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COMMENTARY

A new standard of care for childhood T-cell acute lymphoblastic leukemia?

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The Children's Oncology Group (COG) study AALL0434 (NCT00408005), with an enrollment of 1562 young people, is the largest T-cell acute lymphoblastic leukemia (T-ALL) study yet reported. The overall 5-year event-free survival (EFS) and overall survival (OS) rates were 83.7% (95% confidence interval (CI 81.5–85.9%) and 89.5% (95% CI 87.7–91.3%) as most recently reported.[1]

In August 2018, Winter et al. reported a statistically significant disease-free survival (DFS) and OS advantage for patients treated with Capizzi methotrexate/early whole brain irradiation (C-Mtx) over 5 g/m^2 methotrexate/late whole brain irradiation (HD-Mtx), despite a careful limitation of leucovorin rescue.[2] Randomization excluded patients with overt CNS or testes disease and those not achieving remission at end induction. The 5-year DFS was 91.5% for C-MTX and 85.3% for HD Mtx (p = 0.005, log rank, two-sided). C-Mtx resulted in fewer isolated marrow and isolated CNS relapses. The finding that Capizzi Mtx was superior to 5 g/m^2 Mtx reversed the findings from AALL0232 for B-ALL, though on AALL0434 most patients received whole brain irradiation therapy (WB XRT) while on AALL0232, most patients did not.[3]

In August 2020, Dunsmore et al. reported a DFS advantage for six 5-day courses of nelarabine in the 2 × 2 factorial design.[1] The populations overlapped but were not identical. Randomization excluded patients with preexisting seizures or neuropathy, those designated lower risk (age 1–10 years, WBC < 50,000/ µl, no overt testes or CNS disease, D15 marrow M1 by microscopy, and day 29 MRD < 0.1 by flow cytometry), and those not achieving remission at end induction. For 659 randomized patients, the 5-year DFS was 88.2% for nelarabine and 82.1% for control—a 6 percentage point difference. A one-sided log rank p_value = 0.029 is reported. The frequency of isolated and combined CNS relapse was substantially lower with nelarabine. Nelarabine showed no advantage for higher risk T-lymphoblastic lymphoma.[4]

A new standard of care was declared for T-ALL.[5] However promising, do these reports constitute a new standard of care?

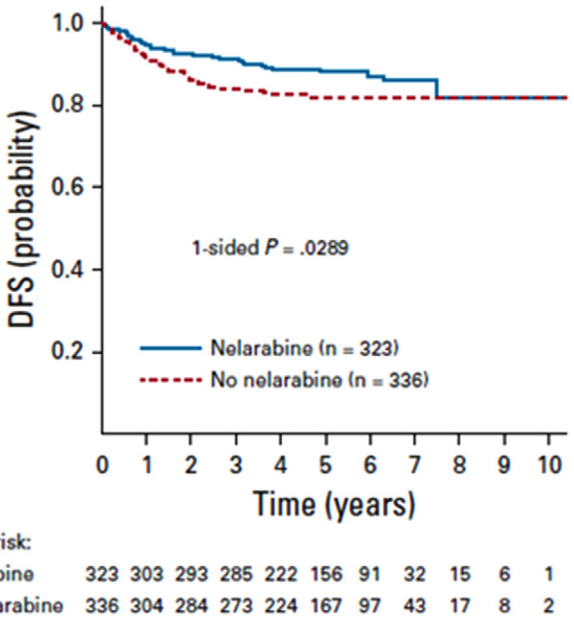

FIGURE 1 Figure 3A from Dunsmore et al.[1]

Figure 3A in Dunsmore et al. (Figure 1) shows late DFS events after 5 years on the nelarabine arm (see below), the nature of which are not detailed.[1] Rare in T-ALL treated with conventional high-risk regimens, events after 5 years were not seen in the control arm, challenging the long-term benefit of nelarabine on DFS.

Early findings may not always be sustained with further follow-up. CNS relapse tends to occur earlier than marrow relapse[6] and marrow relapse may eventually "catch up." Nelarabine had a major effect on isolated CNS relapse. CCG-1882 compared 18 Gy WB XRT and additional intrathecal methotrexate in young people with high-risk ALL. A platform presentation of the preliminary results at the American Society of Clinical Oncology Meeting in 1994 reported that WB XRT

TABLE 1 Outcomes by regimen

AALL0232[3]		
Age 1–9 years	**Capizzi methotrexate**	**5 g/m² Methotrexate**
Prednisone (5-year EFS)	81%	82%
Dexamethasone (5-year EFS)	83%	91%
Age ≥ 10 years (4-year DFS)	77%	79%
AALL0434[1]	C-Mtx	HD-Mtx*
Nelarabine (4-year DFS)	92%	86%
No nelarabine (4-year DFS)	90%	78%

