Optimal approach to T-cell ALL

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T-lineage acute lymphoblastic leukemia (T-ALL) is curable for most children and adolescent and young adult patients with contemporary frontline chemotherapy regimens. During the past decade, improved survival rates have resulted from the optimization of frontline chemotherapy regimens, the use of minimal residual disease (MRD) assessment for evaluating a patient's risk for relapse, and the intensification of treatment based on the persistence of MRD. Optimization of initial therapy is critical because relapsed T-ALL after initial intensive chemotherapy is incurable for most adult patients. Current T-ALL salvage chemotherapy regimens are minimally effective, and unlike in B-cell ALL, there are no approved antibody therapies or chimeric antigen receptor T-cell therapies for relapsed disease. Immunotherapy and small-molecule inhibitors are beginning to be tested in relapsed T-ALL and have the potential to advance the treatment. Until effective salvage strategies are discovered, however, intensive frontline therapy is required for cure. In this article I review the current frontline chemotherapy regimens for adult patients with T-ALL, summarize the novel targeted and immune therapeutics currently in early-phase clinical trials, and outline how these therapies are helping to define an optimal approach for T-ALL.

LEARNING OBJECTIVES

- Understand that intensive frontline therapy is the current strategy for cure
- Understand the outcomes associated with the use of nelarabine in frontline regimens
- Understand the key prognostic factors for T-ALL and the indications for allogeneic hematopoietic stem cell transplantation

CLINICAL CASE

A 32-year-old elementary school librarian who was 3 months post partum presented to her primary physician's office with a 1-week history of bilateral cervical lymphadenopathy that developed following her first COVID-19 vaccine. The lymphadenopathy was attributed to the vaccine, but following her second COVID-19 vaccine, she developed progressive tender cervical lymphadenopathy, joint pain, and swelling. An x-ray of the right elbow revealed an effusion, and the patient was referred to orthopedic surgery and underwent a joint aspiration of the right elbow. The fluid was not sent for cytology analysis, however. A computed tomographic scan of the neck revealed bilateral cervical and supraclavicular lymphadenopathy (1.7×1.7 cm). A CT scan of the chest, abdomen, and pelvis revealed no enlarged lymph nodes and a normal-sized spleen. The complete blood count revealed a white blood cell count of 8.4×10^9/L; hemoglobin level, 11.3 g/dL; hematocrit, 33%; platelet count, 140×10^9/L; and absolute neutrophil count, 1.9×10^9/L. There were 61% blasts in the white cell differential count. The patient was referred to an academic medical center.A cell suspension from a marrow aspirate was examined by flow cytometry, and the blast population expressed cytoplasmic TdT, cytoplasmic CD3/CD34/CD38/CD5 (partial, dim)/CD7, human leukocyte antigen-DR, and partial CD123/CD33 (partial). The blast population was negative for surface CD3/CD1a/CD2/CD4/CD8, myeloperoxidase, and CD117. Chromosome analysis revealed a complex karyotype. The molecular profile revealed no mutations in *NOTCH1*, *FLT3* or *IDH1*, or *IDH2*. The spinal fluid did not contain leukemia cells. The lactate dehydrogenase was 233U/L (normal range, 118–225U/L). Her diagnosis was early T-cell precursor acute lymphoblastic leukemia (ETP-ALL). She was started on a standard 4-drug induction regimen that included vincristine, dexamethasone, daunorubicin, and PEG-L-asparaginase (pegaspargase)

and intrathecal chemotherapy for central nervous system (CNS) prophylaxis.

A bone marrow aspirate, biopsy, and minimal residual disease (MRD) assessment was performed on day 29 of induction therapy, and the aspirate specimen contained 60% blasts, and the MRD assessment revealed 28% residual disease. The patient continued on a pediatric consolidation regimen of the augmented Berlin-Frankfurt-Munster (aBFM) protocol with the addition of nelarabine. Following completion of the consolidation course, a marrow and MRD assessment was repeated (day 78 following consolidation) and showed no detectable disease (≤0.01%). Given the high risk of relapse based on the end of induction marrow and MRD assessment, however, the patient was referred for an allogeneic hematopoietic stem cell transplant (allo-HSCT). She underwent a conditioning regimen of total body irradiation (TBI) and cyclophosphamide followed by a 10/10 matched sibling donor HSCT. Her posttransplant course was uncomplicated, without symptoms of graft-versus-host disease. She remains in complete MRD-negative (MRD^{neg}) remission at day 160.

