

# Improving outcomes in childhood T-cell acute lymphoblastic leukemia: promising results from the Children's Oncology Group incorporating nelarabine into front-line therapy

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T-cell acute lymphoblastic leukemia (T-ALL), classified by the World Health Organization together with T-cell lymphoblastic lymphoma (T-LBL), is an uncommon disease, comprising only 15% of pediatric, and 25% of adult cases of acute lymphoblastic leukemia (ALL) (1). Relative to B-lineage ALL, the incidence of T-ALL peaks in later adolescence, with a more than 2-fold higher incidence among males than females (2). In addition to distinct clinical characteristics such as an increased propensity for extramedullary and central nervous system (CNS) involvement, it is increasingly recognized that T-ALL is a heterogeneous disease with an array of unique biological and molecular features which may be of prognostic relevance (3).

Historically, a diagnosis of T-ALL portended a worse prognosis than other forms of ALL in children. However, the outcome for childhood T-ALL has improved in recent decades, with the advent of high-dose, multi-agent chemotherapy regimens which have become the backbone of pediatric ALL therapy, resulting in long-term event free survival (EFS) rates of 70-75% for T-ALL (4-6). More recently, Pediatric Oncology Group (POG) 9404 demonstrated a significant survival advantage when high-dose methotrexate (HDM) was added to a successful Dana Farber Cancer Institute (DFCI) multi-agent chemotherapy backbone (5-year EFS 79.5% with HDM compared to 67.5% without HDM,  $P=0.047$ ) (7). In spite of the progress made, 20-25% of children with T-ALL experience relapse, most of whom cannot be salvaged with standard therapies. In adults, although T-ALL is considered a favorable ALL subtype, outcomes remain substantially inferior to those

seen in children (8), and survival for relapsed or refractory adult T-ALL has historically been very poor (9). Clearly, there is room for improvement of cure rates in T-ALL, and this will likely require novel approaches with more effective T-ALL specific agents.

Nelarabine, a synthetic, water soluble pro-drug of deoxyguanosine derivative ara-G, may be the most promising T-ALL specific drug to have emerged in recent years (10). Nelarabine is preferentially cytotoxic to T-lymphoblasts through the accumulation of ara-GTP, which occurs to a greater extent in T-cells than in B-cells, resulting in inhibition of ribonucleotide reductase and subsequent DNA synthesis (11). As a single agent in both children and adults with relapsed or refractory T-ALL, nelarabine demonstrated remarkable activity (12-14). In the Children's Oncology Group (COG) phase II open-label, single-arm, multicenter study of nelarabine in children and adolescents with recurrent or refractory T-ALL, 55% of children in first relapse, and 27% in second relapse had an objective response (CR + PR) to nelarabine at a daily dose of 650 mg/m<sup>2</sup> administered over 5 days (12). Similar efficacy was demonstrated in adult phase II studies by the Cancer and Leukemia Group B (CALGB) and the German Multicenter ALL Group (GMALL), evaluating single agent nelarabine at a dose of 1.5 g/m<sup>2</sup> per day delivered on days 1, 3, and 5 in relapsed or refractory adult T-ALL (13,14). These encouraging results led the approval of nelarabine by the US Food and Drug Administration for the treatment of relapsed/refractory T-ALL in children and adults. Toxicities common to more traditional cytotoxic therapeutics were infrequent in preclinical and phase I studies of nelarabine.

However, neurotoxicity involving the peripheral and central nervous systems (CNS) was frequent and dose limiting, yet fortunately reversible below the maximum-tolerated dose (MTD) of 60 mg/kg/day in children and 40 mg/kg/day in adults (15). In the COG phase II study, the nelarabine dose was reduced from the MTD to 650 mg/m<sup>2</sup> for 5 consecutive days out of concern for neurotoxicity. At doses of  $\leq 650$  mg/m<sup>2</sup>, 22 of 133 (17%) patients had  $\geq$  grade 3 neurologic adverse events, including seizures, somnolence, and severe peripheral neuropathy. A similar rate of neurotoxicity was seen in the adult CALGB trial. Given the impressive single-agent activity seen in relapsed or refractory T-ALL, substantial interest developed in evaluating nelarabine in the up-front treatment of T-ALL. However, the potential for serious neurotoxicity, particularly when given in conjunction with multi-agent chemotherapy regimens, remained cause for concern.

