How I Treat Newly Diagnosed T-cell Acute Lymphoblastic Leukemia (T-ALL) and T-cell Lymphoblastic Lymphoma in Children

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COI: Dr. Teachey serves on advisory boards for Amgen, Jannsen, La Roche, and Humanigen. His institution receives grant funding from Novartis. Dr. O’Connor declares no competing financial interests.

Contribution: D.T. and D.O.C contributed equally to conceiving, writing, and reviewing the manuscript.

Abstract Word Count: 145
Text Word Count: 4432
Number of Figures: 1
Number of Tables: 1
Abstract

T-cell acute lymphoblastic leukemia (T-ALL) is an aggressive malignancy that has historically been associated with a very poor prognosis. Nevertheless, despite a lack of incorporation of novel agents, the development of intensified T-ALL focused protocols has resulted in significant improvements in outcome in children. Through the use of several representative cases, we highlight the key changes that have driven these advances including asparaginase intensification, the use of induction dexamethasone, and the safe omission of cranial radiotherapy (CRT). We discuss the results of recent trials to explore key topics including the implementation of risk stratification with minimal residual disease (MRD) measurement and how to treat high-risk subtypes such as early T cell precursor (ETP) ALL. In particular, we address current discrepancies in treatment between different cooperative groups, including the use of nelarabine, and provide rationales for current treatment protocols for both T-ALL and T-lymphoblastic Lymphoma (T-LL).
Introduction

Acute Lymphoblastic Leukemia (ALL) is the most common malignancy in children. It can be divided based on immunophenotype into two major subtypes, B-cell ALL (B-ALL) and T-cell (T-ALL), with T-ALL accounting for approximately 15% of cases. Historically, outcomes for children with T-ALL were markedly inferior to B-ALL; however, with modern intensive T-ALL focused-chemotherapy backbones the prognosis for pediatric T-ALL is nearly equivalent to B-ALL with the majority of children cured.1,1 The improved outcome results from randomized phase 3 trials performed by multiple international cooperative groups, which use similar backbone schemas and result in comparable outcomes. Protocol differences can make direct comparisons difficult and a number of key questions frequently arise regarding the “standard of care” treatment of pediatric T-ALL, which we address from our North American and European perspectives. Questions include which corticosteroid should be used during induction, which patients should receive CRT, how should patients be risk-stratified, which patients should receive nelarabine, and who should be considered for hematopoietic stem cell transplant (HSCT) in first complete remission (CR). Moreover, many groups treat children with T-cell lymphoblastic lymphoma (T-LL) the same as T-ALL with minor modifications, raising the questions whether this is the best approach and whether any of these modifications are data-driven.

Case 1: A child with T-ALL who has poor initial response to therapy, develops Candida sepsis, but ultimately does well with conventional therapy

A 12-year-old previously healthy boy presented with pallor, fatigue, and bony pain. His CBC demonstrated anemia (HgB 7gm/dl) with normal white cell and platelet count. Imaging demonstrated a small mediastinal mass with no vessel impingement or tracheal deviation. Bone marrow aspirate revealed >60% T-cell lymphoblasts with the early T-cell precursor (ETP) phenotype (cytoplasmic CD3+, CD1a-, CD4-, CD5 dim, CD8-, MPO-, CD19-, CD117+, CD34+, TdT+). CSF was negative for leukemia (CNS1, 0 WBC, no blasts on
cytospin). Cytogenetic and molecular profiling were unremarkable aside from IL7R and EZH2 mutations. He was started on therapy as per the control arm of the Children’s Oncology Group (COG) study AALL1231 (NCT02112916), which included a four-drug induction (dexamethasone, pegylated aspargase (PEG-ASP), vincristine, and daunorubicin) along with intrathecal chemotherapy. At end-Induction (Day 29), a bone marrow aspirate demonstrated 4.2% residual blasts by flow cytometric minimal residual disease (MRD). He continued on AALL1231-like therapy with an augmented BFM-like (aBFM) consolidation. During consolidation he developed Candida tropicalis sepsis that was successfully treated with caspofungin. An end of consolidation bone marrow revealed 0% blasts by MRD. He continued on AALL1231-like therapy and remains in remission 1 year after completing treatment.

