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Research Article

The challenge to further improvements in survival of patients with T-ALL: Current treatments and new insights from disease pathogenesis

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ABSTRACT

Survival rates for children and adult patients with T-cell acute lymphoblastic leukemia (T-ALL) have improved during the past decade due to optimization of frontline multiagent chemotherapy regimens. The outcome for relapsed T-ALL after initial intensive chemotherapy is frequently fatal, however, because no effective salvage regimens have been developed. Immunotherapy and small molecule inhibitors are beginning to be tested in T-ALL and have the potential to advance the treatment, especially the frontline regimen by eradicating minimal residual disease thus inducing more durable remissions. In this paper, I review the current chemotherapy regimens for adult patients with T-ALL and summarize the novel immunotherapies and small molecule inhibitors that are currently in early phase clinical trials.

Introduction

A patient's wife recently compared her husband's fight against T-cell acute lymphoblastic leukemia (T-ALL) to the act of slaying a dragon. Unfortunately, unlike in fairy tales, where the dragon is vanquished and the knight returns home triumphant, the ending for her husband and too many others is not scripted in that way. Progress in the clinical management of patients with T-ALL has been slow and resistant to new approaches during the past several decades. In the past several years, however, the standard of care chemotherapy regimen for children and young adults has improved survival as a result of an adjustment of the cytotoxic chemotherapy agents and the addition of nelarabine [1-4]. The cure rates in children now approach 90% [1] and in young adults they approach 70% [2]. Optimization of initial therapy is critical because relapsed T-ALL in incurable for most adult patients, with less than 10% of patients experiencing long-term survival [5]. Thus, research efforts during the last 10 years have been focused on discovery of the T-ALL "genomic landscape," which has created avenues for novel drug discovery. Although these efforts have uncovered a great deal about the central genes, signaling pathways, and mechanisms of disease biology of T-ALL, the discoveries have not translated into clinical breakthroughs, yet. Recent progress in the treatment of other lymphoid malignancies, such as B-cell ALL and non-Hodgkin lymphoma, has come from the development of novel immunotherapies and targeted therapies. These advances provide new opportunities for investigation in T-ALL, offering hope that these innovative approaches will transform the treatment of this challenging disease.

Clinical presentation and diagnostic testing

Age of onset

T-ALL results from the malignant transformation of T-lineage progenitor cells at distinct stages of differentiation. It is a rare cancer: it is estimated that 6150 new cases of ALL will be diagnosed in 2020, and adult (generally defined as ≥ 18 years) T-ALL accounts for approximately 25% of these cases [6]. Among adult patients, T-ALL is predominantly a disease of the adolescent and young adult (AYA) population (defined as ages 15-39 years); occurring most commonly in young adult male patients with a median age of 29 years [7].

Signs and symptoms

Patients typically present with a high white blood cell count, diffuse infiltration of the marrow by lymphoblasts, and extramedullary involvement presenting as bulky lymphadenopathy, a mediastinal mass, or pleural effusions, all of which can lead to life-threatening respiratory emergencies. Central nervous system involvement at the time of diagnosis occurs in approximately 10% of adult patients [3,7].

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Table 1
Immunophenotypic classification of T-ALL.

Cell surface antigen	(Pro-T-ALL, EGIL T-1)	Pre-T/immature, (EGIL T-II)	Cortical T (EGIL T-III)	Mature T (EGIL T-IV)	ETP[†]	Near ETP
cCD3	+	+	+	+	+	+
sCD3	-	-	+/-	+	-	-
CD1a	-	-	+	-	-	-
CD2	+	+	+	+	+	+
CD5	-	+	+	+	Dim (<75%+)	+
CD7	+	+	+	+	+	+
CD4/8	-/- "double negative"	-/- "double negative"	+/+	+/+	variable/-	variable/-
TdT[*]	+	+	+	+	+	+
HLA-DR	+	-	-	-		
CD34	+	-	-	-	Variable myeloid markers (HLA-DR, CD13, CD33, CD34, or CD117	Variable myeloid markers (HLA-DR, CD13, CD33, CD34, or CD117

Adapted from Bene, 2016 WHO, and Szczepariski T.
[*] TdT is usually positive in T-ALL and important to distinguish it from mature lymphoid malignancies.
[†] many cases previously classified as Pre-T likely meet criteria for ETP ALL.

