peripheral motor and Gr4 sensory neuropathy).

Of 21 evaluable patients, the overall best response rate (CR+CRp+PR) was 38% (8/21), with 4/12 (33%) responses in the T-ALL cohort and 4/9 (44%) responses in the T-LBL cohort. The combined complete response rate (CR+CRp) was 24% (5/21), with 2/12 (17%) CR/CRp in the T-ALL cohort and 3/9 (33%) CRs in the T-LBL cohort; one patient each with T-ALL and T-LBL had concurrent CR in bone marrow and PR in a mediastinal mass. At the RP2D, 3/8 (38%) evaluable T-ALL and 0/2 evaluable T-LBL patients responded, for an overall response rate of 30% at the RP2D; of note, 3 T-LBL patients had responses at doses below the RP2D. Ten subjects received a second course of NECTAR across all dose levels; 10 of 19 subjects for whom follow-up data were available underwent HSCT however no details about their transplant course were collected. MRD levels were available for 1 of 4 responding T-ALL patients; one subject attained CR after one course, with a corresponding end-course 1 MRD level of 0.027%; the MRD level at D8 of a second course was 18.4%, and at

end-course 2 was 0.07%. There was no correlation with prior nelarabine treatment and response in four patients previously exposed to nelarabine.

The low number of samples submitted for the optional correlative biology studies precluded meaningful analyses for these planned studies; disappointingly, only four patients submitted samples. Abbreviated observations are noted in the Supplemental Materials.

Discussion

Recurrent T-cell leukemia and lymphoblastic lymphoma represent formidable management challenges for oncologists. Despite the availability of potentially curative modalities such as HSCT, the inability to achieve remission in a patient with relapsed T-ALL or LBL essentially precludes a successful outcome with HSCT; most transplant centers are reluctant to offer HSCT to patients with resistant disease. Based on several reports[13,18], patients with T-LBL may have a lesser chance of responding to NEL and thus NECTAR or other regimens tested to date, emphasizing the need for novel therapeutic approaches for patients with bulky disease. Of note, 8 of ten responding patients underwent subsequent HSCT, underscoring the potential value of the NECTAR regimen for re-induction prior to HSCT, which remains the only known curative approach for this patient population.

Most standard reinduction therapies for ALL and LBL have poor activity in patients with T-cell immunophenotype compared to those with B-lineage disease. In COG study AALL01P2, a 4-drug reinduction regimen utilizing vincristine, steroid, pegaspargase and doxorubicin for children and adolescents with first relapse of either marrow or combined ALL, second CR rates were 96% for B-lineage ALL relapses occurring ≥36 months from initial diagnosis, 68% for B-lineage ALL relapses occurring <36 months from initial diagnosis, yet only 29% (2/7) for T-ALL patients in first relapse. The UKALLR3 and ALL-REZ BFM 2002 trial reported 22% and 32% rates for T-ALL in good versus poor MRD responders respectively.[13]

One strategy to improve remission rates for recurrent and refractory leukemias is the introduction of agents with novel mechanisms of action. In a subsequent study from COG (AALL07P1), the proteasome inhibitor bortezomib was combined with the first and second reinduction blocks of the AALL01P2 reinduction regimen for children with first marrow or combined relapse of ALL. CR2 rates were 63/99 (64%) for B-cell-precursor ALL patients and15/22 (68%) for T-ALL patients.[28] Proteasome inhibition thus appeared to be an attractive strategy for acute T-cell malignancies and based on these promising results, bortezomib in newly diagnosed T-ALL and T-LBL patients was evaluated in a randomized manner during induction therapy in COG trial AALL1231 (NCT02112916).

Clofarabine, a novel second-generation purine nucleoside, demonstrated favorable single-agent activity against relapsed/refractory ALL and AML in early-phase

trials.[29,30] However, subsequent studies evaluating regimens which incorporated clofarabine with cyclophosphamide and etoposide showed activity in remission induction in recurrent B-lineage, but not T-lineage, ALL.[22,23]

The UKALL R3 protocol [31] historically produced some of the best survival results reported to date for children with first relapse of ALL, including both B- and T-lineage. This regimen included dexamethasone, rather than prednisone, and randomized idarubicin and mitoxantrone, an anthracenedione, during remission re-induction. The estimated 3-year progression-free survival was 65% in the mitoxantrone group versus 36% in the idarubicin group, with the benefit derived primarily from a reduction in progression, second relapse, and disease-related deaths. Reinduction rates for T-ALL were not included in the original published data, however, the reinduction rate for patients with first relapse of T-ALL was subsequently reported for R3 and ALL-REZ BFM 2002 trials[13]. Although the basis for these excellent results is not fully understood, preclinical and clinical data suggest that mitoxantrone may be a beneficial agent in the treatment of relapsed acute T-cell malignancies. [32, 33]