**Early Treatment Intensification**

A number of clinical trials have established that early intensification of therapy improves T-ALL outcomes.\(^1\) Historically, the Berlin-Frankfurt-Münster (BFM) 86 and Dana Farber Cancer Institute Consortium (DFCI) 85-01 protocols demonstrated superior outcomes in T-ALL patients treated with more intensive consolidation regimens that included cyclophosphamide and asparaginase.\(^2,3\) The subsequent randomized trials, CCG-1882 and CCG-1961, confirmed the benefit of an aBFM-like consolidation, including additional asparaginase, with a single delayed intensification block in all T-ALL patients irrespective of the early morphological response to chemotherapy.\(^4,5\)

While some groups, including COG and the UK successfully employ a three-drug induction for low risk B-ALL patients, all groups use a four-drug anthracycline containing induction for T-ALL. The rationale for an intensive induction in low risk T-ALL patients was demonstrated in the UKALL 2003 trial, which initially allocated NCI standard risk (SR) T-ALL subjects with rapid early response (RER) to a three-dug induction and low intensity consolidation.\(^12\) Surprisingly these patients had a worse outcome than NCI high risk (HR)
patients with a RER who received a four-drug Induction and a more intensive BFM style Consolidation (5-year EFS 80.1 vs. 86.7%) and we therefore now treat all T-ALL patients on the more intensive arm.

As part of intensifying therapy, multiple groups have compared different corticosteroid regimens. Dexamethasone has been shown to have more infectious morbidity and mortality compared to prednisone, but this is counterbalanced by relapse reduction through increased potency and CNS penetration. UKALL2003 was a phase 3 trial performed by the United Kingdom Medical Research Council (UK MRC) that tested whether therapy could be stratified using MRD. T-ALL patients treated UKALL2003 had significantly improved survival compared to the prior trial UKALL97/99 (86 vs 77% 3-year event-free survival (EFS); 90% vs 78% 3-year overall survival (OS)). The major modifications between the trials were the use of dexamethasone as the only corticosteroid for all patients and the transition from native E.coli asparaginase to PEG-ASP. Induction using dexamethasone at 6mg/m²/day for 28 days resulted in relatively low rates of life-threatening infections and avascular necrosis. Nevertheless, invasive fungal infections (IFIs) were seen with an incidence of 2-6% depending on treatment arm.

The AIEOP-BFM (Associazione Italiana di Ematologia Pediatrica and BFM Cooperative Groups) 2000 trial randomized patients to receive dexamethasone at 10mg/m2/day vs prednisone at 60mg/m2/day for 21 days after a prednisone prephase. Increased toxicity and treatment-related mortality (2.5% vs 0.9%) were seen on the dexamethasone arm, but these were counterbalanced by a reduction in relapse rates (5-year cumulative risk of relapse: 10.8% vs 15.6%). The incidence of IFIs was higher on the dexamethasone arm (1.6% vs. 0.5%). T-ALL patients on the dexamethasone arm with a prednisone good response (PGR) had a 1/3 reduction in relapse rates from 17% to 7% and significant improvements in EFS and OS (5-year OS 91.4% vs 82.6%). B-ALL patients and T-ALL patients with a prednisone poor response (PPR) did not have a survival benefit with dexamethasone.
The benefit of dexamethasone has been confirmed in blocks after induction. The DFCI ALL Protocol 00-01 randomized B- and T-ALL patients to 120 mg/m2/day of prednisone vs. 18 mg/m2/day of dexamethasone, during a 30-week intensification phase and 40 mg/m2/day of prednisone vs. 6 mg/m2/day of dexamethasone during a 72-week continuation phase.\textsuperscript{11} While the number of T-ALL patients was small (n=39), the advantage for dexamethasone was striking (5-year EFS of 96\% vs. 65\%).