Introduction

T-lineage ALL (T-ALL) is an aggressive, rare leukemia caused by the malignant transformation of T-lineage progenitor cells at distinct stages of differentiation. Of the estimated 6660 new ALL diagnoses in the United States in 2022, T-ALL in adult patients (typically defined as >18 years) accounts for approximately 10% to 25% of these cases.[1-3] T-ALL is predominantly a disease of the adolescent and young adult (AYA) population (ages 15-39 years), occurring more frequently in young adult male patients and with a modestly higher incidence in black patients.[3] The median age of diagnosis is 29 years.[4] Interestingly, the overall incidence and male prevalence of T-ALL both begin to decline after age 40.[2] The clinical characteristics associated with T-ALL include hyperleukocytosis and extramedullary involvement manifesting as lymphadenopathy, a mediastinal mass, hepatosplenomegaly, and an increased frequency of CNS involvement, occurring in approximately 10% of adult patients at the time of diagnosis.[4,5] The chromosome translocations and genomic abnormalities that characterize T-ALL have been intensely studied and catalogued. Specific abnormalities have not been shown to independently predict prognosis and thus are not used at present to define patients who are at higher risk of relapse or to stratify postremission therapy. For an overview of the genetics and molecular biology of T-ALL, the interested reader is referred to comprehensive reviews on this topic.[6,7]

Currently, intensive multiagent chemotherapy regimens are the most effective treatment approaches for adult patients with T-ALL.[5,8-11] The protocol regimens that have been developed to treat adult patients have been adapted mostly from the pediatric experience and have focused on optimizing the use of conventional chemotherapy—with intensification of dexamethasone, pegaspargase, intrathecal chemotherapy, methotrexate, and maintenance therapy. This approach now yields high remission rates (~90%), with cure rates approaching 70% in young adult patients.[5,8-10] Despite the success of these established pediatric-inspired protocols, approximately 30% of adult patients have subclinical disease, or MRD, following induction and consolidation chemotherapy, likely the most important risk factor for relapse in ALL.[12] Furthermore, the majority of patients with T-ALL/T-LLy who relapse do so during the course of frontline treatment.[4] Once relapse occurs, T-ALL is incurable for most AYA and adult patients, with the overall survival (OS) rate for adults less than 10%.[4,13] The major reason for the poor prognosis after relapse is that the current salvage chemotherapy regimens are minimally effective, preventing most patients from achieving a durable second complete remission (CR2) and thereby prohibiting them from proceeding to allo-HSCT for potential curative therapy. Thus, the optimization of initial therapy is essential for cure in the present-day treatment era. Current clinical research efforts are focused on adding agents to the backbone chemotherapy regimen that have selective activity for T-ALL, with the goal to eradicate MRD early in the treatment course and prevent the emergence of chemotherapy-resistant clones and thus induce more durable remissions and improve survival. Importantly, research efforts from several laboratories have developed CD7- and CD5-targeted chimeric antigen receptor (CAR) T-cell platforms for relapsed disease, and early-phase clinical trials are underway. Early clinical investigations involving CD38-targeted CAR T-cell constructs are also ongoing.[14] For an overview of CAR T-cell therapy for T-ALL, I refer the interested reader to recent reviews and early-phase trials on this topic,[15-20] but novel therapy for relapsed disease is not reviewed in this article due to space constraints.

Impact of nelarabine on the frontline regimen

Nelarabine is the prodrug of 9-β-D-arabinofuranosylguanine (ara-G) and belongs to the class of purine nucleoside analogues. Nelarabine is converted to ara-G by adenosine deaminase, and ara-G is transported selectively into T lymphoblasts by a nucleoside transporter. Ara-G is then phosphorylated to its triphosphate form, ara-guanosine triphosphate, by a series of enzymatic phosphorylation steps. Ara-guanosine triphosphate competes with deoxyguanosine triphosphate in the leukemia blasts for incorporation into DNA, inhibits DNA synthesis, resulting in chain termination, and exerts its cytotoxic action by inducing apoptosis.[21]

Given the selective toxicity of nelarabine to T lymphoblasts, the potential clinical benefit of nelarabine for T-ALL/LLy has been recognized for nearly 40 years.[22,23] Consequently, 3 phase 2 trials and 1 phase 4 trial have demonstrated the efficacy of nelarabine in pediatric and adult patients with relapsed and refractory disease, with objective response rates of 55% and 27% in pediatric patients with the first or second relapse of T-ALL, respectively, and complete responses in adult patients of approximately 30% (Table 1).[24-27] In both pediatric and adult patients, neurotoxicity was dose limiting, though it was manageable and reversible. In 2005 the US Food and Drug Administration granted accelerated approval for nelarabine treatment of patients with T-ALL and T-lymphoblastic lymphoma (T-LLy) whose disease has not responded to or has relapsed following treatment with at least 2 chemotherapy regimens.[28] The use and efficacy of nelarabine in frontline treatment has been demonstrated for children and young adults by a large randomized clinical trial (RCT) conducted by the Children's Oncology Group (COG),[8] but in adult patients the use of nelarabine in the frontline regimen is still being studied.[11,29,30]