Diagnostic criteria, extent of disease and immunophenotype

The diagnosis of T-ALL requires a marrow aspirate and biopsy to determine the nature of the abnormal cell morphology, immunophenotype, central nervous system (CSF) sampling, and computed tomography scans for patients with symptoms of extramedullary disease. The conventional classification system by the European Group for the Immunological Classification of Leukemia reflects subtypes of T-ALL based on immunological markers and the physiologic degree of thymocyte differentiation and includes pro-T, pre-T/immature, cortical T, and mature-T [8]. Thus, there is considerable variability in the immunophenotype of T-ALL (Table 1). The contemporary classification system, the 2016 WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues [9], defines the immunophenotype of T-ALL as usually terminal deoxynucleotidyl transferase (TdT)-positive with variable expression of CD1a, CD2, CD3, CD4, CD5, CD7, and CD8. CD3(cytoplasmic or membrane) is the only T-lineage specific antigen, and it should be positive in every case of T-ALL. CD3 is used as a marker of maturation: cytoplasmic CD3 reflecting immature T-cells and surface CD3 indicating more mature T-cells. The early thymic precursor (ETP) subtype of T-ALL is recognized as a new provisional entity in the 2016 WHO classification. Identified in 2009 from gene expression profiling of leukemia cells from pediatric patients with T-ALL [10]. It has a transcriptional profile and immunophenotype that is similar to its hematopoietic counterpart, early T-cell precursors, a subset of immature thymocyte progenitor cells that have freshly migrated from the marrow to the thymus and retain multilineage differentiation potential (T-lymphoid, natural killer, dendritic and myeloid differentiation potential) [11,12]. ETP is recognized now as a unique subgroup of childhood and adult T-ALL that is associated with intrinsic resistance to chemotherapy with higher end of induction minimal residual disease (MRD) detection and induction failure rates [13,14]. It represents approximately 15% of pediatric cases of T-ALL and approximately 20% of cases in adult T-ALL. The ETP lymphoblast phenotype is defined as CD1a-, CD8-, CD5-/weak, and positive for CD2, CD7, and cytoplasmic CD3 and may express CD4, along with one or more stem cell and/or myeloid antigen (CD117, CD34, HLA-DR, CD13, CD33, CD11b, and/or CD56. Following the classification of ETP and based on further evaluation of gene expression profiling, a subtype related to ETP called "near ETP" has been described [15,16], but is not formally recognized as a provisional entity in the WHO classification.

Risk classification and minimal residual disease

The key prognostic factor for risk classification of T-ALL is MRD, measured by flow cytometry or quantitative polymerase chain reaction [17]. Pediatric and adult trials have demonstrated that the kinetic pattern of disease response is slower for T-ALL as compared to B-cell ALL [3,18], such that detection of MRD at the end-of-induction (Day 29) treatment occurs commonly and is not associated with high-relapse rates. It is the end-of-consolidation (Day 78) MRD assessment that is the most significant predictor of relapse risk and is used also to inform the decision for allogeneic hematopoietic stem cell transplant (HSCT). Although multiple chromosome translocations have been identified in T-ALL, the cytogenetic abnormalities are not used presently to define patients who are at higher risk of relapse or to stratify post-remission therapy. Similarly, the majority of genomic abnormalities that have been identified in T-ALL do not independently predict outcome and thus are not used presently for risk stratification. A novel 4-gene profile (NOTCH1/FBXW7/RAS/PTEN), has been identified by the Group for Research on Adult Acute Lymphoblastic Leukemia (GRAALL) as having potential prognostic value in T-ALL, especially when combined with MRD assessments [19]. This 4-gene classifier has not been incorporated into the risk models in the United States, but an ongoing clinical trial in Europe is testing the predictive power of this 4-gene signature, which is discussed in more detail below.

Current treatment for T-ALL: Age-specific treatments

Treating young adult patients with pediatric type regimens

Intensive, multiagent chemotherapy regimens are the most effective treatment approaches for adult patients with T-ALL. Based on the work pioneered by Dr Wendy Stock et al [20], we know that the pediatric regimens adopted from the Children's Oncology Group-augmented Berlin-Frankfurt Munster (aBFM) chemotherapy protocols [21] produce high-remission rates with the most durable MRD-negative remissions. These pediatric regimens are prolonged (2-3 years), multiagent chemotherapy regimens with complex schedules that include central nervous system prophylaxis with intrathecal chemotherapy and are organized into 4 phases: induction, consolidation, delayed intensification, and maintenance. With these pediatric-based contemporary chemotherapy regimens, T-ALL is curable for approximately 80% of children and 68% of older adolescents and young adults (AYAs; defined broadly as patients aged 15-39 years) [1,2]. Approximately 30% of adult patients will have subclinical, or detectable MRD, following induction and consolidation chemotherapy, arguably the most important risk factor for relapse in ALL [3]. Relapsed T-ALL remains the most common cause of treatment failure and cure of children or adults following relapse is uncommon, with the overall survival rate after relapse for children being less than 30%, and for adults, less than 10% [5,7,22]. With no frequently effective salvage therapy, the clinical research

effort has focused on optimizing initial treatment with the goal to increase the MRD-negative remission rates as a means to improve survival.