The best published outcomes for children with T-ALL are from the nelarabine and Capizzi methotrexate arms of the Children’s Oncology Group (COG) AALL0434 clinical trial (discussed below), which used prednisone throughout therapy.\textsuperscript{12,13} Far more patients received CRT on AALL0434 as compared with the aforementioned trials that demonstrated the superiority of dexamethasone. Thus, in theory, the benefit of dexamethasone over prednisone might be mitigated on a backbone containing nelarabine, additional asparaginase, and CRT. Nevertheless, the majority of cooperative groups now use dexamethasone-based backbones for children with T-ALL. In the COG, based on results from the European trials and in order to eliminate CRT for most patients, we adopted a dexamethasone-based induction on AALL1231, the recently closed successor trial to AALL0434.

The child described in Case 1 had a fairly classic presentation for T-ALL. As most T-ALL relapses occur early and while on therapy, he is likely ultimately cured despite suffering a potentially life-threatening infection.\textsuperscript{1} This highlights the importance of intensive chemotherapy for relapse-prevention while reminding of the need for vigilant monitoring for and aggressive management of infectious and other toxicities. As invasive fungal infections are more frequent in dexamethasone-containing regimens, it raises the question regarding the utility of anti-microbial prophylaxis. Drug-drug interactions make it difficult to
combine safely azole antifungals with chemotherapy; clinical trials are needed before routine antifungal prophylaxis can be recommended.

We recommend T-ALL patients receive early intensified therapy, with a 4-drug induction containing dexamethasone and an anthracycline followed by augmented BFM-like consolidation containing cyclophosphamide.

**MRD-based risk stratification**

B-ALL patients are often allocated into risk groups based on a combination of disease biology, including sentinel genetic abnormalities such as BCR-ABL1 or KMT2A-R, clinical variables, including white cell count and age, and response to therapy, including assessment of bone marrow MRD.\(^1\) In contrast, in T-ALL no clinical variables or genetic alterations have been identified that are reproducibly prognostic across trials independent of MRD.\(^1,6,15-17\) Thus, risk stratification is currently limited to MRD and morphologic bone marrow response in most cooperative groups.

The kinetics of MRD response are different in T-ALL as compared with B-ALL. Most B-ALL patients have low to undetectable MRD by end of induction.\(^1\) High-level MRD at end-Induction correlates with inferior outcome in B-ALL.\(^1\) In contrast, a large percentage of patients with T-ALL have detectable MRD at end-Induction, and their outcomes remain favorable if they have low level or undetectable MRD at the end of consolidation (~3 months of therapy).\(^1\) This was best demonstrated by the AIEOP-BFM 2000 trial, in which T-ALL patients with MRD <10\(^{-4}\) at Day 78 had similar outcome regardless of MRD status at Day 33.\(^1\) In contrast, patients who were MRD positive at Day 78 had inferior outcome that was related to MRD level. The 7-year cumulative incidence of relapse was 26%, 33%, and 45% for MRD of <10\(^{-3}\), 10\(^{-3}\), or >10\(^{-3}\), respectively.\(^1\) Similar data have subsequently been reported by other groups.\(^18,19\) While the later MRD
timepoint most effectively identifies high risk patients, the earlier end-Induction timepoint can be used to identify lower risk patients who can safely receive less intensive therapy. In the UKALL2003 trial, T-ALL patients with end-Induction MRD <10^{-4} received standard BFM consolidation with a standard interim maintenance phase instead of Capizzi and had a 5yr EFS of 93.1% (87.2-99.0).\textsuperscript{7}