Table 1. Trials using nelarabine for adult T-ALL

Study	Years of accrual	N	Age of cohort, years	Phase of trial	Patient population	Nelarabine dose	Outcome
COG	1997-2002	153	0.6-21.7	Phase 2	R/R T-ALL/LLy	650 mg/m^2 IV, days 1–5	ORR: 33% First salvage RR: 55%
CALGB 19801	1998-2001	39	16-66	Phase 2	R/R T-ALL/LLy	1500 mg/m^2 IV, days 1, 3, 5	CR+CRi rate: 31% 1-y OS: 28%
GMALL	2001-2008	126	18-81	Phase 2	R/R T-ALL/LLy	1500 mg/m^2 IV, days 1, 3, 5	CR rate: 36% 1-y OS: 24%
CAMPUS ALL	2007-2018	118	18-74	Phase 4	R/R T-ALL/LLy	1500 mg/m^2 IV, days 1, 3, 5	CR rate: 36% 1-y OS: 38%
COG AALL0434	2007-2014	1895	1-30	Phase 3 RCT	Frontline T-ALL/LLy	650 mg/m^2 IV, days 1–5 for 6 total courses	5-y DFS: 82% aBFM 5-y DFS: 88% aBFM + N CNS RR: 6.9% aBFM CNS RR: 1.3% aBFM + N
MDACC	2007-2016	67	18-78	Phase 2	Frontline T-ALL/LLy	650 mg/m^2 IV, days 1–5 for 4 total courses	3-y CRD: 66% 3-y OS: 65% RR: 31%
UKALL14 NCT01085617	2012-2018	144	25-65	Phase 3 RCT	Frontline	1500 mg/m^2 IV, days 1, 3, 5 for 1 postremission course	3-y EFS: 57% SOC 3-y EFS: 62% SOC+N 3-y OS: 62% SOC 3-y OS: 66% SOC+N 3-y RR: 29% SOC 3-y RR: 28% SOC+N
GRAALL-2014/T NCT02619630	2015-2020	275	18-59	Phase 2	Frontline	1500 mg/m^2 IV, days 1, 3, 5 for 5 postremission courses	Primary end point: 4-y DFS Ongoing study

CALGB, Cancer and Leukemia Group B; CRD, complete remission duration; GMALL, German Multicenter Study Group for Adult ALL; N, nelarabine.

COG AALL0434

The COG trial, AALL0434, tested nelarabine in combination with the aBFM chemotherapy backbone in the largest phase 3 RCT to date for children and young adult patients with newly diagnosed T-ALL (n=1596) or T-LLy (n=299).[8] All T-ALL patients were randomly assigned to receive aBFM high-dose methotrexate or an escalating dose of methotrexate and pegaspargase (known as Capizzi methotrexate). Patients with an intermediate or high risk of recurrence (defined by day-29 marrow morphology and MRD assessment) were randomized to also receive or not receive six 5-day courses of nelarabine (650 mg/m^2/dose) during consolidation, delayed intensification, and maintenance. All intermediate- and high-risk patients received prophylactic (1200 cGy) or therapeutic (1800 cGy for CNS3) cranial irradiation. The AALL0434 trial revealed that the addition of nelarabine to the aBFM chemotherapy backbone was superior to chemotherapy without nelarabine with respect to disease-free survival (DFS), with a 5-year DFS of 88% with nelarabine vs 82% without nelarabine. Patients randomized to receive Capizzi methotrexate and nelarabine had the best outcome, with a 5-year DFS of 91%. The 5-year OS rates were similar, with 90.3% for nelarabine compared with 87.9% without nelarabine; however, AALL0434 was not powered to definitively evaluate OS. Notably, patients who received nelarabine had a lower incidence of CNS relapse; the 5-year cumulative incidence rates of CNS relapse were 1.3% for nelarabine compared to 6.9% without nelarabine.