With this backdrop, the recent report by Dunsmore *et al.* in the *Journal of Clinical Oncology* describing the tolerability and outcomes from COG study AALL00P2, the first study to add nelarabine to intensive chemotherapy in children with newly diagnosed T-ALL, is all the more encouraging (16). As is often the case with clinical trials of new cancer drugs, toxicity was reduced and efficacy was enhanced, when evaluated in a newly diagnosed cohort as compared to a heavily pre-treated population.

AALL00P2 was designed as a two-stage pilot study in children aged 1-22 years with higher-risk, newly diagnosed T-ALL, testing the feasibility and toxicities associated with incorporating nelarabine into an intensive modified BFM (Berlin-Frankfurt-Munster) 86 regimen. During the first stage 12 evaluable patients with a slow early response (SER), defined as either a poor response to prednisone pre-phase (PPR) treatment or elevated minimal residual disease (MRD) at the end of induction therapy, received five or six courses of nelarabine 400 mg/m<sup>2</sup> for 5 days in addition to the chemotherapy backbone, whereas 16 patients with rapid early response (RER) to induction therapy received chemotherapy alone. In the second stage, 21 SER and 38 RER received nelarabine in addition to chemotherapy. All patients received cranial irradiation (18 Gy for CNS involvement or 12.6 Gy for prophylaxis if no CNS involvement) at the end of re-induction. Of the 88 eligible patients, nearly all were deemed to have high-risk T-ALL based on age at diagnosis of  $\geq 10$  years and initial white blood cell count of  $\geq 50,000$  / $\mu$ L; 7 had CNS involvement.

Toxicities in those who received nelarabine were surprisingly low. Significant myelosuppression occurred

in most patients regardless of receiving nelarabine; however, the prevalence of grade 3 or 4 neutropenic infection was actually higher in those who were treated without nelarabine (81% *vs.* 42%,  $P=0.005$ ). Grade 3 or 4 neurotoxicity occurred in 15 (21%) of those who received nelarabine compared to 4 (25%) who did not. Neurotoxicity in those receiving nelarabine included 3 with CNS toxicity excluding seizure, 11 with peripheral neuropathies, and 4 with seizures, although none of these occurred in conjunction with the nelarabine administration. The rate of CNS toxicity seen in AALL00P2 compares favorably with the 11% reported in the COG phase II trial evaluating single-agent nelarabine in children with relapsed or refractory T-ALL, suggesting again that newly diagnosed, chemotherapy-naïve patients may better tolerate therapies that yield significant toxicity in the relapsed setting.

The addition of nelarabine to intensive chemotherapy was also quite effective at both 400 and 650 mg/m<sup>2</sup>, as demonstrated by the impressive 5-year EFS of 69% for the 32 SER patients receiving nelarabine. This is substantially higher than the survival rates of comparable patient cohorts reported in the literature, and was identical to the 5-year EFS of RER patients who did not receive nelarabine in this study. The 5-year EFS of 74% for the 38 RER patients receiving nelarabine is also encouraging, given that the majority of these patients were high risk by National Cancer Institute criteria.

Given these encouraging findings, will there be a future for nelarabine in newly diagnosed T-ALL? The COG is currently accruing patients to COG AALL0434, a randomized phase III study evaluating 5 day courses of nelarabine at 650 mg/m<sup>2</sup> in addition to an augmented BFM chemotherapy backbone in children and young adults with newly diagnosed T-ALL. The North American adult cooperative groups are also developing a front-line study incorporating nelarabine into the treatment of newly diagnosed adults with T-ALL. Hopefully, these studies will confirm the low toxicity and high efficacy seen in AALL00P2, and thus establish nelarabine's role in improving the cure rate of patients with T-ALL.

