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How I treat newly diagnosed T-cell acute lymphoblastic leukemia and T-cell lymphoblastic lymphoma in children

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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. We discuss the results of recent trials to explore key topics including the implementation of risk stratification with minimal residual disease measurement and how to treat high-risk subtypes such as early T-cell precursor 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. (*Blood*. 2020;135(3):159-166)

Introduction

Acute lymphoblastic leukemia (ALL) is the most common pediatric malignancy. It can be divided into 2 major subtypes, B-cell ALL (B-ALL) and T-cell (T-ALL), with T-ALL accounting for ~15% of cases. Historically, outcomes for children with T-ALL were inferior to B-ALL; however, with modern intensive T-ALL–focused chemotherapy backbones, the prognoses for childhood T-ALL and B-ALL are nearly equivalent.[1] The improved outcome results from randomized phase 3 trials performed by multiple international cooperative groups. These trials used similar backbones and had comparable outcomes. A number of key questions 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 cranial radiotherapy (CRT), how patients should 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 question of whether this is the best approach.

Case 1

A 12-year-old previously healthy boy presented with pallor and bony pain. Complete blood count demonstrated anemia (hemoglobin, 7 g/dL) with normal white cell and platelet count. Imaging demonstrated a small mediastinal mass. Bone marrow aspirate revealed >60% T-cell lymphoblasts with the early T-cell precursor (ETP) phenotype (cytoplasmic $CD3^+$, $CD1a^-$, $CD4^-$, CD5 dim, $CD8^-$, myeloperoxidase negative, $CD19^-$, $CD117^+$, $CD34^+$, terminal deoxynucleotidyl transferase positive). Cerebrospinal fluid was negative for leukemia (0 white blood cell [WBC], no blasts on cytospin). Cytogenetic and molecular profiling using a next-generation sequencing panel were unremarkable. He was started on therapy as per the control arm of the Children's Oncology Group (COG) AALL1231 study (NCT02112916), which included a 4-drug induction (dexamethasone, pegylated asparagase [PEG-ASP], vincristine, and daunorubicin) along with intrathecal chemotherapy. An end-induction (day 29) bone marrow aspirate demonstrated 4.2% residual blasts by flow cytometric minimal residual disease (MRD). He continued on AALL1231-like therapy with an augmented Berlin-Frankfurt-Münster (BFM; aBFM)-like consolidation. During consolidation, he developed *Candida tropicalis* sepsis that was successfully treated with caspofungin. 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 established that early intensification of therapy improves T-ALL outcomes.[1] Historically, the BFM 86 and Dana-Farber Cancer Institute Consortium (DFCI) 85-01 protocols demonstrated superior outcomes in T-ALL patients treated with intensive consolidation regimens that included cyclophosphamide and asparaginase.[2,3] Subsequent randomized trials (CCG-1882 and CCG-1961) confirmed the benefit of an aBFM-like consolidation.[4,5]

Although some groups, including COG and the United Kingdom, successfully use a 3-drug induction for low-risk (LR) B-ALL patients, all groups use a 4-drug anthracycline-containing induction

for T-ALL. The rationale for intensive induction in LR T-ALL patients was demonstrated in the UKALL 2003 trial, which initially allocated National Cancer Institute (NCI) standard-risk (SR) T-ALL subjects with rapid early response (RER) to a 3-drug induction and low-intensity consolidation.[6] These patients had a worse outcome than NCI high-risk (HR) patients with an RER who received a 4-drug induction and a more intensive BFM-style consolidation (5-year event-free survival [EFS], 80.1% vs 86.7%). The Medical Research Council (MRC) therefore now treats all T-ALL patients on the more intensive arm. Other studies that treated some children with T-ALL with a 3-drug induction, including CCG-1952 and CCG-1991, had worse outcomes than more recent studies treating similar patients with 4-drug inductions.[7,8] The type, dose, and schedule of anthracyclines used during induction differs between some cooperative groups, but these have not been compared directly and outcomes are similar on the different anthracycline-containing backbones.