To this end, the Children's Oncology Group trial, AALL0434, tested nelarabine in combination with aBFM-based chemotherapy in the largest randomized, phase 3 clinical trial to date for children and young adult patients with newly diagnosed T-ALL or T-lymphoblastic lymphoma (T-LLy) [1]. Nelarabine is the pro-drug of 9-β-arabinofuranosylguanine (ara-G) and belongs to the class of purine nucleoside analogs. Nelarabine is converted to ara-G by adenosine deaminase and transported into cells by a nucleoside transporter. Ara-G is subsequently phosphorylated to Ara-G triphosphate (GTP), which exerts its therapeutic effect by inhibition of DNA synthesis. Pharmacokinetic studies have demonstrated that ara-GTP preferentially accumulates in malignant T-cells likely accounting for the extreme sensitivity of T-lymphoblasts to the cytotoxic effects of nelarabine observed in vitro and in preclinical animal studies [23,24]. Several studies demonstrated the efficacy of nelarabine in pediatric and adult patients with relapsed or refractory T-ALL [25-27], and in 2005, nelarabine was approved by the United States Food and Drug Administration for the treatment of T-ALL and T-LLy that was refractory to at least 2 chemotherapy regimens [28].

The AALL0434 trial enrolled 1895 patients (ages 1-30 years) from 2007 until 2014. All T-ALL patients were randomly assigned to receive aBFM high-dose methotrexate (HD-MTX) or escalating dose of methotrexate (known as Capizzi methotrexate, CMTX). Patients with intermediate and high risk of recurrence were also randomized to receive or not receive six 5-day courses of nelarabine. Risk assessment was based on MRD detection at the end of induction therapy (Day 29) and used the following MRD values: low-risk <0.1%, intermediate risk <1%, and high-risk >1%. All intermediate and high-risk patients received prophylactic (1200 cGy) or therapeutic (1800 cGy for CNS3) cranial irradiation.

For the entire cohort, the 4-year rate of disease-free survival (DFS) was 84.1%, and the 4-year overall survival (OS) rate was 90.2%. The 5-year DFS for CMTX as compared to HD-MTX treated patients was 91.5% versus 85.3% ($P = .005$), respectively. The 5-year OS for CMTX as compared to HD-MTX treated patients was 93.7% versus 89.4% ($P = .036$), respectively. The 4-year DFS rate for T-ALL patients who received nelarabine (n = 323) or did not receive nelarabine (n = 336) was 88.9% and 83.3% ($P = .0332$), respectively. Patients randomized to CMTX and nelarabine (n = 147) had a 4-year DFS of 92.2%, whereas patients receiving CMTX without nelarabine, had an 89.8% DFS ($P = .3825$). Patients (n = 176) randomized to HD-MTX with nelarabine had a 4-year DFS of 86.2%, whereas patients (n = 185) not receiving nelarabine (n = 185) had a 78% DFS, $P = .024$. Overall toxicity, including myelosuppression and neurotoxicity were not significantly different among the 4 arms of the study. There were no isolated CNS relapses in the CMTX and nelarabine arm, although 90% of patients enrolled on AALL0434 received prophylactic or therapeutic cranial irradiation.

Subgroup analysis revealed that 11.3% of the cohort was categorized as ETP ALL by flow cytometry [13]. Induction failure rates were significantly higher for patients with ETP compared to patients without the ETP immunophenotype (7.8% versus 1.1%, $P < .0001$). Also, the end of induction MRD positive (defined as >0.01%) remission rate was higher in patients with ETP compared to patients without the ETP immunophenotype (81.4% versus 30.5%, respectively). Unexpectedly, there was no difference in EFS or OS between ETP ALL and non-ETP ALL. Five-year EFS was 87% (ETP) versus 86.9% (non-ETP), and OS was 93% (ETP) versus 92% (non-ETP).

Although the age eligibility of the AALL0434 trial was 1 to 30 years, only 3% of the 1895 patients enrolled were in the age range of 20 to 30 years. Because of the efficacy and tolerability data from the AALL0434 trial, the young age of the majority of patients who are diagnosed with T-ALL, and the poor prognosis for relapsed T-ALL, many adult leukemia experts recommend the pediatric AALL0434 backbone that incorporates nelarabine for children and AYAs with T-ALL. Other experts are concerned about the potential for neurotoxicity in older patients, however, and await further data on the use of nelarabine with initial chemotherapy for adult patients with T-ALL. There are 2 ongoing studies testing the addition of nelarabine to standard chemotherapy regimen that should further inform us. The UK National Cancer Research Institute UKALL14 trial (NCT01085617) is conducting a randomized phase 3 trial for patients to determine whether the addition of nelarabine to standard chemotherapy improves outcomes for adult patients with T-ALL ages 25 to 65 years. Patients were recruited between December 2010 and July 2018. The primary end point of 3-year event-free survival has not been reported yet. The second study is led by The Group for Research on Adult Acute Lymphoblastic Leukemia (GRAALL) and is a phase 2 multicenter study of risk adapted treatment for T-lineage ALL of young adults (18-59 years), GRAALL-2014/T (NCT02619630). This European trial is testing the efficacy of nelarabine to improve outcomes in patients with 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. These patients will receive a maximum of 5 blocks of nelarabine-based chemotherapy during consolidation and maintenance. The study began in December 2015 is expected to complete the planned enrollment of 275 patients in December 2020. The primary end point is 4-year disease free survival and will be reported in 2025.