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### Footnote

*Conflicts of Interest:* The authors have no conflicts of interest

to declare.

## References

1. Pui CH, Robison LL, Look AT. Acute lymphoblastic leukaemia. *Lancet* 2008;371:1030-43.
2. Dores GM, Devesa SS, Curtis RE, et al. Acute leukemia incidence and patient survival among children and adults in the United States, 2001-2007. *Blood* 2012;119:34-43.
3. Kraszewska MD, Dawidowska M, Szczepański T, et al. T-cell acute lymphoblastic leukaemia: recent molecular biology findings. *Br J Haematol* 2012;156:303-15.
4. Reiter A, Schrappe M, Ludwig WD, et al. Chemotherapy in 998 unselected childhood acute lymphoblastic leukemia patients. Results and conclusions of the multicenter trial ALL-BFM 86. *Blood* 1994;84:3122-33.
5. Goldberg JM, Silverman LB, Levy DE, et al. Childhood T-cell acute lymphoblastic leukemia: the Dana-Farber Cancer Institute acute lymphoblastic leukemia consortium experience. *J Clin Oncol* 2003;21:3616-22.
6. Seibel NL, Steinherz PG, Sather HN, et al. Early postinduction intensification therapy improves survival for children and adolescents with high-risk acute lymphoblastic leukemia: a report from the Children's Oncology Group. *Blood* 2008;111:2548-55.
7. Asselin BL, Devidas M, Wang C, et al. Effectiveness of high-dose methotrexate in T-cell lymphoblastic leukemia and advanced-stage lymphoblastic lymphoma: a randomized study by the Children's Oncology Group (POG 9404). *Blood* 2011;118:874-83.
8. Stock W, Johnson JL, Stone RM, et al. Dose intensification of daunorubicin and cytarabine during treatment of adult acute lymphoblastic leukemia: Results of Cancer and Leukemia Group B Study 19802. *Cancer* 2013;119:90-8.
9. Thomas DA, Kantarjian H, Smith TL, et al. Primary refractory and relapsed adult acute lymphoblastic leukemia: characteristics, treatment results, and prognosis with salvage therapy. *Cancer* 1999;86:1216-30.
10. Larson RA. Three new drugs for acute lymphoblastic leukemia: nelarabine, clofarabine, and forodesine. *Semin Oncol* 2007;34:S13-20.
11. Ravandi F, Gandhi V. Novel purine nucleoside analogues for T-cell-lineage acute lymphoblastic leukaemia and lymphoma. *Expert Opin Investig Drugs* 2006;15:1601-13.
12. Berg SL, Blaney SM, Devidas M, et al. Phase II study of nelarabine (compound 506U78) in children and young adults with refractory T-cell malignancies: a report from the Children's Oncology Group. *J Clin Oncol* 2005;23:3376-82.
13. DeAngelo DJ, Yu D, Johnson JL, et al. Nelarabine induces complete remissions in adults with relapsed or refractory T-lineage acute lymphoblastic leukemia or lymphoblastic lymphoma: Cancer and Leukemia Group B study 19801. *Blood* 2007;109:5136-42.
14. Gökbüget N, Basara N, Baumann H, et al. High single-drug activity of nelarabine in relapsed T-lymphoblastic leukemia/lymphoma offers curative option with subsequent stem cell transplantation. *Blood* 2011;118:3504-11.
15. Kurtzberg J, Ernst TJ, Keating MJ, et al. Phase I study of 506U78 administered on a consecutive 5-day schedule in children and adults with refractory hematologic malignancies. *J Clin Oncol* 2005;23:3396-403.
16. Dunsmore KP, Devidas M, Linda SB, et al. 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. *J Clin Oncol* 2012;30:2753-9.

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