As part of intensifying therapy, multiple groups have compared different corticosteroid regimens.[9] Dexamethasone has more infectious morbidity and mortality compared with prednisone, but this is counterbalanced by relapse reduction through increased potency and central nervous system (CNS) penetration.[9] UKALL2003 was a phase 3 trial performed by the UK MRC.[10,11] T-ALL patients treated on UKALL2003 had significantly improved survival compared with the prior trial UKALL97/99 (90% vs 78% 3-year overall survival [OS]).[10,12] The major modifications between the trials were the use of dexamethasone as the only corticosteroid for all patients and the transition from native *Escherichia coli* asparaginase to PEG-ASP. Induction using dexamethasone at 6 mg/m^2 per day for 28 days resulted in relatively low rates of life-threatening infections and avascular necrosis. The incidence of invasive fungal infections (IFIs) was 2% to 6% depending on treatment arm.[10] In the subsequent trial, UKALL 2011, the MRC tested whether a 2-week induction schedule (10 mg/m^2 per day $\times$ 14 days) would be less toxic than the UKALL 2003 dexamethasone dose and schedule, but this trial was stopped early due to futility concerns raised by the data monitoring committee (IDMC), as there were no statistically significant differences in relapse-free survival or steroid-related toxicity between the arms with early follow-up.[13]

The Associazione Italiana di Ematologia e Oncologia Pediatrica (AIEOP)-BFM Cooperative Groups 2000 trial randomized patients to receive dexamethasone at 10 mg/m^2 per day vs prednisone at 60 mg/m^2 per day for 21 days.[14] 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 had a one-third 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 and T-ALL patients with a prednisone poor response did not have a survival benefit with dexamethasone.

The benefit of dexamethasone has been investigated in blocks after induction. DFCI ALL protocol 00-01 randomized B- and T-ALL patients to 120 mg/m^2 per day of prednisone vs 18 mg/m^2 per day of dexamethasone during a 30-week intensification phase, and 40 mg/m^2 per day of prednisone vs 6 mg/m^2 per day of dexamethasone during a 72-week continuation phase.[15] Although the number of T-ALL patients was small (n = 39), the advantage for dexamethasone was striking (5-year EFS, 96% vs 65%). Based on the small sample size, the 95% confidence interval (CI) overlapped (87% to 100% vs 42% to 87%), thus these results should be interpreted with caution.[6]

The best published pediatric T-ALL outcomes are from the nelarabine and Capizzi methotrexate arms of the COG AALL0434 clinical trial, which used prednisone throughout therapy.[8,16] Far more patients received CRT on AALL0434 as compared with the aforementioned trials that demonstrated the superiority of dexamethasone. Thus, 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 childhood T-ALL. In the COG, based on results from the European trials and 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 T-ALL presentation. As most T-ALL relapses occur early and while on therapy, he is likely ultimately cured despite suffering a potentially life-threatening infection.[1] This highlights the importance of intensive chemotherapy for relapse prevention while providing a reminder of the need for vigilant monitoring for, and aggressive management of, infectious and other toxicities. As IFIs are more frequent in dexamethasone-containing regimens, it raises questions regarding the utility of antimicrobial 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. Both the COG and UK groups have adopted a dexamethasone schedule of 6 mg/m^2 per day for 28 days and this is the schedule we currently favor. Nevertheless, other doses and schedules are reasonable. Future studies need to explore whether there are certain patient populations, such as adolescents and adults, in whom the benefit of dexamethasone is mitigated by excess toxicity, warranting consideration for alterative doses, schedules, or type of steroids.

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

MRD-based risk stratification

B-ALL patients are allocated into risk groups based on a combination of disease biology, clinical variables, and response to therapy, including MRD.[17] In T-ALL, no clinical variables or genetic alterations have been identified that are reproducibly prognostic across trials independent of MRD.[1,9,18-20] 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 and B-ALL. Most B-ALL patients have low to undetectable MRD by end of induction, whereas high-level MRD correlates with inferior outcome.[17] In contrast, a large percentage of T-ALL patients