**Who to Transplant in First Remission**

Most T-ALL and T-LL patients can be cured with chemotherapy alone, and HSCT should be reserved for those with poor prognosis. It is beyond the scope of this review to review all available data on T-ALL transplant outcomes but based on the poor outcome for children with high MRD at the end of Consolidation, we recommend HSCT with the best available donor be strongly considered. Earlier data suggested that T-ALL patients who failed induction (M2 or M3 marrows) may benefit from HSCT in CR1 although studies did not include assessment of MRD at additional time-points.\textsuperscript{20} Given the very poor outcomes for refractory T-ALL recently reported on the UKALL2003 trial, in the UK we recommend HSCT for all patients with end-Induction MRD \geq 5\% unless they achieve an MRD negative (<10^{-4}) remission with nelarabine-based consolidation therapy.\textsuperscript{21} In North America, based on the data demonstrating end-Consolidation MRD is superior at identifying poor outcome as compared with end-Induction response, for patients who fail induction (M2/M3 marrow) and are MRD <0.1\% at end-Consolidation, we do not recommend HSCT in first remission.\textsuperscript{10} It is important to have a thoughtful conversation with patients and families about the relative paucity of data and support the decision to transplant if requested. For patients with both T-ALL and T-LL, HSCT should only be pursued for patients in a durable remission with low level disease (negative PET and MRD <0.1\% and not rising).
Based on the poor outcome for children with high MRD (US >0.1%, UK >0.05%) at the end of consolidation, we recommend HSCT with the best available donor be strongly considered. In addition, in the UK, we recommend HSCT for all patients with end-Induction MRD ≥5% and end of consolidation MRD > 10⁻⁴).

Early T-Cell Precursor (ETP) ALL

Data on the importance of end of consolidation MRD in ETP ALL are more striking. ETP ALL is a type of T-ALL that expresses a unique immunotype compromised of early progenitor cell and myeloid markers.²² It arises from an early T cell lineage clone, represents 10-15% of T-ALL cases, and has genetic alterations distinct from non-ETP T-ALL and more similar to myeloid leukemias or T-myeloid mixed-phenotype acute leukemia (MPAL).²²-²⁴ Early studies suggested ETP ALL portends a dismal prognosis; however, with modern approaches the prognosis for ETP ALL is similar to non-ETP T-ALL.²⁵,²⁶ ETP ALL is often corticosteroid resistant,²⁷ and a high percentage of ETP ALL patients have detectable MRD at Day 29 including many induction failures.²⁸ On the AALL0434 clinical trial, 7.8% of ETP ALL had M3 marrows (>25% blasts by morphology) as compared with 1.1% of non-ETP ALL.²⁸ In addition, only 18.6% of ETP ALL had MRD <0.01% at Day 29, while 69.5% of non-ETP T-ALL had MRD <0.01%. Despite the difference in end-Induction response, the 4-year OS was similar (91.0 +/- 4.8% for ETP and 91.5 +/- 2.0% for non-ETP). Case 1 highlights an example of a patient with ETP ALL who had a poor response to induction therapy with high level MRD, yet was MRD-negative at end-Consolidation and had a favorable outcome, emphasizing the need to continue with conventional therapy in T-ALL patients who have poor end-Induction response. We recommend patients with ETP ALL are treated the same as non-ETP T-ALL, and until more data are available, sentinel genetic alterations are not used to risk stratify de novo T-ALL patients outside of a clinical trial.
Case 2: A 4-year-old with T-ALL and CNS2 who received CRT and has long term neurocognitive deficits

A 4-year-old previously healthy girl presented to an emergency room with increased bruising over the past few weeks and epistaxis. Initial CBC demonstrated an elevated WBC at 150,000/mm3 with anemia (Hgb 8gm/dl) and thrombocytopenia (plt count 12K). Lumbar puncture demonstrated CNS2a (3 WBC, 0 RBC and lymphoblasts on cytopsin). Bone marrow aspirate showed T-ALL with normal cytogenetics. She was started on therapy as per the control arm on AALL0434 which included 12Gy of prophylactic CRT. She had a remarkable response to therapy with no evidence of disease at end-Induction (MRD undetectable) and no significant toxicities during therapy. Two years after completing therapy she was noted to have difficulties in school; a formal neurocognitive evaluation demonstrated intellectual impairment with poor attention and executive function.