The University of Texas - MD Anderson Cancer Center (MDACC) has reported their institution's outcomes of patients with T-ALL treated with the hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) regimen plus nelarabine [29]. In this single arm phase 2 study, patients received eight cycles of hyper-CVAD alternating with high-dose methotrexate and cytarabine, followed by 2 cycles of nelarabine administered as a dose of 650 mg/m^2 dose on days 1 to 5. This high-dose induction/consolidation approach was followed by 30 months of prednisone, vincristine, methotrexate, and mercaptopurine (POMP) maintenance and 2 additional courses of nelarabine. Sixty-seven patients with a median age of 37 years (range, 17-78 years) were enrolled between August 2007 and May 2016 and were eligible for treatment and evaluation. The 3-year overall survival rate was 65%, but when the author's compared this result to historical data from patients receiving the hyper-CVAD regimen alone, no survival benefit was demonstrated from the addition of nelarabine.

In regards to data from trials that have not incorporated nelarabine in the chemotherapy backbone, the Alliance for Clinical Trials in Oncology, conducted a multicenter, phase II, single-arm trial, Cancer Leukemia Group B (CALGB) 10403, to test the efficacy and feasibility of a pediatric regimen for AYA patients with newly diagnosed B-or T-lineage ALL [2]. The study enrolled 318 young adult patients with a median age of 24 years (range, 17-39 years) between November 2007 and September 2012. The protocol treatment was identical to one of the arms in the AALL0434 study, CMTX without nelarabine.

Two hundred and ninety-five patients were eligible for treatment and evaluation. Seventy-one patients had T-cell ALL. The complete marrow response rate was 89% (n = 263). MRD assessment using quantitative polymerase chain reaction was performed on a subset of patients (n = 80) following induction therapy. The MRD negative remission rate was 44% (n = 35). Detection of MRD following induction therapy was associated with an inferior 3-year DFS (54% for patients with detectable MRD ($<10^{-4}$) versus 85% for undetectable ($>10^{-4}$) MRD ($P = .001$). The median follow-up for the cohort was 64 months; 190 patients (64%) are alive and 105

Table 2
Summary of trials that included older adults with T-lineage ALL.

Trial	Years of enrollment	Age of subgroup analysis (years)	N of subgroup analysis	T-lineage Immunophenotype (N)	CR Rate (%)	OS	Reference
MDACC	1980-2006	≥60	122	Not reported	84	20%, 5 year	[32]
SWOG 8417/8419	1985-1991	50-84	85	Not reported	41	Median OS, 15 months	[55]
CALGB 8811, 9111, 9311, 9511, and 19802	1988-2002	≥60	129	Not reported	57	12%, 3 yr	[31]
GIMEMA 0288	1988-1996	50-60	121	Not reported	68	15%, 8 yr	[56]
PETHEMA ALL96	1996-2006	56-77	33	5	58	39%, 2 yr	[57]
MRC/ECOG UKALL12/E2993	1993-2006	55-65	100	14	70	21%, 5 yr	[30]
SWOG 9400	1995-2000	50-65	43	Not reported	63	23%, 5 yr	[58]
EWALL	2007-2008	56-73	40	7	85	61%, 1 yr	[59]

CALBG, Cancer and Leukemia Group B; EWALL = European Working Group on Adult Acute Lymphoblastic Leukemia; GIMEMA = Gruppo Italiano Malattie Ematologiche dell'Adulto; MDACC = MD Anderson Cancer Center; MRC = Medical Research Council; PATHEMA = Program for the Study and Treatment of Malignant Hemopathies, Spanish Society of Hematology; SWOG = Southwest Oncology Group.

(36%) have died. The median EFS was 78.1 months (95% confidence interval [CI], 41.8-not reached), the 3-year EFS was 59% (95% CI, 54%-65%), and the estimated 3-year OS was 73% (95% CI, 68%-78%). There was no significant difference in outcomes between patients with a B-cell versus T-cell phenotype. And, there was no significant difference in outcomes between patients age 20 to 30 years and 30 to 40 years. These outcome data are a significant improvement in outcomes in comparison to historical controls, among whom the 3-year OS was 58% (95% CI, 52%-64%) and median EFS was 30 months (95% CI, 22-38).