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).[14] This was best demonstrated by the AIEOP-BFM 2000 trial, in which T-ALL patients with MRD $< 10^{-4}$ at day 78 had similar outcomes regardless of MRD status at day 33.[14] In contrast, patients who were MRD^{+} at day 78 had inferior outcome; 7-year cumulative risk of relapse was 26%, 33%, and 45% for MRD of $<10^{-3}$, 10^{-3}, or $>10^{-3}$, respectively.[14] Similar data have subsequently been reported by other groups.[21,22] Although the later MRD time point most effectively identifies HR patients, the earlier end-induction time point 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-escalating methotrexate (MTX; CMTX) with asparaginase and had a 5-year EFS of 93.1% (87.2% to 99.0%).[10]

Whom to transplant in first remission

Most children with T-ALL do not need HSCT for cure, and it is beyond the scope to review all available data on T-ALL transplant outcomes. Based on the poor outcome for children with high MRD at the end of consolidation, we recommend that 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 first CR (CR1), but these studies did not include MRD assessment at additional time points.[23] Given the very poor outcomes for refractory T-ALL recently reported in the UKALL2003 trial, in the United Kingdom, we recommend HSCT for all patients with end-induction MRD $\geq$ 5% except those under 16 years of age who achieve an MRD^{-} ($<10^{-4}$) remission at the end of consolidation therapy.[24] Of note, consolidation therapy now includes nelarabine for these HR patients in the United Kingdom. In North America, based on the data demonstrating that 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.[14] It is important to have a thoughtful conversation with patients and families about the relative paucity of data and support transplant if requested. For patients with T-ALL and T-LL, HSCT should only be pursued for patients in a durable remission with low-level disease (negative positron emission tomography and low MRD [United States $<$0.1%, United Kingdom $<$0.01%]).

Based on the poor outcome for children with high MRD (United States $>$0.1%; United Kingdom $>$0.05%) at the end of consolidation, we recommend that HSCT with the best available donor be strongly considered. In addition, in the United Kingdom, we recommend HSCT in patients with end-induction MRD $\geq$ 5% except those under 16 years with negative ($<10^{-4}$) end-of-consolidation MRD.

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 composed of early progenitor cell and myeloid markers.[25] It arises from an early T-cell lineage clone, represents 10% to 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).[25-27] Early studies suggested that ETP ALL portends a dismal prognosis; however, with modern approaches, the prognosis for ETP ALL is similar to non-ETP T-ALL.[28,29] ETP ALL is often corticosteroid resistant,[30] and a high percentage of ETP ALL patients have detectable MRD at day 29 including many induction failures.[31] In 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.[31] In addition, only 18.6% of ETP ALL had MRD $<$ 0.01% at day 29, whereas 69.5% of non-ETP T-ALL had MRD $<$ 0.01%. Despite the difference in early response, the 4-year OS was similar (91.0% $\pm$ 4.8% for ETP and 91.5% $\pm$ 2.0% for non-ETP). Case 1 highlights an example of a patient with ETP ALL who had a poor response to induction therapy, yet was MRD negative at end consolidation and had favorable outcome, emphasizing the need to continue with conventional therapy in T-ALL patients who have poor end-induction response. We recommend that patients with ETP ALL are treated the same as non-ETP T-ALL, following the same recommendations, and that until more data are available, sentinel genetic alterations are not used to risk-stratify de novo T-ALL patients outside of a clinical trial.

Currently, genetic alterations are not routinely used outside of clinical trials to modify treatment in de novo T-ALL, as there are no data to suggest novel targeted therapies improve outcome. The main exception is the use of tyrosine kinase inhibitors to treat *BCR-ABL1* T-ALL, which is more rare in T-ALL than B-ALL. For relapsed and refractory patients, the use of targeted agents may be of benefit for some patients. It is beyond the scope of this manuscript to discuss the different available therapies for relapsed and refractory patients, although these have been reviewed in other recent publications.[1,32,33] We recommend that all patients receive routine cytogenetic testing and fluorescence in situ hybridization for *BCR-ABL1*. We also recommend more comprehensive molecular profiling evaluating for sequencing alterations (next-generation cancer sequencing panels or whole-exome sequencing or whole-genome sequencing), for copy-number analysis (single-nucleotide polymorphisms), and transcriptome profiling (RNA sequencing) be considered if clinically available, especially in relapsed and refractory patients. As it can be very difficult to salvage patients with relapsed and refractory disease, targeted therapy can be considered in these patients, including tyrosine kinase inhibitors for patients with *NUP214-ABL1* or Jak/Stat inhibitors in patients with *JAK* mutations or fusions.