**Cranial Radiotherapy (CRT)**

The percentage of ALL patients who receive CRT has decreased significantly over the past 30 years. Although effective at reducing CNS relapse, the benefit is offset by significant long-term morbidity, including endocrinopathies, secondary cancers, and neurocognitive defects, especially in younger children.20,35 The European Organization for the Research and Treatment of Cancer (EORTC) was the first cooperative group to eliminate prophylactic CRT successfully in randomized trials (EORTC 58831 and 58832) in a subset of ALL patients by intensification of chemotherapy.30 In subsequent trials (EORTC 58881 and 58951), they eliminated CRT in all B-ALL and T-ALL patients with further intensification of chemotherapy.30,31 SJCRH has also successfully eliminated CRT while maintaining excellent outcomes through intensification of therapy starting with their Total Therapy XV trial.32 Based on these studies, the Dutch Childhood Oncology Group (DCOG), Israeli National Studies (INS) Group, and the UK Group successfully eliminated CRT while preserving outcomes in most patients with T-ALL.9,33,34 COG limited CRT to patients with CNS3 in the recent AALL1231 trial. Common themes in the trials included intensification
of asparaginase, use of dexamethasone, additional intrathecal chemotherapy, and systemic high-dose methotrexate (HDMTX). Recently a comprehensive meta-analysis from 10 international pediatric cooperative groups that pooled data on 16,623 patients with childhood ALL found only patients with CNS3 had a reduction in CNS relapse from the inclusion of CRT with modern therapy, although even this subgroup did not have an improved OS.35

Case 2 highlights the consequences of CRT in a young child. Chemotherapy can impact long term neurocognitive outcomes, but the use of CRT significantly increases the likelihood of impairment, which can be severe and worsen with time.29 We recommend only patients with frank CNS leukemia at diagnosis (CNS3) be considered for CRT as part of planned therapy. We do not recommend CNS1 or CNS2 patients receive routine prophylactic CRT as long as they are treated with systemic chemotherapy that reduces CNS relapse including intrathecal chemotherapy.

CNS-directed systemic chemotherapy: Methotrexate, Nelarabine, and Asparaginase

While CRT can be safely omitted in the majority of patients, CNS relapses occur more frequently in T-ALL than B-ALL suggesting that CNS-directed chemotherapy could be further improved. AALL0434 was a phase 3 international randomized trial that used a 2 x 2 pseudo-factorial randomization comparing Capizzi-style escalating methotrexate plus PEG-ASP (CMTX) vs. HDMTX, ± six 5-day courses of nelarabine.12 Post-induction, patients were classified as low, intermediate or high risk based on NCI risk group and early treatment response. All T-ALL patients were randomized to receive CMTX vs. HDMTX, and patients with intermediate or high-risk T-ALL were randomized to receive nelarabine or not.

Unexpectedly, CMTX was superior to HDMTX; the five-year disease-free survival (DFS) and OS rates were 91.5% and 93.7% for CMTX, and 85.3% and 89.4% for HDMTX, respectively.12 These results were surprising
as HDMTX was hypothesized to be superior to CMTX, and a similar trial in B-ALL (AALL0232) demonstrated superior efficacy of HD-MTX over CMTX in high-risk B-ALL.\textsuperscript{36} The AALL0434 investigators highlight in their paper that the randomization was not only a comparison of different methotrexate doses and schedules.\textsuperscript{12} 90% of patients received prophylactic CRT but the timing of radiation was different; the CMTX arm received CRT in consolidation and the HDMTX arm received it during delayed intensification, 5 months later in therapy. It is conceivable that the timing of CRT could have impacted outcome; however, in our opinion, this is unlikely given the results of previously mentioned meta-analysis that found little benefit of CRT with modern therapy.\textsuperscript{35} If prophylactic CRT does not improve outcomes with modern therapy, it seems unlikely that delivering it five months earlier would substantially improve outcomes. The CMTX interim maintenance (IM) phase included two extra doses of asparaginase, which, as discussed earlier, has been shown to be highly effective in reducing CNS relapses \textsuperscript{1} and could explain the superiority of the CMTX arm. The recently closed UKALL2011 trial randomized patients to CMTX plus PEG-ASP or HDMTX plus PEG-ASP and may provide further answers to the relative benefits of CMTX and PEG-ASP in T-ALL.