HyperCVAD plus nelarabine

The investigators at the University of Texas MD Anderson Cancer Center (MDACC) reported on their institutional experience with nelarabine for adult patients with T-ALL. In a single center phase 2 trial, nelarabine was administered at 650 mg/m^2/d intravenously (IV) for 5 days for 2 cycles after the standard 8 courses of the hyperCVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with methotrexate and high-dose cytarabine) regimen and again for 2 cycles during maintenance therapy.[11] In their initial analysis of the data, the addition of nelarabine did not improve survival compared to historical hyperCVAD without nelarabine. The regimen was amended, however, to administer nelarabine earlier during the frontline treatment (as course 5 and 7 of the induction/consolidation regimen). With longer follow-up of this cohort in a landmark analysis, the earlier addition of nelarabine to the hyperCVAD regimen improved OS in non-ETP ALL, with a 5-year OS rate of 83% for patients who received hyper-CVAD plus nelarabine vs 38% with hyper-CVAD alone.[29] Interestingly, these data also lend support to the idea that early eradication of disease resistance can improve outcomes in T-ALL. Their ongoing trial for adult patients with T-ALL will test this concept, as it has modified the hyperCVAD regimen further with the incorporation of pegaspargase as well as venetoclax (NCT00501826).

Based on the results of the phase 3 COG RCT AALL0434 and the adult hyperCVAD plus nelarabine regimen, many adult leukemia specialists in the United States have adopted a chemotherapy backbone with the addition of nelarabine and consider it the optimal chemotherapy regimen for AYA patients. Still, other leukemia specialists are uncertain that the response rates from nelarabine, though impressive in children and AYA patients with T-ALL, will lead to improved survival when tested further in all adult patients, particularly those over 30 years of age who were

not eligible for the AALL0434 trial and patients with other subtypes of T-ALL who did not appear to benefit from the hyperCVAD plus nelarabine regimen. Another source of doubt stems from the lack of a demonstrated OS benefit from the AALL0434 trial, though the trial was not designed to detect this, as discussed above. It should be noted, however, that a significant improvement in DFS in T-ALL, a disease especially refractory to existing chemotherapy salvage regimens upon relapse, is an important outcome. Moreover, data from 2 ongoing international phase 3 RCTs evaluating the use of nelarabine with initial chemotherapy for adult patients with T-ALL will further inform its efficacy for the frontline treatment of T-ALL (NCT01085617, NCT02619630).

Trials in progress testing nelarabine in the frontline regimen

UKALL14

The UK National Cancer Research Institute conducted a phase 3 RCT (UKALL15, NCT01085617) to determine whether the addition of nelarabine to standard chemotherapy (SOC) improves outcomes for adult patients with T-ALL aged 25 to 65 years. The trial randomized 144 patients to SOC (n=75) or SOC plus nelarabine (n=69). One cycle of nelarabine (1.5g/m^2 IV, days 1, 3, and 5) was administered following the second phase of induction. The first analysis of the randomization was reported at the 2021 American Society of Hematology Annual Meeting.[30] At a median follow-up of 51.9 months, the 3-year event-free survival (EFS) was 57% in the SOC arm vs 61.7% in the SOC/nelarabine arm (hazard ratio [HR], 0.88; 0.52-1.46; *P*=.61). Three-year OS was 61.5% vs 65.7% for the SOC arm and SOC/nelarabine arm, respectively (HR, 0.91; 0.53-1.56; *P*=.73). The relapse rates (RRs) were similar for all patients: 29.1% in the SOC arm compared to 28.0% in the SOC/nelarabine arm (HR, 0.97; 0.48-1.92; *P*=.91). The rates of severe adverse events, including grade 3 to 4 neurotoxicity, were similar between the arms (9% for SOC vs 11.9% for SOC/nelarabine). The authors concluded the following: (1) nelarabine added to SOC was safe and did not cause excess toxicity, (2) the addition of 3 doses of nelarabine after induction therapy did not improve 3-year EFS or OS, and (3) perhaps too few doses of nelarabine were used in the trial to result in a benefit. Overall, both the number of doses of nelarabine (3 total doses in UKALL14 vs 30 total doses in AALL0434) and the timing of nelarabine delivery (following the second induction in UKALL14 and following the first induction in AALL0434) may have had an impact on outcomes in this trial. The final analysis of this trial has not been reported to date.

GRAALL-2014/T

The Group for Research on Adult Acute Lymphoblastic Leukemia (GRAALL) is leading a phase 2 multicenter study of risk-adapted treatment for T-ALL in young adults (aged 18-59; GRAALL-2014/T, NCT02619630). This trial is testing the efficacy of nelarabine to improve outcomes in patients with a high risk of recurrence as defined by the unfavorable 4-gene classifier (*NOTCH1/FBXW7/RAS/PTEN*) and/or detectable MRD following induction and first consolidation. This novel 4-gene profile has been identified previously by the GRAALL investigators as having potential prognostic value in T-ALL, especially when combined with MRD assessments.[31] These patients will receive a maximum of 5 "blocks" of nelarabine (1.5g/m^2 on days 1, 3, and 5) during consolidation and maintenance. The study began in December 2015 and was expected to complete the planned enrollment of 275 patients in December 2020. The primary end point is 4-year DFS, which is estimated to be reported in 2025.