Case 2

A 4-year-old previously healthy girl presented to an emergency room with increased bruising over the past few weeks and epistaxis. Complete blood count demonstrated an elevated WBC at 150 $\times$ 10^{9}/L with anemia (hemoglobin, 8 g/dL) and thrombocytopenia (platelet count, 12 $\times$ 10^{9}/L). Lumbar puncture demonstrated CNS2a (3 WBC, 0 red blood cell, and lymphoblasts on cytospin). Bone marrow aspirate showed T-ALL with normal cytogenetics. She was started on therapy as per the control arm on AALL0434, which included 12 Gy of prophylactic CRT. She had a remarkable response to therapy 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.

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.[34,35] 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.[35] In subsequent trials (EORTC 58881 and 58951), they eliminated CRT in all B-ALL and T-ALL patients with further chemotherapy intensification.[35,36] St. Jude Children's Research Hospital has successfully eliminated CRT while maintaining excellent outcomes through intensification of therapy starting with their Total Therapy XV trial.[37] 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 T-ALL patients.[12,38,39] 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 MTX (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.[40]

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.[34] We recommend that only patients with frank CNS leukemia at diagnosis (CNS3) be considered for CRT as part of planned therapy. We do not recommend that 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

Although CRT can be safely omitted in most 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 × 2 pseudofactorial randomization comparing CMTX plus PEG-ASP vs HDMTX, ±6, 5-day courses of nelarabine.[8] Postinduction, patients were classified as LR, intermediate-risk (IR), or HR based on NCI-risk group and early treatment response. All T-ALL patients were randomized to receive a CMTX vs HDMTX interim maintenance (IM) phase, and patients with IR or HR T-ALL were randomized to receive nelarabine or not.

Unexpectedly, CMTX was superior to HDMTX; the 5-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.[8] These results were surprising as HDMTX was hypothesized to be superior, and a similar trial in B-ALL (AALL0232) demonstrated superior efficacy of HDMTX over CMTX in HR B-ALL.[41] Of note, the randomization was not just a comparison of different MTX doses and schedules.[8] Ninety percent of patients received prophylactic CRT but the timing of radiation was different. The CMTX IM included an extra dose of vincristine, 2 extra doses of asparaginase, and cranial radiation was given during consolidation. The HDMTX IM included ~2 months of mercaptopurine and the cranial radiation was given 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.[40] If prophylactic CRT does not improve outcomes, it seems unlikely that delivering it 5 months earlier would substantially improve outcomes. As mentioned earlier, asparaginase has been shown to be highly effective in reducing CNS relapses and the 2 extra doses in the CMTX arm could explain the superiority.[1] The recently closed UKALL2011 trial randomized patients to CMTX or HDMTX plus PEG-ASP and may provide further answers to the relative benefits of CMTX and PEG-ASP in T-ALL. It is also possible that if the same trial was performed on a different backbone or on a backbone that did not include prophylactic radiation for the majority of patients then a different result would have been seen. In North America, we recommend CMTX for all patients with T-ALL, and, in the United Kingdom, we recommend CMTX for patients with high end-induction MRD (MRD ≥ 0.005%).

Nelarabine was superior to no nelarabine. The 4-year DFS for IR or HR patients on the nelarabine vs no-nelarabine randomized arms was 88.9% ± 2.2% vs 83.3% ± 2.5%.[16] The CMTX-plus-nelarabine arm had the best outcome with a 4-year DFS of 92.2% ± 2.8%.[8,16] In contrast, the 4-year DFS on the HDMTX/no-nelarabine arm, which was the control arm and represented the standard of care throughout much of the world was 78.0% ± 3.7%.[8,16] The factorial design meant that the trial could determine whether nelarabine was an active drug, but not whether nelarabine adds specific benefit to different backbones with different IM blocks, that is, it was not designed to determine whether nelarabine plus CMTX was better than CMTX alone. Importantly, no significant interaction was seen between the nelarabine and MTX randomizations ($P = .41$). 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.[8,16] Indeed, there were no isolated CNS relapses on the arm that received CMTX plus nelarabine.[16]