Treating adult patients (>40 years of age) with pediatric type regimens and standard adult regimens

Since the completion of the CALBG 10403 trial, multiple groups have demonstrated the feasibility of delivering a pediatric-like regimen to patients up to the age of 50 years, with certain age-based adjustments. Two important data sets that achieved excellent outcomes for adult patients with T-ALL came from the Nordic Society of Pediatric Hematology and Oncology (NOPHO) ALL2008 protocol [3] and the Dana Farber Cancer Institute (DFCI) ALL Consortium [4].

The NOPHO ALL2008 is a population-based study that utilized an unmodified pediatric ALL protocol as initial treatment for patients 1-45 years of age with B-ALL and T-ALL [3]. The study enrolled 1,815 patients between July 2008 and March 2016 (B-ALL n = 1488 and T-ALL n = 278), and the treatment protocol utilized intensive consolidation chemotherapy "blocks" based on MRD risk assessment. The proportion of T-cell immunophenotype increased across the age spectrum from 9.9% in the 1 to 9 year group to 25.5% in the 10-17 year group to 30.3% in the 18 to 45 years. The 5-year OS of the T-cell cohort was 75%, but varied across age groups with the adults showing inferior outcomes as compared to children: 82% for the 1 to 9 year group, 76% for the 10 to 17 year group, and 65% for the 18 to 45 year group. Relapse was the major cause of treatment failure, but for older adults on the trial, the risk of death in remission was 12%. Most of the deaths in remission occurred after the most intensive chemotherapy "blocks" suggesting that dose modifications of a pediatric protocol are necessary for some patients.

The DFCI ALL Consortium conducted a prospective trial (DFCI Adult ALL Consortium Protocol 00-175) that used an intensive pediatric regimen for patients age 18 to 50 years and included patients with B-cell and T-cell ALL [4]. The trial enrolled 100 patients between June 2002 and February 2008; 48 patients were 18 to 29 years and 44 patients were 30 to 50 years of age. This treatment plan used a 5-drug induction regimen that included high-dose methotrexate, 30 weeks of intensification with weekly asparaginase therapy, and 2 years of maintenance. The complete remission (CR) rate was 85%, and the 4-year overall survival (OS) for the entire cohort was 67%. For the patients with T-ALL, the CR rate was 89%, the 4-year disease-free survival was 87%, and the OS was 76%. The majority of the older adults in this trial were able to tolerate the intensive asparaginase therapy, which was likely determinative of the very good outcomes.

Though the diagnosis of T-ALL is uncommon in adults 50 years and older, the older patient population with T-ALL presents a particular challenge for clinicians, mainly because the pediatric-type chemotherapy regimens when utilized for this age group cause more treatment-associated toxicities, the majority of which are due to myelosuppression associated infections, and therefore limits the use of curative chemotherapy strategies in adults older than 50 years. Thus, outcomes for older adult patients are inferior compared to younger patients, both in terms of response to induction chemotherapy and long-term survival. Multiple trials have reported the outcomes for the older patient cohort with ALL, noting, however, that most data on older adults with T-ALL is embedded within the report of the entire cohort of ALL patients, the majority of which is for B-ALL (Table 2). These analyses do provide insight into the reasons for the poor outcomes in older T-ALL patients, which include higher rates of death during induction therapy, primary induction failure, and death in remission. The majority of the deaths are due to higher incidence of serious infection during induction and consolidation therapy, resulting from the combination of myelosuppression and the use of high-dose steroids. Also, chemotherapy dose reductions, delays and omissions are more frequent in older patients, further impacting the effectiveness of the chemotherapy. The data is scant for the role of biologic differences in T-ALL in older patients and its impact on outcomes, but it is likely that the biology of the leukemia is associated with chemotherapy resistance and poorer outcomes as compared to younger patients. Nonetheless, when faced with an older patient with T-ALL, the optimal chemotherapy regimen is undefined, so a regimen from the trial of E2993/UKALL12, CALGB protocols or the MDACC dose adjusted hyper-CVAD can be carefully administered [30-32]. For patients in remission, allogeneic HSCT utilizing a reduced intensity conditioning regimen should be considered, though data on HSCT in this population is very limited [33,34].

In summary, initial therapy based on pediatric chemotherapy regimens that include nelarabine, blocks of intensive cytotoxic chemotherapy or blocks of intensive asparaginase treatment, have improved outcomes for adult patients younger than 50 years of age with T-ALL. These intensive regimens, however, have likely reached the limit of tolerance of cytotoxic chemotherapy in young adults and treatment-related toxicity limits the chemotherapy approach in adults 50 years and older. Further advances will require novel agents with nonoverlapping toxicity, such as small molecule targeted agents or immunotherapies. Unlike in B-lineage ALL (B-ALL), where immunotherapies targeted to CD19 or CD22 have significantly improved survival rates in relapsed disease and are now being incorporated into the frontline regimens, comparable therapies

are not available or effective in T-ALL. Thus, for T-ALL, novel therapy is needed for (1) high-risk disease as defined by detectable MRD following induction and consolidation therapy; (2) relapsed T-ALL, which has no effective salvage therapies; and (3) frontline treatment for older adults who cannot tolerate the intensity of pediatric regimens.