Novel agents being developed for frontline treatment

The current intensive chemotherapy backbone regimens, especially those that include nelarabine, have likely reached the limit of tolerance of cytotoxic chemotherapy for AYA patients and for older adult patients with T-ALL. Further advances in the frontline regimen designed to prevent relapse will require novel agents with nonoverlapping toxicity, such as immunotherapies or small-molecule targeted agents.

Immune-targeting CD38 cell surface antigen

CD38 is a type II transmembrane glycoprotein found on the surface of lymphocytes, including T and B lymphocytes, plasma cells, and natural killer cells. Its functions include the regulation of intracellular calcium and signal transduction in immune cells. Preclinical and early-phase clinical data support the rationale for targeting CD38 in T-ALL for the following reasons[32]: (1) lymphoblasts from pediatric patients with T-ALL, both ETP-ALL and non-ETP subtypes, have robust cell surface CD38 expression at the time of diagnosis, and CD38 expression is maintained following chemotherapy; (2) normal lymphoid and myeloid cells and nonhematopoietic organs have low CD38 expression, suggesting minimal "off-target" toxicity; and (3) daratumumab, a human immunoglobulin G1k monoclonal antibody that binds CD38 and is approved for the treatment of multiple myeloma, has been tested in patient-derived xenograft models of T-ALL and shown to have efficacy in 14 of the 15 xenografts. The best responses in the patient-derived xenograft models were observed when the mice were treated in an MRD state. Collectively, the data suggest that CD38 is a potential therapeutic target for T-ALL. An international multicenter phase 2 trial (DELPHINUS) testing daratumumab in combination with the vincristine, prednisone, pegaspargase, and doxorubicin reinduction backbone is ongoing for children and AYA patients (aged 1-30 years) with relapsed or refractory T-ALL or T-LLy ALL (NCT03384654). The first analysis of this trial was reported at the 2022 American Society of Clinical Oncology annual meeting.[33] Twenty-four pediatric (aged 1-17 years) and 5 young adult (aged 18-30 years) T-ALL patients and 10 patients (aged 1-30 years) with T-LLy were treated with at least 1 dose of daratumumab. The overall response rate (ORR) was 83.3% (CR + incomplete CR [CRi]) in pediatric and 60% (all CR) in AYA ALL patients and 40% (all CR) in LLy patients. The MRD^{neg} remission rate was 41.7% in pediatric patients (the MRD^{neg} rate for AYA patients was not reported). The safety profile of the immunochemotherapy regimen was manageable.

A second trial in progress testing daratumumab in T-ALL is in the frontline clinical setting of detectable MRD following cytotoxic chemotherapy, as CD38 expression seems to be preserved following exposure to chemotherapy.[32] The Eastern Cooperative Oncology Group is testing this hypothesis with a phase 2 trial (NCT05289687) for adult patients in hematologic CR1 with persistent or recurrent MRD. Patients receive 4 weekly doses of daratumumab, and the complete MRD response is assessed by flow cytometry. Whether this strategy can eliminate MRD is of great interest.

Small-molecule targeting of BCL2 proteins

The B-cell lymphoma/leukemia 2 (BCL2) family of proteins regulate the mitochondrial (or intrinsic) pathway of apoptosis.[34] This family of proteins includes proapoptotic (BAX and BAK), antiapoptotic (BCL2, BCLXL, MCL-1, BCLw, BFL-1), and BH3-only proteins (BID, BIM, BAD, BIK, NOXA, HRK, BMF, PUMA).[35] Their direct binding interactions determine whether a cell commits to mitochondrial apoptosis. Several small molecules have been discovered that mimic the normal binding of the BCL2 proteins and their partners and directly induce apoptosis in cancer cells, accordingly referred to as "BH3 mimetics." Among the most clinically studied BH3 mimetics are (1) navitoclax, a first-generation BCL2 inhibitor that binds BCL2, BCL-XL, and BCL-w,[36] and (2) venetoclax, a selective and potent second-generation BCL2 inhibitor approved by the US Food and Drug Administration for the treatment of chronic lymphocytic leukemia and acute myeloid leukemia.