LR T-ALL patients were not included in the nelarabine randomization on AALL0434, because of concerns of neurotoxicity in early-phase relapse trials.[36,42] Nelarabine was well-tolerated and toxicities were similar in both arms on AALL0434.[37] Moreover, the incidence of severe neurotoxicity was very low. As nelarabine is an active and safe drug, if available, it is reasonable

to treat all T-ALL patients regardless of risk stratification with nelarabine. This is the common practice in many North American centers; however, there are centers that reserve nelarabine for higher risk patients.

Despite the excellent results, there are several important caveats. 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 UKALL2011 and COG AALL1231 trials, 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. In the United Kingdom, it currently costs approximately £120 000 ($150 000) to treat 1 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 no clear consensus on which de novo patients, if any, should receive nelarabine, leading to a difference between T-ALL treatment in the United States and the rest of the world. Based on these caveats, it is also reasonable to reserve nelarabine for patients with poor initial response to therapy (MRD $\geq$ 5%) and relapsed disease. This is the common practice in many European centers.

Case 3

A 12-year-old girl presented with significant cervical lymphadenopathy and was diagnosed with T-LL on excisional lymph node biopsy. Bone marrow demonstrated no blasts by morphology or MRD. Cerebrospinal fluid was also negative for blasts. Computed tomography 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 delayed intensification 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 positron emission tomography–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.[43,44] Many cooperative groups now treat T-ALL and T-LL patients on the same trial using slightly modified therapy, and therapeutic differences have narrowed with time.[44] Biologically, the genetic alterations and spectrum of immunophenotypic changes are the same in T-LL and T-ALL.[9,44] Furthermore, the line can be blurred between the 2 entities as T-ALL patients can present with lymphomatous disease whereas T-LL patients often have low level (5% to 25%) marrow involvement.[45] T-LL is less likely to involve the CNS at diagnosis or relapse.[44] T-LL patients 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" extralymphatic spaces.

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.[44,46,47] AALL0434 excluded CNS3 T-LL patients. 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.[46,47] HR T-LL subjects did participate in the nelarabine randomization.

The 4-year DFS for T-LL patients treated with nelarabine (60 patients) vs no nelarabine (58 patients) was 85.0% $\pm$ 5.6% vs 89.0% $\pm$ 4.7% ($P = .2788$). Importantly, the trial was not powered to investigate the impact of nelarabine in T-LL.[48] Thus, the question of whether nelarabine should be included in the treatment of T-LL patients remains unclear. Nelarabine was active and well tolerated in de novo T-ALL on AALL0434[16] and relapsed T-ALL and T-LL in early-phase trials.[49,50] 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.[44] The counterargument 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; T-LL has less propensity to relapse in the CNS. As is frequently done in North America, it is reasonable to treat de novo T-LL patients with nelarabine. As is frequently done in the United Kingdom, it is also reasonable to reserve nelarabine for patients not responding to treatment or with relapsed disease.

AALL1231, the successor trial to AALL0434, did have some differences in risk stratification and therapy for T-ALL and T-LL patients. The prognostic significance of bone marrow MRD at end-induction or end-consolidation in T-LL is unknown. T-LL patients on AALL1231 were risk-stratified by radiographic response at end-induction and end-consolidation, as well as diagnostic bone marrow MRD. 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.[48,51,52] Future studies are needed to determine whether there is an MRD cutoff 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. Although the response data in T-LL are less robust, we recommend that 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, historically, male patients with ALL were treated with an extra year of maintenance chemotherapy as compared with girls.[53] 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.[54] Male patients continue to