Insights into T-ALL through genetics and molecular biology

The genomic landscape of T-ALL has been investigated by numerous laboratories, and the investigations have explored the genetic alterations, dissected the mechanisms of leukemic transformation of T-ALL and furthered our understand of the pathobiology of T-ALL [35-38]. It, also, has created avenues for novel drug discovery. Several excellent reviews have been published that summarize the genomic landscape in T-ALL and describe potential drug targets including Notch, Jak/Stat, PI3K/Akt/mTOR, and MAPK [37,39]. The most promising therapeutics being incorporated into clinical trials are immunotherapies, including chimeric antigen receptor T-cell (CAR-T) platforms and monoclonal antibodies, and targeting antiapoptotic proteins BCL2 and BCLx. These therapies have been successful in a variety of lymphoid malignancies and their application to the treatment for T-ALL requires urgent study.

Targeting the Survival Pathway

Aberrant overexpression of antiapoptotic BCL-2 family members is one mechanism malignant cells utilize to circumvent apoptosis and survive [40]. Several lymphoid malignancies, including T-ALL, overexpress antiapoptotic proteins including BCL-2, Bcl-xL and MCL-1 [41,42]. Antiapoptotic BCL-2 family members, each with distinct sensitivities to inhibitors, are variably abundant in T-ALL, suggesting that matching inhibitors to the specific BCL-2 family member may be necessary for maximal therapeutic effect. The specific BCL-2 family member expressed in a tumor varies with the maturation state of the T-ALL [43]. Immature subtypes of T-ALL, such as the ETP, have higher expression levels of BCL-2 and relatively lower levels of expression of Bcl-x_L. In contrast, mature subtypes of T-ALL express lower levels of BCL-2 and relatively higher levels of expression of Bcl-x_L. In addition to the heterogeneity between patients' tumors (inter-patient heterogeneity) there is often heterogeneity within an individual patient's blast population (intrapatient heterogeneity). For example, the bulk blast population may have a dependence on BCL-2, while an earlier progenitor cell is dependent on Bcl-xL. There may be temporal heterogeneity in a single patient: BH3 profiling in patients with relapsed or refractory ALL has shown that the bulk blast population is dependent on BCL-2 at the time of diagnosis, but develops dependence on Bcl-x_L or combined BCL-2/ Bcl-x_L at the time of disease progression (personal communication with Dr. Wendy Stock). Thus, optimizing the use of BCL-2 pathway inhibitors may require precisely matching the inhibitors and the maturation state of the T-ALL to eliminate resistant blast populations.

Venetoclax and navitoclax

To this end, a phase 1, multicenter, dose escalation study was designed to evaluate the safety and efficacy of combining venetoclax with low-dose navitoclax in pediatric and adult patients with relapsed/refractory T-cell and B-cell ALL and lymphoblastic lymphoma (NCT03181126). Navitoclax is a first generation *Bcl-2* inhibitor that also has activity against Bcl-x_L and Bcl-w. Navitoclax demonstrated significant efficacy as a single agent in relapsed CLL, but the dose-limiting toxicity of profound thrombocytopenia, due to Bcl-x_L inhibition, stalled its clinical development in hematologic malignancies. Venetoclax is a selective and potent second-generation *Bcl-2* inhibitor and has shown significant clinical efficacy in the treatment of hematological malignancies, including chronic lymphocytic leukemia and acute myeloid leukemia. The hypothesis of the study was that inhibition of Bcl-2 and Bcl-x_L is required for optimal efficacy and that using low-dose navitoclax would mitigate the profound thrombocytopenia when combined with standard dose venitoclax.

Patients received venetoclax, 200 mg (weight-adjusted equivalent for pediatric patients), on day 1 and 400 mg equivalent daily thereafter. On Day 3, patients received navitoclax at three dose levels (25, 50, or 100 mg) based on patient weight. In addition, patients could receive 2 cycles of chemotherapy at the treating physician's discretion with vincristine, asparaginase and dexamethasone. Response to therapy was assessed by flow cytometry on days 8 and 36. Minimal residual disease evaluation ($<10^{-4}$ cutoff for undetectable MRD) was performed at the time of disease assessment if clinically indicated.