Nelarabine was also superior to no nelarabine. The 4-year DFS rates for IR or HR patients on the nelarabine vs. no nelarabine randomized arms were 88.9 ± 2.2% versus 83.3 ± 2.5%.\textsuperscript{13} The CMTX plus nelarabine arm had the best outcome with a 4-year DFS of 92.2% ± 2.8%.\textsuperscript{12,13} In contrast, the 4-year DFS on the HD-MTX/no nelarabine arm, which was the control arm and represented the standard of care throughout much of the world was 78.0% ± 3.7%.\textsuperscript{12,13} The factorial design meant the trial could determine if nelarabine was an active drug, but not whether nelarabine adds specific benefit to different backbones with different IM blocks, ie it was not designed to determine if nelarabine plus CMTX was better than CMTX alone. No significant interaction was seen between the nelarabine and MTX randomizations (p = 0.41). Both systemic and CNS relapses were reduced by CMTX and nelarabine; however, the reduction in CNS relapses (combined and isolated) was the most striking. CMTX and nelarabine both individually significantly
reduced isolated and combined CNS relapses.\textsuperscript{12,13} Indeed, there were no isolated CNS relapses on the arm that received CMTX plus nelarabine.\textsuperscript{13}

Despite the excellent results, there are several caveats. First, results for the nelarabine randomization have only been published in abstract form with outcomes reported as DFS, making direct comparison with other groups difficult. The benefit of CMTX and nelarabine was demonstrated on a prednisone-based backbone and a similar benefit may not be evident on a dexamethasone-based backbone. The aforementioned UKALL2011 trial and the COG AALL1231 trial, which did not include nelarabine, but did treat all patients with dexamethasone and CMTX, may provide additional data. Finally, the improvement seen with nelarabine is relatively small, meaning a large number of patients need to be treated to benefit a single patient. This has potential implications for toxicity and health economics. In the UK, it currently costs approximately £120,000 ($150,000) to treat one patient with 6 cycles of nelarabine; the substantial cost required to treat all patients is unlikely to be approved by the responsible funding body. For the time being, this means that there is a marked difference between the treatment of T-ALL in the US and the rest of the world. \textbf{In North America, we recommend CMTX and nelarabine for all patients with T-ALL.}

Although low-risk (LR) T-ALL patients were not included in the nelarabine randomization on AALL0434, nelarabine was well-tolerated with similar toxicity rates in both arms and a low incidence of severe neurotoxicity.\textsuperscript{37} \textbf{In the UK we recommend CMTX for patients with high end-Induction MRD and recommend reserving nelarabine for patients with poor response to initial therapy}

\textbf{Case 3: A 12-year old child with T-LL}

A 12-year-old girl presented with significant cervical lymphadenopathy and was diagnosed with T-cell lymphoblastic lymphoma on excisional lymph node biopsy. Bone marrow and CSF were not involved. CT imaging demonstrated no disease outside of her neck. She was treated with a 4-drug induction and had
no evidence of disease at end-Induction. Subsequent treatment included aBFM consolidation, CMTX and a single DI block. She did not receive nelarabine or CRT. Three months after starting maintenance chemotherapy she is noted to have pancytopenia and bone marrow demonstrated >25% lymphoblasts. Imaging revealed marked PET-avid lymphadenopathy in her neck, axilla, and abdomen. She responded to intensive reinduction chemotherapy followed by allogeneic HSCT and remains in remission.