T-ALL lymphoblasts overexpress various BCL2 proteins, including BCL2, BCL-XL, and MCL-1. Moreover, the specific BCL2 family member expressed in a given T-ALL specimen appears to vary with the maturation state of the T-ALL.[37] Hence, immature subtypes of T-ALL, such as the ETP subtype, have higher expression levels of BCL2 and relatively lower levels of BCL-XL expression. In contrast, mature subtypes of T-ALL express lower levels of BCL2 and relatively higher levels of BCL-XL. Further, BH3 profiling—a functional assay to measure the cell's susceptibility to apoptosis and the cell's dependence on specific BCL2 proteins for survival—of specimens from patients with relapsed or refractory ALL has shown that the bulk blast population is dependent on BCL2 at the time of diagnosis but can develop dependence on BCL-XL or combined dependence on BCL2/BCL-XL at the time of disease progression.[38,39] On the basis of these data, T-ALL should be susceptible to BCL2 inhibition, and the BH3 mimetic drugs venetoclax and navitoclax, used either as single agents or in combination, have been of considerable interest in T-ALL.

A phase 1 multicenter dose-escalation study was conducted to evaluate the safety and efficacy of combining venetoclax with low-dose navitoclax and chemotherapy in pediatric and adult patients with relapsed/refractory (R/R) T- and B-cell ALL and T- and B-LLy.[40] Because of the potential for resistance from upregulation and reliance on additional antiapoptotic proteins, such as BCL-XL, that are not inhibited by venetoclax, the investigators utilized a combination approach in the relapsed and refractory ALL population. Forty seven patients with advanced B-ALL (n=25), T-ALL (n=19), or T-LLy (n=3) were treated with the experimental regimen. The ORR was 60% (n=20/36). Ten of 19 patients with T-ALL (55.6%) achieved a CR/CRi/partial CR, including patients with the ETP phenotype (8/12, 68%), a phenotype known to be inherently chemoresistant. Six patients with T-ALL (32%) had undetectable MRD. Based on these encouraging data, a trial concept is being developed by the adult cooperative cancer groups in the United States to incorporate venetoclax and navitoclax in the frontline treatment of T-ALL as a second strategy to eliminate MRD early in the disease course.

Allo-HSCT as postremission therapy in T-ALL

Allo-HSCT continues to be a recommended course of postremission treatment for adult patients with high-risk T-ALL in CR1 and with R/R disease.[41] The prognostic factors to define high-risk disease are less clear in T-ALL, however. Historically, high-risk features are defined as age over 35 years, a white blood cell count at diagnosis higher than 100 000/mm^3, residual disease in the bone marrow at day 15 postinduction, CNS involvement, high-risk cytogenetic features, and more than 1 induction regimen to achieve CR[4]. In the contemporary era of pediatric-inspired regimens for young adult patients with T-ALL and the use of MRD assessments to predict the risk of relapse, high-risk features are now considered generally to be immunophenotype, such as ETP-ALL,[42] adverse genetic features (*NOTCH1/FBXW7*– or *N/K-RAS*+ or *PTEN*+),[31] or detectable MRD (>10^{-3} by multiparameter flow cytometry) following induction or at the end of consolidation.[5,12,43] Recent retrospective analyses and prospective, though nonrandomized, trials for patients with standard-risk ALL and undetectable MRD support continuing with postremission chemotherapy without allo-HSCT in CR1.[44-46] For patients with high-risk disease based on detectable MRD or adverse genetic features, however, allo-HSCT in CR1 remains an important postremission therapy for patients able to tolerate a myeloablative conditioning regimen (MAC) with TBI (Table 2).[47-49] An ongoing RCT led by Dr Nicola Gokbuget for the German Multicenter Study Group for Adult ALL is focused on the role of allo-HSCT in high-risk patients with molecular CR (NCT02881086), and these data may reveal whether allo-HSCT is warranted in patients with high-risk disease but who have a good response to chemotherapy as assessed by MRD. Trials that have reported the outcomes for allo-HSCT and T-ALL prior to the use of pediatric-inspired regimens are included in Table 3. Note that most contemporary data for patients with T-ALL are embedded within the report of the entire cohort of ALL patients.

Conclusion

In 2022 the optimal approach for the treatment of T-ALL focuses on improving the frontline regimen to prevent relapse. Ongoing trials testing nelarabine will further inform us about its optimal use in regard to dose, schedules, toxicities, and efficacy in patients older than 30 years and for high-risk subtypes of T-ALL. Data are emerging on the optimal use of HSCT in CR1 in the contemporary era of pediatric-inspired regimens for young adult patients with T-ALL and with the use of MRD assessments to predict the risk of relapse and to decide postremission therapy. Ideally, T-ALL should be studied as a distinct entity in allo-HSCT, separately from B-ALL. The addition of monoclonal antibodies and targeted small-molecule therapy to the frontline chemotherapy backbone is the next strategy to achieve undetectable MRD remissions and improve outcomes.