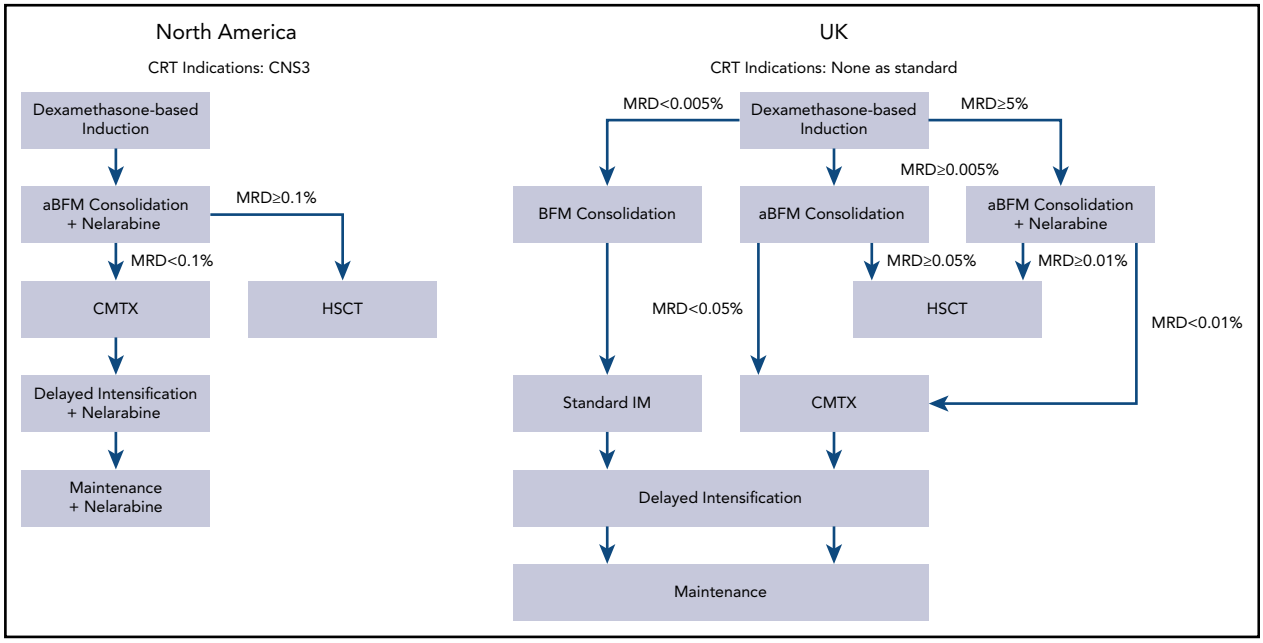

Figure 1. Overview of current North American and UK T-ALL recommended treatment approaches.

have a slightly worse outcome than female patients on COG trials, despite the extra year of treatment.[17] In the COG, it has not been the practice to treat male patients with T-LL for an extra year of maintenance.[44] Most other cooperative groups, including St. Jude Children's Research Hospital, BFM, DFCI, and Nordic Society for Pediatric Hematology and Oncology (NOPHO), treat male and female patients with ALL with identical therapy and have similar outcomes as the COG.[55-58] In future COG and UK trials, the plan is to abandon the extra year of maintenance therapy in male patients. Most patients with T-ALL who do relapse, relapse early, for example, well before a third year of maintenance therapy.[1] It is reasonable to treat both male and female patients with T-ALL and T-LL with identical therapy. The use of identical therapy also reduces the risk of medical error.

Table 1. Summary recommendations for de novo T-ALL and T-LL

Recommendations
1. Offer an open clinical trial if available
2. Dexamethasone-based induction
3. Early intensified therapy including a 4-drug induction with anthracycline and multiagent 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 of all patients with T-ALL and T-LL
8. HDMTX is not needed for T-ALL, if CMTX and nelarabine are included in the backbone
9. Consider HSCT for patients with persistent disease after 3 mo of intensive therapy

Conclusion and future directions

An overview of the recommended treatment approaches for de novo T-ALL in North America and the United Kingdom is shown in Figure 1. A summary of our recommendations is included in Table 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 as up to 1 in 5 children still experience refractory disease, relapse, or treatment-related mortality. Improvements have been driven by optimization of protocols but it is probable that we have reached the limit of what we can achieve with conventional chemotherapy. Further advances will likely require the use of targeted agents and immunotherapy. It is vital to remember that treatment is a long and arduous journey and many patients experience toxicity. There are almost certainly patients who 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.

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Authorship

Contribution: D.T.T. and D.O. conceived, wrote, and reviewed the manuscript.

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Footnote

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