**T-cell Lymphoblastic Lymphoma**

Approximately 25% of pediatric non-Hodgkin lymphoma is lymphoblastic, and the majority (~75%) of lymphoblastic lymphomas derive from early T cell progenitors. Historically, therapy has transitioned from lymphoma-like therapy to leukemia-like therapy, as multiple studies have demonstrated superior efficacy with ALL-type therapy.\(^{38,39}\) Many cooperative groups now treat patients with T-ALL and T-LL on the same trial using slightly modified therapy, and therapeutic differences have narrowed with time.\(^{39}\) Biologically, the genetic alterations and spectrum of immunophenotypic changes, such as the ETP phenotype, are the same in T-LL and T-ALL.\(^{6,39}\) Furthermore, the line can be blurred between the two entities as patients with T-ALL can present with lymphomatous disease while patients with T-LL often have low level (5-25%) marrow involvement\(^{40}\) although T-LL is less likely to involve the CNS at diagnosis or relapse.\(^{39}\) Patients with T-LL can relapse into the marrow and meet the definition of T-ALL (>25% marrow blasts) as seen in Case 3. Essentially, T-ALL and T-LL are the same disease with the only major difference being the proclivity of T-ALL to “invade” extra-lymphatic spaces, including the bone marrow microenvironment and CNS.

Intensive CNS-directed systemic chemotherapy is needed to cure T-LL, but the use of prophylactic CRT was abandoned before it was in T-ALL. For example, >90% of T-ALL patients but no T-LL patients received CRT on the AALL0434 clinical trial,\(^{39,41,42}\) although CNS3 T-LL patients were excluded. T-ALL and T-LL subjects were considered separately with regard to analysis of the randomized questions. T-LL subjects
did not participate in the HDMTX vs CMTX randomization: all subjects received CMTX, as prior studies had demonstrated HDMTX is not needed on a backbone with multiple intrathecals. High-risk T-LL subjects did participate in the nelarabine randomization.

The four-year DFS for T-LL patients treated with nelarabine (60 patients) vs. no nelarabine (58 patients) was $85.0 \pm 5.6\%$ versus $89.0 \pm 4.7\%$, $p=0.2788$. Importantly, the trial was not powered to investigate the impact of nelarabine in T-LL. Thus, the question of whether nelarabine should be included in the treatment for patients with T-LL remains unclear which, again, results in regional differences in treatment recommendations. As discussed earlier, nelarabine was active and well-tolerated in \textit{de novo} T-ALL on AALL0434 and relapsed T-ALL and T-LL in early phase trials. The prognosis for relapsed T-LL is dismal with salvage rates of <15%; therefore, the best available therapy should be used in newly diagnosed patients. The counter-argument to using nelarabine in T-LL is that no benefit has yet been proven and the main benefit of nelarabine in T-ALL was a reduction in CNS relapses, and T-LL has less propensity to relapse in the CNS. \textbf{Therefore in North America, it is considered reasonable to treat all patients with \textit{de novo} T-LL with nelarabine. In the UK, nelarabine is reserved for patients not responding to treatment or for relapsed disease.}

AALL1231, the successor trial to AALL0434, did have some differences in risk stratification and therapy of patients with T-ALL as compared with T-LL. There are no data on the prognostic significance of bone marrow MRD at end-Induction or end-Consolidation in T-LL. T-LL patients on AALL1231 were risk stratified by radiographic response at end-Induction and end-Consolidation, as well as bone marrow MRD at diagnosis. Earlier trials demonstrated T-LL patients with >1% bone marrow blasts at diagnosis based on MRD had worse outcome; however, it was recently shown on AALL0434 that diagnostic MRD may no longer be prognostic on more intensive backbones. Future studies are needed to determine if there
is an MRD cutoff either at diagnosis or after initiating therapy with sufficient prognostic significance to justify changing therapy. Similar to T-ALL, a number of studies have attempted to identify genetic lesions that are independently prognostic of disease response; however, none have been validated sufficiently to justify modifying therapy outside of a clinical trial. While the response data in T-LL are less robust, we recommend patients with T-LL who are not in remission by the end of consolidation be considered for HSCT once they achieve remission.