Underlying this discussion, when we encounter a patient with T-ALL, the experience is something very different than the statistics, the biology, and the treatments we know. The patient in front of us may be a letter carrier and favorite uncle, an expectant father and head brewer, a young mother of 3, a recent college graduate training for her first marathon, or a teenager with dreams of becoming a professional motocross racer. It is this human element that makes the consistent use of currently optimal treatments as well as the relentless pursuit of new and better treatments of such great consequence.

Table 2. Select trials that have compared pediatric-inspired regimens to allo-HSCT for ALL, some with MRD risk stratification[a]

	Group Study					
	DFCI – CIBMTR[44]	**CALGB 10403 – CIBMTR[45]**	**GRAALL 2003/2005[46]**	**PETHEMA ALL-AR-03[47]**	**PETHEMA ALL-HR-11[48]**	**NILG ALL 10/07[49]**
Analysis	Retrospective	Retrospective	Retrospective	Phase 2, prospective	Phase 2, prospective	Phase 2, prospective
Study period (date range)	2002-2011	2002-2012	2003-2011	2003–2012	2011–2019	2008-2012
Age range, years	18-50	16-39	15-55	15-60	15-60	18-65
No. of patients	108 (chemo) vs 422 (HSCT)	217 (chemo) vs 263 (HSCT)	240 (chemo) vs 282 (HSCT)	108 (chemo) vs 71 (HSCT)	218 (chemo) vs 106 (HSCT)	203
Patient risk category	Standard and high risk	Standard and high risk	High risk	High risk	High risk	Standard risk, high risk, very high risk
No. of T-ALL patients	24 (chemo) vs 61 (HSCT)	65 (chemo) vs 43 (HSCT)	80 (chemo) vs 99 (HSCT)	29 (chemo) vs 27 (HSCT)	71 (chemo) vs 32 (HSCT)	11 (chemo) vs 33 (HSCT)
T-ALL subgroup analysis*	No	No	Yes	No	No	Yes
MRD analysis used to assign risk/postremission therapy	No	No	Yes ($<1\times10^{-4}$)	Yes ($< 5\times10^{-4}$ at EOC)	Yes (<0.1% EOI, <0.01% EOC)	Yes, ($>10^{-4}$ at week 10 of therapy)
Outcome measure for whole series	4-y DFS, OS, TRM	3- and 5-y DFS, OS, NRM, CIR	3-y CIR, NRM, RFS, OS for allo-HSCT; effect of allo-HSCT by MRD levels	DFS, OS, impact of MRD on DFS and OS	OS, rates of morphologic and MRD response, EFS, and CIR	5-y RFS, OS, CIR, TRM
Chemo as postremission therapy (whole series)	4-y DFS: 71%; 4-y OS: 73%; TRM: 6%	5-y DFS: 58%; 5-y OS: 66%; 5-y NRM: 8%; 5-y CIR: 34%	Not reported in manuscript, but no significant difference observed between chemo and allo-HSCT	5-y DFS 55%, 5-y OS 59%	5-y OS 59%, 5-y CIR 45%	5-y OS 71%, 5-y RFS 58%, TRM 6%, relapse risk 34%
Allo-HSCT as postremission therapy (whole series)	4-y DFS: 40%; 4-y OS: 45%; TRM: 37%	3-y DFS: 50%; 3-y OS: 53%; 3-y NRM: 24%; 5-y DFS: 44%; 5-y OS: 47%; 5-y NRM: 29%; 5-y CIR: 23%	3-y CIR: 18.5%; 3-y NRM: 13.3%; 3-y RFS: 68.1%; 3-y OS: 72.5%	5-y DFS 32%; 5-y OS 37%	5-y OS 38%, 5-y CIR 40%	5-y OS 54%, 5-y RFS 53% The 5-y CIR 36% TRM was 18%
Conclusion	Chemotherapy without allo-HSCT favored	Chemotherapy without allo-HSCT favored even though relapse risk was higher in chemotherapy cohort.	No significant effect of allo-HSCT on RFS or OS in entire study population. Allo-HSCT favored for patients with detectable MRD.	MRD clearance after induction and early consolidation is the only prognostic factor for DFS and OS. Allo-HSCT could be avoided for patients with good early cytologic response and MRD $<5\times10^{-4}$.	Patients with adequate MRD response after induction and consolidation do well with chemotherapy without allo-HSCT. B- and T-cell patients had similar outcomes, but ETP-ALL had inferior outcomes.	MRD clearance and age ≤55y were the most favorable independent prognostic factors. Entire cohort of T-ALL patients: 5-y OS 73%, 5-y RFS 60%, CIR 30%.