*The HD-Mtx arms include CNS3 patients, at higher risk for CNS relapse, while CNS3 patients were excluded from the C-Mtx arms.

was necessary to prevent excess CNS relapse and preserve event-free survival. Patients randomized to no WB XRT were called back for WB XRT. However, later marrow relapses on the WB XRT arm eventually reversed the recommendation and that newer recommendation stands today.[7] Two trials of intrathecal triple therapy showed a statistically significant decrease in earlier CNS relapse with no benefit on long-term EFS[8,9] because of increased later marrow relapses. Similarly, whether the early findings from AALL0434 showing a DFS advantage for nelarabine will be sustained with further follow-up remains an open question.

In addition, do these findings apply to all treatment platforms? On AALL0434, a greater effect of nelarabine was seen on the inferior HD-Mtx arm (see Table 1). Among patients on the inferior HD-Mtx arm, the DFS was 86% and 78% in favor of nelarabine, and on the superior C-Mtx arm, which included no CNS3 patients, the DFS was 92% and 90%—a 2-percentage point difference (see Table 1).[1] While data were consistent with no interaction between the methotrexate therapy and nelarabine in a formal test ($p = 0.41$), such an interaction is not excluded and the magnitude of the nelarabine benefit on DFS for patients receiving C-Mtx is unclear and remains of interest. C-Mtx will be part of future therapy.

Of note, the treatment backbone for T-ALL has changed substantially since AALL0434. On AALL0434, patients received prednisone in induction and either 5 g/m^2 methotrexate with late WB XRT (HD-Mtx) or Capizzi methotrexate with early WB XRT (C-Mtx). HD-Mtx appeared inferior to C-Mtx.[2] Based on Medical Research Council (UK) and Berlin Frankfurt Münster Group data, the current COG trial for T-ALL (on AALL1231, NCT02112916) has a dexamethasone-based induction for all patients.[10] Dexamethasone enhances CNS control. Furthermore, all patients receive a second dose of pegaspargase in induction and only CNS3 patients receive WB XRT.

Data from the AALL0232 (NCT00075725) in B-ALL demonstrate the effect of differences in the induction backbone on the benefit of an intervention during a subsequent phase of chemotherapy. In AALL0232, the benefit of 5 g/m^2 methotrexate in interim maintenance was diminished in the subset of younger patients who received prednisone in induction (see Table 1).[3] The totally unexpected interaction reached statistical significance among patients younger than 10 years. Had AALL0232 been limited to prednisone in induction, no benefit for 5 g/m^2 methotrexate may have appeared. Induction dexamethasone is now employed for younger patients on the succeeding AALL1131 (NCT02883049) B-ALL and subsequent trials. Might outcomes with 5 g/m^2 methotrexate on AALL0434 been better with dexamethasone in induction as in AALL0232 but nelarabine less helpful with better CNS control from dexamethasone? On AALL0434, most patients received WB XRT. Currently, only CNS3 patients receive WB XRT. Might the benefit of nelarabine be increased in the absence of WB XRT?

The importance of re-examining the benefit of an agent when the underlying chemotherapy backbone changes is highlighted by previous cooperative group studies investigating the benefit of double delayed intensification. CCG-1891 found an EFS advantage with double versus single delayed intensification (DI) for standard risk patients.[11] CCG-1891 patients received prednisone in induction. When the induction steroid was switched from prednisone to dexamethasone, the question was re-examined. With dexamethasone in induction, neither CCG-1991 nor UKALL 2003 found an advantage for double DI.[12,13] Current and future patients are spared an unhelpful second 2-month DI phase. Might the impact of 5 g/m^2 methotrexate been different had patients received induction dexamethasone and no WB XRT? Might the impact of nelarabine been different if patients received induction dexamethasone, Capizzi methotrexate, and no WB XRT?

These challenges are acknowledged.[5] However, six 5-day courses of nelarabine constitute a substantial burden and expense. If nelarabine offers a 6-percentage point advantage in long-term DFS, treating 100 patients will prevent six relapses (one relapse prevented for about 17 patients treated), that is, 510 nelarabine days per relapse prevented. If nelarabine offers a 2-percentage point advantage, treating 100 patients will prevent two relapses (one relapse prevented for 50 patients treated), that is, 1500 nelarabine days per relapse prevented. Thus, determining the DFS benefit of nelarabine in the context of the current chemotherapy backbone is critical for the evaluation of the true cost–benefit ratio for nelarabine.