In the COG and the UK, historically males with ALL but not LL were treated with an extra year of maintenance chemotherapy as compared with girls.\textsuperscript{48} This became the practice after a meta-analysis from the early 1980s suggested a potential EFS advantage but not OS advantage for the extra year in boys.\textsuperscript{49} Males continue to have a slightly worse outcome than females on COG trials, despite the extra year of treatment.\textsuperscript{14} It has not been the practice to treat males with T-LL for an extra year of maintenance.\textsuperscript{39} Most other cooperative groups, including SJCRH, BFM, DFCI, and NOPHO (Nordic Society for Pediatric Hematology and Oncology) treat males and females with ALL with identical therapy and have similar outcomes as the COG.\textsuperscript{50-53} In the next generation of COG trials and future UK protocols, the plan is to abandon the extra year of maintenance therapy in males. Most patients with T-ALL who do relapse, relapse early, eg well before a third year of maintenance therapy.\textsuperscript{1} It is reasonable to treat both males and females with T-ALL and T-LL with identical therapy. The use of identical therapy also reduces the risk of medical error.

**Conclusion and Future Directions**

An overview of the recommend treatment approaches for *de novo* T-ALL in North America and UK are shown in Figure 1. Although minor differences in strategies remain, the vast majority of children with T-ALL and T-LL now attain long-term cure without exposure to the potential harmful late effects of CRT.
Significant challenges remain with up to 1 in 5 children still experiencing refractory disease, relapse or treatment-related mortality. Improvements have been driven by optimization of protocols but it is probable we have reached the limit of what we can achieve with conventional chemotherapy. Further advances will likely require the use of novel targeted agents and immunotherapeutic approaches. The genomic heterogeneity and the rarity of some subtypes necessitates international cooperation to ensure feasibility of trials. Furthermore, it is vital to remember that treatment is a long and arduous journey and many patients experience toxicity. There are almost certainly patients that can be cured with reduced therapy but this will require large scale comprehensive genomic profiling of T-ALL cases to identify prognostic aberrations that will improve risk stratification.
Table 1
Summary Recommendations for *de novo* T-ALL and T-LL

1. Offer an open clinical trial if available
2. Dexamethasone-based Induction
3. Early intensified Therapy including a 4-drug Induction with anthracycline and multi-agent augmented consolidation, including cyclophosphamide
4. Patients with ETP ALL should be treated the same as their non-ETP counterparts
5. Risk stratification in T-ALL primarily based on bone marrow MRD. Risk stratification in T-LL primarily based on radiographic response.
6. Only consider CRT in patients with overt CNS disease (CNS3) at diagnosis
7. If available, consider including nelarabine in the treatment for all patients with T-ALL and T-LL.
8. High Dose MTX is not needed for T-ALL, if Capizzi MTX and nelarabine are included in the backbone.
9. Overall recommendation for How I Treat T-ALL and T-LL in North America: Dexamethasone-based 4-drug induction followed by AALL0434-like Arm B therapy post-induction, including an augmented BFM consolidation, a single interim maintenance phase with Capizzi MTX, and nelarabine for all patients with T-ALL and T-LL. Only radiate patients with CNS3. T-ALL patients with MRD >0.1% at end of consolidation and T-LL patients not in remission at end of consolidation should proceed to HSCT in CR1 with the best available donor after durable disease control.
10. Overall recommendation for How I Treat T-ALL and T-LL outside of North America: Dexamethasone-based 4-drug induction followed by MRD-based risk stratification. Low risk patients treated with standard BFM consolidation and interim maintenance. High risk patients receive augmented BFM consolidation and Capizzi MTX. No CRT as standard. Induction failure patients (MRD ≥5%) who fail to clear MRD and patients with MRD >0.05% post-consolidation proceed to HSCT.
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Figure 1. Overview of current North American and United Kingdom (UK) T-ALL recommended treatment approaches

CRT Cranial Radiotherapy, BFM, Berlin-Frankfurt-Munich, aBFM, augmented BFM, HSCT Hematopoietic Stem Cell Transplant, CMTX Capizzi Methotrexate IM Interim Maintenance, MRD Minimal Residual Disease