An updated analysis on 47 patients enrolled on this trial was presented at the 2020 European Hematology Association Congress [44]. Eighteen patients with T-ALL have been enrolled in the study. The overall response rate (ORR) was 56% (n = 20/36). Six of 16 patients with T-ALL (38%) achieved a CR/CRi/CRp. Of the 6 patients with T-ALL and CR/CRi/CRp, 4 (66.7%) had undetectable MRD. Dose limiting toxicities occurred in 7 patients, and the most common dose limiting toxicities was delayed count recovery. The recommended phase 2 dose (RP2D) for navitoclax (in combination with venetoclax 400 mg) is 50 mg for patients ≥45 kg and 25 mg for patients <45 kg. The most common Grade 3/4 adverse events were febrile neutropenia (39%), neutropenia (26%), and hypokalemia (24%). Nonhematologic grade 3/4 adverse events related to venetoclax or navitoclax included vomiting (n = 3), increased ALT (n = 2), and sepsis (n = 2). Longer follow-up is needed to determine the durability of the response, but this combination of BCL inhibitors is encouraging for improved treatment in T-ALL. In fact, the US adult cooperative cancer groups are proposing to add Bcl-2 and Bcl-x_L inhibitors to the current standard of care regimen for adult patients with T-ALL. This randomized trial is designed to detect an improvement in MRD negative remissions and improvement in event free survival.

Antibody targeting of CD38

Cluster of differentiation 38 (CD38), also known as cyclic ADP ribose hydrolase, is a 45-kD, type II transmembrane glycoprotein that is expressed on the surface of normal T and B lymphocytes, plasma cells, natural killer cells, and some nonhematopoietic tissues. CD38 regulates cytoplasmic calcium flux and mediates signal transduction myeloid and lymphoid cells. Convincing preclinical data from several laboratories have characterized CD38 expression in T-ALL to determine whether CD38 would be an effective target in T-ALL [45]. The Teachey laboratory has shown that cell surface CD38 is expressed on T-ALL lymphoblasts at the time of diagnosis, and that CD38 expression is maintained following chemotherapy exposure. There was low CD38 expression on normal lymphoid and myeloid cells and nonhematopoietic organs, suggesting minimal "off target" toxicity. The lab expanded the work to test daratumumab, a human immunoglobulin G1k monoclonal antibody that binds CD38 and is approved for myeloma therapy, and to determine its efficacy in patient cell-derived xenograft models of T-ALL. Daratumumab was highly effective in their model. In addition to the preclinical data, there are clinical case reports of compassionate use of daratumumab in relapsed T-ALL that have demonstrated prolonged responses [46]. Finally, daratumumab is being tested in combination with cytotoxic chemotherapy in an international multicenter phase I/II trial (NCT03384654) for children

Table 3
Selected immunotherapy trials for T-lineage acute lymphoblastic leukemia.

T-cell antigen	Immunotherapy	Trial phase	Clinical trial
CD5	CD5 CAR T	Phase I	NCT03081910/Baylor College of Medicine
CD7	CD7 CAR T	Phase I	NCT03690011/Baylor College of Medicine
CD7	UCART7	Phase I	Not yet recruiting/Washington University
TRBC1	TRBC1 CAR T	Phase I	NCT03590574/United Kingdom
TruUCAR GC027	CD7 CAR T	Phase 1	China
CD38	Daratumumab	Phase I/II	NCT03384654/Multiple international sites

and AYA patients (ages 1-30 years) with relapsed or refractory B-cell and T-cell ALL and lymphoblastic lymphoma. CD38 could be a good therapeutic target for T-ALL, and daratumumab may be particularly useful in patients with detectable MRD following cytotoxic chemotherapy. To this end, the COG is designing their next randomized phase 3 trial and testing whether daratumumab in combination with Capizzi methotrexate based interim maintenance course can eradicate MRD in the pediatric population. Given the comparably limited data in the adult T-ALL population for the use of daratumumab, the US adult cooperative groups are designing a pilot study for T-ALL patients with detectable MRD and testing the efficacy of daratumumab to eradicate MRD.

CAR-T therapy

CD19-directed chimeric antigen receptor T-cell (CAR-T) therapy induces CR in approximately 80 percent of children and adults with relapsed or refractory B-cell acute lymphoblastic leukemia (B-ALL). There are several biologic hurdles to developing CAR-T therapy for the treatment of T-lineage leukemia, however. First, in order to create the CAR-T construct, adequate numbers of normal T-cells must be collected from the patient in need of the therapy. In a patient with T-ALL, harvesting normal T-cells from the patient without contamination of malignant T-cells is difficult. An alternative approach would be the use of genetically modified CAR-Ts from healthy allogeneic donors, but this approach may result in life-threatening graft-versus-host disease (GVHD) when the allogeneic cells are infused into immunocompromised patients. Second, the targeting of lineage-restricted cell-surface antigens on malignant T cells could result in 2 clinically important adverse consequences: (1) fratricide, which in this scientific context refers to the nonspecific killing of the CAR-T construct; and (2) prolonged T-cell aplasia. In regards to fratricide, because the most widely expressed tumor antigen targets for malignant T cells are also expressed on normal T cells, the engineered T cells can result in CAR-T fratricide during manufacturing and therefore limit ex vivo expansion and therapeutic potency of the autologous cell product. If fratricide can be overcome by clever technology and design of the CAR-T construct, there remains the issue of prolonged T-cell aplasia. CAR-T cytotoxicity against normal lymphocytes and their early precursors will suppress overall T-cell function and induce temporary or prolonged immunodeficiency, clinically similar to that observed following HSCT. There is no easy, clinically useful treatment to help with prolonged T-cell aplasia as there is for prolonged B-cell aplasia from targeting CD19 in B-cell malignancies. B-cell aplasia can be treated with intravenous immunoglobulin, but only time or potentially curative HSCT (as allogeneic HSCT terminates the activity of CAR-Ts) restores normal hematopoiesis and, ultimately, replenishes T-cell populations. There, also, is a risk of genetically modifying circulating malignant T-lymphoblasts, which could facilitate a treatment-resistant tumor clone [47].