The 2020 nelarabine report was based on data through June 30, 2018—almost three years have now passed. An updated analysis would be welcome.

Just as double DI, the nelarabine question may require a second randomized test with a contemporary induction regimen with dexamethasone, Capizzi methotrexate, and no WB XRT for CNS1 or CNS2 patients. Nelarabine may be less helpful with dexamethasone or Capizzi methotrexate but more helpful with restriction of WB XRT. In majority part of the world, 5 g/m^2 Mtx remains standard. Perhaps an opportunity exists to re-examine Capizzi Mtx? With induction dexamethasone, 5 g/m^2 Mtx might be more helpful.

AALL0434 is the largest randomized trial in pediatric T-ALL and provides critical data regarding administration of methotrexate and a new agent, nelarabine in upfront therapy. Best outcomes were obtained with Capizzi methotrexate/early WB XRT and nelarabine. However, treatment has changed. Claims of a new standard of care may be premature. Evaluation of treatment elements out of context may

miss useful interventions or burden future patients with unneeded or redundant interventions that impede future introduction of more helpful elements.

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REFERENCES

1. Dunsmore KP, Winter SS, Devidas M, et al. Children's Oncology Group AALL0434: a phase III randomized clinical trial testing nelarabine in newly diagnosed T-cell acute lymphoblastic leukemia. *J Clin Oncol*. 2020;38:3282-3293.
2. Winter SS, Dunsmore KP, Devidas M, et al. Improved survival for children and young adults with T-lineage acute lymphoblastic leukemia: results from the Children's Oncology Group AALL0434 methotrexate randomization. *J. Clin. Oncol*. 2018;36:2926-2934.
3. Larsen EC, Devidas M, Chen S, et al. Dexamethasone and high-dose methotrexate improve outcome for children and young adults with high-risk B-acute lymphoblastic leukemia: a report from Children's Oncology Group study AALL0232. *J Clin. Oncol*. 2016;34:2380-2388.
4. Hayashi RJ, Winter SS, Dunsmore KP, et al. Successful outcomes of newly diagnosed T lymphoblastic lymphoma: results from Children's Oncology Group AALL0434. *J Clin. Oncol*. 2020;38:3062-3070.
5. Teachey DT, O'Connor D. How I treat newly diagnosed T-cell acute lymphoblastic leukemia and T-cell lymphoblastic lymphoma in children. *Blood*. 2020;135:159-166.
6. Masurekar AN, Parker CA, Shanyinde M, et al. Outcome of central nervous system relapses in childhood acute lymphoblastic leukaemia—Prospective open cohort analyses of the ALLR3 trial. *PLoS ONE*. 2014;9:e108107.
7. Nachman J, Sather HN, Cherlow JM, et al. Response of children with high-risk acute lymphoblastic leukemia treated with and without cranial irradiation: a report from the Children's Cancer Group. *J Clin Oncol*. 1998;16:920-930.
8. Matloub Y, Lindemulder S, Gaynon PS, et al. Intrathecal triple therapy decreases central nervous system relapse but fails to improve event-free survival when compared with intrathecal methotrexate: results of the Children's Cancer Group (CCG) 1952 study for standard-risk acute lymphoblastic leukemia, reported by the Children's Oncology Group. *Blood*. 2006;108:1165-1173.
9. Salzer WL, Burke MJ, Devidas M, et al. Triple intrathecal therapy (methotrexate/hydrocortisone/cytarabine) does not improve disease-free survival versus intrathecal methotrexate alone in children with high risk B-lymphoblastic leukemia: results of Children's Oncology Group Study AALL1131. *Blood*. 2018;132:35-35.
10. Raetz EA, Teachey DT. T-cell acute lymphoblastic leukemia. *Hematol Am Soc Hematol Educ Program*. 2016;2016:580-588.
11. Lange BJ, Bostrom BC, Cherlow JM, et al. Double-delayed intensification improves event-free survival for children with intermediate-risk acute lymphoblastic leukemia: a report from the Children's Cancer Group. *Blood*. 2002;99:825-833.
12. Matloub Y, Bostrom BC, Hunger SP, et al. Escalating intravenous methotrexate improves event-free survival in children with standard-risk acute lymphoblastic leukemia: a report from the Children's Oncology Group. *Blood*. 2011;118:243-251.
13. Vora A, Goulden N, Wade R, et al. Treatment reduction for children and young adults with low-risk acute lymphoblastic leukaemia defined by minimal residual disease (UKALL 2003): a randomised controlled trial. *Lancet Oncol*. 2013;14:199-209.

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