Although definitive conclusions in this study were limited by the inability to complete the planned expansion cohort, both the activity and toxicities seen in this phase I dose escalation cohort appear to be relatively comparable to the 55% CR rate seen in children with first bone marrow relapse of T-ALL treated on a phase II trial of single-agent nelarabine administered at the same dose of 650 mg/m^2/day for 5 consecutive days.[18] As in prior trials of nelarabine, the primary toxicities observed in this trial were neurologic events related to nelarabine, including peripheral sensory and motor neuropathies. The 13% (3/23) incidence of Gr3 and 4 neurologic toxicities reported here is comparable to those in pediatric and adult studies of single agent nelarabine, which reported a 3-18% incidence of Gr3 and 4 neurologic toxicities.[18,34,35] The mechanism of nelarabine-induced neurologic toxicities remains unclear. Although the trial included a correlative biologic study which sought to elucidate the potential relationship of nelarabine toxicity to deficiencies in the vitamin B12 pathway, the small number of patients participating in this optional correlative study and the low incidence of nelarabine-related toxicities observed in this study precluded meaningful analysis. The finding that the four patients analyzed had B12 pathway metabolite levels consistent with folate deficiency is not surprising, as these patients had all undergone chemotherapy known to affect folate metabolism.

Finally, the problems encountered in completing timely accrual to this study highlight the challenges that exist in studying treatments for uncommon recurrent malignancies that have increasingly high cure rates at initial presentation. The initial recruitment base for T2008-002 was subsequently expanded by adding 15 European centers in the ITCC consortium to the 34 TACL and POETIC consortia members participating in this trial; nevertheless, the rarity of relapsed T-ALL/LBL cases at almost 50 of the largest childhood cancer centers in North America, Australia and Europe, together with the ready availability of study drugs via commercial supply

contributing to off-study protocol use, ultimately led to premature closure of the planned expansion cohort. Future considerations to avoid these challenges could include embedding studies for recurrent T-ALL/LBL within protocols for frontline treatment of the same disorders, similar to the approach adopted by the Histiocyte Society for its recent international trial for another rare childhood disorder, Langerhans cell histiocytosis (NCT02205762).

Taken together, the combination of nelarabine, etoposide and cyclophosphamide showed acceptable activity and toxicities in children, adolescents and young adults with first relapse of T-ALL and T-LBL, with a 38% overall response rate and a 13% incidence of Grade 3 and 4 neurologic toxicities overall. The recommended phase 2 doses (RP2D) for nelarabine, etoposide and cyclophosphamide on a daily x 5 every 3 weeks schedule were determined to be NEL 650 mg/m^2/day, ETOP 100 mg/m^2/day, and CPM 400 mg/m^2/day. Response and toxicity rates are comparable to those seen with single agent nelarabine when administered in the same setting and when NEL, CPM, and ETOP are used in selected combinations and sequence as reported by Commander et al.[36] Based on the results of this study, we conclude that the addition of concurrent cyclophosphamide and etoposide to nelarabine does not appear to increase either the response rate or the incidence of neurologic toxicities beyond single-agent nelarabine in children with first relapse of T-ALL and T-LBL and could be considered for further use.

As final outcomes of the AALL1231 study are now known[37], evaluations of the anti-CD38 antibodies daratumumab and Isatuximab, immunotherapeutic strategies, cyclin-dependent kinase inhibitors, BCL-2 inhibitors, mTOR inhibitors, and T-cell directed chimeric-antigen T-cell therapies are increasingly hoped to bring more promise to patients with relapsed/refractory T-ALL and T-LBL. These patients remain with a significantly unmet medical need. Many of these newer approaches and regimens will likely require some contribution of conventional cytotoxic chemotherapy to reduce disease burden, in which case the NECTAR regimen could be considered for some patients.

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TABLE 1 Characteristics of patients enrolled on T2008-002 NECTAR

Characteristic	Number (%)
Age (years)	
• Median	9.7
• Range	1.4-18.8
Gender	
• Female	8 (35%)
• Male	15 (65%)
Diagnosis	
• T-ALL	13 (57%)
• T-LBL	10 (43%)
Dose Level	
• DL1 (NEL 480mg/m^2, CPM 330 mg/m^2)	6 (26%)
• DL2 (NEL 650mg/m^2, CPM 330mg/m^2)	7 (30%)
• DL3 (NEL 650 mg/m^2, CPM 400mg/m^2)	10 (43%)