Despite the technical and clinical challenges, several laboratories have developed CAR-T constructs, using strategies that address each of the technical and clinical hurdles described above, and early-phase clinical trials are underway (Table 3). Investigators at Baylor University have designed a second generation CD5 directed CAR construct with a CD28 costimulatory endodomain that results in minimal and transient fratricide when expressed in T cells. Because of the potential that the CAR-T product would target and eliminate normal T-cell subsets (CD5 is expressed on malignant and normal T-lymphocytes) and cause profound immunosuppression, the clinical trial was designed to evaluate the safety and feasibility of the CAR T cells as a "bridge" to allogeneic HSCT [48,49]. The results of the first nine patients with relapsed and refractory T-cell malignancies enrolled on this trial (NCT03081910) were presented at the 2019 annual meeting of the American Society of Hematology [50]. The median age of the patient's treated was 62 years. Four patients had T-ALL and 5 patients had T-non-Hodgkin's lymphoma. Patients had received a median of 5 prior therapies (range, 2-18). All patients were eligible for allogeneic HSCT and had HLA-matched donors identified at the time of enrollment. Patients underwent lymphodepleting chemotherapy with cyclophosphamide and fludarabine and then received CAR T cells at dose level 1 (1×10^7 CAR T cells/m^2, $n = 3$) or dose level 2 (5×10^7 CAR T cells/m^2, $n = 6$). CAR T cell expansion was observed in all patients, and CAR T-cell persistence was durable at both cell dose levels. Prolonged and complete T cell aplasia was not observed. Cytokine release syndrome occurred in 3 patients, all in the dose level 2 cohort and all were <Grade 3. Three patients achieved a CR (2 with T-NHL and 1 with T-ALL), but none proceeded to the planned HSCT (2 patients did not wish or were unable to proceed and one relapsed during HSCT planning). One patient with T-NHL achieved a mixed response and received a second infusion of CAR T cells, proceeded to transplant, and remained in CR at Day 125 post-transplant. This trial is ongoing with plans to test higher cell dose levels of CD5 CAR T cells.

In the United Kingdom, scientists have used T-cell receptor beta chain 1 (TRBC1) as a target, which is expressed in approximately 35% of T-ALL cases. This approach was designed to spare large subsets of normal T-cells and thus reduces T-cell aplasia [51]. In an alternative approach utilizing CRISPR/Cas9 gene editing technology, scientists at Washington University in St. Louis have designed an "off-the-shelf" CAR-T construct, UCART7, which is resistant to fratricide, exhibits no alloreactivity or GVHD potential, and expands and persists, and efficiently eliminates $CD7^+$ T-ALL in vivo [52,53]. The team has plans to open a phase 1 trial with this CAR-T construct. Preliminary results from five patients with relapsed and refractory T-ALL treated in China with an "off-the-shelf" CAR T-cell product, TruUCAR GC027, were presented at the 2020 Virtual Meeting of the American Association for Cancer Research (AACR) [54]. Similar to the Washington University UCART7 product, the TruUCAR product was developed using CRISPR technology that removed the CD7 target to avoid fratricide and the T-cell receptor alpha chain to eliminate GVHD. The patients were aged 19 to 38 years, and received a single infusion of the CAR T product. Four of the 5 patients achieved MRD negative remission at Day 28. No patients developed GVHD, but all patients developed CRS. The follow-up data from this trial should provide evidence of the durability of the responses.

Summary

The recent modifications in the chemotherapy regimens for patients with T-ALL have led to improved survival. The road to achieve cure remains difficult, however, and treating relapse is indeed like trying to "slay a dragon". The adult cooperative cancer groups, together with the Children's Oncology Group, are designing the next series of clinical trials for T-ALL, some of which plan to incorporate daratumumab in the initial regimen as a means to eliminate MRD, while an alternative trial concept for the initial regimen will incorporate combination BCL inhibitors as another attempt to eliminate MRD. CAR-T trials in progress could lead to an effective treatment for the children and adults who have relapsed or refractory T-ALL. The insightful laboratory efforts underway should continue to enrich our understanding of the pathobiology of T-ALL and facilitate targeted therapy for this disease.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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