[a]Data for T-ALL outcomes embedded within the report of the entire cohort of ALL patients, the majority of which is B-ALL.

CIR, cumulative incidence of relapse; EOC, end of consolidation; EOI, end of induction; LFS, leukemia free survival; NRM, nonrelapse mortality; RFS, relapse-free survival; TRM, treatment-related mortality.

Table 3. Retrospective analyses of allo-HSCT for T-ALL prior to the use of pediatric-inspired regimens

	Group study				
	UKALL XII/E2993[4]	**ASBMT[50]**	**EBMT[51]**	**King Faisal Specialist Hospital and Research Center[52]**	**MDACC/OHSU/NUH[53]**
Analysis	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective
No. of T-ALL patients	356	208	601	53	102
Study period (date range)	1993-2006	2000-2014	2000-2010	1995-2009	2000-2015
Age range, years	15-59	17-72	18-63	14-51	2-72
ETP phenotype analysis	No[a]	No	No	No[a]	Yes
MRD analysis for risk stratification	No	No	No	No	Yes
Disease status at time of HSCT	CR1 100%	CR1 43%, CR2+39%, R/R 38%	CR1 72%, CR2 13%, CR2+ or R/R 15%	CR1 60.3%, CR2+34%, R/R 5.7%	CR1 37%, CR2+39%, PIF/CR1 6%, R/R 18%
Conditioning regimen	MAC + TBI 100%	MAC 84%, MAC + TBI 86%	MAC 100%, MAC with TBI 87%	MAC 100%, MAC + TBI 94.3%	MAC 77%, MAC + TBI 41%
Outcome measure	5-y OS, CIR, RFS, donor vs no donor comparison	1-y and 5-y OS, RR, RM, NRM, GVHD	Impact of TBI on MAC, 5-y OS, LFS, NRM	OS, DFS, relapse, NRM, aCVHD, cGVHD	OS, PFS, RR, NRM, aGVHD and cGVHD
Survival outcome	5-y OS 48%, 2-y CIR 35%, 5-y CIR 42%, NRM 26%	1-y OS 58%, 5-y OS 34% 1-y RR 35%, 5-y RR 42% 1-y RM 24%, 5-y RM 39% 1-y NRM 18%, 5-y NRM 27% aGVHD 3 mo 55%, cGVHD 1y 28%	5-y OS 45%, 5-y DFS 41%, 5-y NRM 25%, 5-y CIR 35%, aGVHD 3m 38%, 5-y cGVHD 42%	5-y OS 43.5%, 5-y DFS 41.8%, 5-y NRM 22.5%, aGVHD 40.2%, cGVHD 43.7%, 5-y CIR 35.6%	3-y OS 35%, 3-y PFS 33%, CI of NRM was 5% at 100 d, 10% at 1 y and 11% at 3 y. CI disease progression 44% at 1 y and 55% at 3 y. 3-y OS for ETP was 29%, with CI disease progression 63% at 3 y. ETP + allo-HSCT in CR1, OS was 47% at 3 y.
Conclusion	Pts >35 y had inferior outcomes, no benefit to autologous HSCT, sibling donors had benefit over no sibling donor (RR 26% vs 50.9%)	Relapse is main cause of treatment failure. Disease status at time of transplant is most important risk factor for survival. TBI associated with better survival, especially in CR2.	Disease status at allo-HSCT is most important risk factor for survival. TBI associated with better survival (5-y LFS 44% vs 25%, 5-y OS 47% vs 28%, CIR 30% vs 60%), but only for pts <35 y.	Outcomes, relapse significantly associated with disease status at allo-HSCT	Relapse is main cause of treatment failure. Relapse significantly associated with disease status (MRD+) at allo-HSCT. Allo-HSCT can abrogate the negative prognostic impact of ETP-ALL.

[a]Immunophenotypic analysis in this trial was suggestive of ETP phenotype (CD13+/CD1a−, but it was not yet defined as a subtype.
aGVHD, acute graft-versus-host disease; ASBMT, American Society for Blood and Marrow Transplantation; cGVHD, chronic graft-versus-host disease; CI, cumulative incidence; CIR, cumulative incidence of relapse; EBMT, European Group for Blood and Marrow Transplantation; LFS, leukemia free survival; NRM, nonrelapse mortality; NUH; National University Cancer Institute of Singapore; OHSU, Oregon Health and Science University; PIF, primary induction failure; pts, patients; RFS, relapse-free survival; RM, relapse mortality; TRM, treatment-related mortality.

Conflict-of-interest disclosure

Kristen M. O'Dwyer: no competing financial interests to declare.

Off-label drug use

Kristen M. O'Dwyer: nothing to disclose.

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