CPM = cyclophosphamide
DL = dose level
NEL = nelarabine
T-ALL = T-cell acute lymphoblastic leukemia
T-LBL = T-cell lymphoblastic lymphoma

TABLE 2 Dose-limiting toxicities and clinical responses of patients treated on T2008-002 NECTAR

Dose Level	Patient	Dx	SAE	DLT?	# of Courses	Best Response*	HSCT?
1	001	T-ALL	N	N	1	NR	N/A
1	002	T-ALL	N	N	2	CR*	Y
1	003	T-LBL	N	N	2	PR	Y
2	004	T-LBL	N	N	2	NR	Y
2	005	T-LBL	N	N	1	NR	N/A

2	006	T-ALL	Y	NE	N/A	N/A	N
2	007	T-LBL	Y	Y	1	CR*	Y
2	008	T-ALL	Y	N	1	NR	Y
1	009	T-LBL	N	N	2	CR	Y
1	010	T-LBL	N	N	1	NR	N
1	011	T-LBL	Y	NE	N/A	N/A	Y
2	012	T-ALL	Y	N	1	NR	N
2	013	T-LBL	N	N	2	CR	N
3	014	T-ALL	N	N	1	NR	N
3	015	T-ALL	Y	N	2	CR	Y
3	016	T-LBL	Y	Y	1	NR	N
3	017	T-ALL	Y	N	2	CRp	Y
3	018	T-LBL	Y	N	1	NR	N
3	019	T-ALL	Y	N	2	NR	N
EXP	020	T-ALL	Y	N	2	NR	Y
EXP	021	T-ALL	N	N	1	NR	N/A
EXP	022	T-ALL	Y	Y	1	CR	N
EXP	023	T-ALL	Y	N	2	NR	N/A

CR: complete response
CRp: CR with inadequate platelet recovery
EXP: expansion cohort
N/A: not available
NE: not evaluable
NR: no response
T-ALL: T-acute lymphoblastic leukemia
T-LBL: T-lymphoblastic lymphoma

* 2 patients had simultaneous CR in bone marrow and PR in mediastinal mass, best response at end-Course 1 is provided.

TABLE 3 Frequency of grade ≥3 non-hematologic toxicity in course 1 occurring in >5% of subjects on T2008-02 NECTAR

Toxicity Name (CTCAE version 3.0)		Toxicity Attribution			
	Grade 3+	Agent only	Regimen only	Agent & Regimen	Neither
Anorexia	3 (13%)	0	2	1	0
Aspartate aminotransferase increased	3 (13%)	0	0	1	2
Diarrhea NOS	2 (9%)	0	0	1	1
Febrile neutropenia	6 (26%)	0	1	5	0
Hyperkalemia	2 (9%)	0	0	2	0
Hypertension NOS	2 (9%)	0	1	0	1
Hypoalbuminemia	3 (13%)	0	1	1	1
Hypocalcemia	4 (17%)	0	1	2	1
Hypokalemia	8 (35%)	0	1	3	4
Hypotension NOS	2 (9%)	0	1	0	1
Hypoxia	2 (9%)	0	0	0	2
Nausea	3 (13%)	0	1	2	0
Peripheral motor neuropathy	2 (9%)	0	0	2	0
Peripheral sensory neuropathy	2 (9%)	1	0	1	0
Pleural effusion	3 (13%)	0	0	0	3
Vomiting NOS	2 (9%)	0	1	1	0
Pain, Other	2 (9%)	0	0	1	1

CTCAE: Common Terminology Criteria for Adverse Events; NOS: not otherwise specified

TABLE 4 Dose-limiting toxicities on T2008-002 NECTAR

Patient	Diagnosis	Dose	Grade DLT	Type of DLT	Attribution to Nelarabine	Attribution to Regimen	Comments
07	LBL	NEL 650mmg/m^2 CPM 330 mg/m^2	3- Severe	Peripheral sensory neuropathy	4 - Probable	3 - Possible	
			2- Moderate	Peripheral motor neuropathy	4 - Probable	3 - Possible	
16	LBL	NEL 650mmg/m^2 CPM 400 mg/m^2	3- Severe	Peripheral motor neuropathy	4 - Probable	3 - Possible	
22	ALL	NEL 650mmg/m^2 CPM 400 mg/m	4-Life Threatening	Peripheral sensory neuropathy	4 - Probable	2 - Unlikely	Baseline Grade 2, progressed to Grade 4
			3- Severe	Peripheral motor neuropathy	4 - Probable	2 - Unlikely	

ALL: Acute Lymphoblastic Leukemia
CPM: cyclophosphamide
DLT: Dose-Limiting Toxicity
LBL: Lymphoblastic Lymphoma
NEL: Nelarabine