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Leukemia (PH Wiernik, Section Editor)

Biology and Treatment Paradigms in T Cell Acute Lymphoblastic Leukemia in Older Adolescents and Adults

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Opinion statement

T cell acute lymphoblastic leukemia (T-ALL) occurs in approximately 25–30% of adult ALL diagnoses. Historically, B cell ALL (B-ALL) and T-ALL have been treated in the same fashion despite differences in the biology of disease. Outcomes in the adolescent/young adult (AYA) population have improved significantly with the utilization of pediatric-based regimens. In addition, there may now be a role for the addition of nelarabine to frontline treatment in the AYA population. In older adults, choices in which regimen to pursue should account for the potential toxicities associated with pediatric-based regimens. Measurable residual disease (MRD) has taken on increasing prognostic value in T-ALL and may help to identify which patients should receive an allogeneic stem cell transplant. T cell lymphoblastic lymphoma (T-LBL) has traditionally been treated similarly to T-ALL, but additional management questions must be considered. Mediastinal irradiation does not seem to clearly improve outcomes, and there is considerable heterogeneity in the central nervous system (CNS) prophylaxis strategy used in prospective trials. CNS prophylaxis in AYA patients with T-ALL, on the other hand, can be safely achieved with intrathecal chemotherapy alone. Prospective data regarding CNS prophylaxis strategies in older adults

are currently not available. Nelarabine-based regimens currently remain the standard in relapsed/refractory T-ALL; however, novel therapies targeting molecular aberrations in T-ALL are actively being investigated.

Introduction

Acute lymphoblastic leukemia (ALL) is a heterogeneous group of leukemias defined by the proliferation of lymphoblasts. The estimated incidence of ALL in 2019 was 5930, and its prevalence in 2016 was 85,764 [1]. These disorders are broadly divided into precursor B cell ALL (B-ALL) and precursor T cell ALL (T-ALL), based on the specific lineage of the immature lymphoblasts. Historically, B-ALL and T-ALL have been treated similarly despite differences in demographics, clinical presentation, immunophenotype, cytogenetics, molecular aberrations, and prognostic features. We aim to highlight the differences pertinent to T-ALL in addition to reviewing current treatment regimens in adults, analyzing the role for allogeneic stem cell transplantation (allo-SCT) in high-risk disease, mentioning management considerations for T cell lymphoblastic lymphoma (T-LBL), discussing treatment strategies for the central nervous system (CNS), reviewing available therapies in the relapsed/refractory setting, and evaluating novel therapies undergoing investigation.

Disease biology

T-ALL makes up approximately 25% of adult cases (with predominance in the young adult population) and 15% of childhood cases of ALL [2]. T-ALL has a higher rate of leukocytosis, extramedullary involvement (including mediastinal disease), and CNS involvement in comparison to B-ALL [2, 3]. Over the past 20 years, we have made significant inroads into understanding the genetics and molecular biology of T-ALL (Table 1). Deletion of the *CDKN2A* locus at chromosome 9p is seen in over 70% of T-ALL patients, leading to cell cycle dysregulation due to the loss of the *p16INK4A* and *p14ARF* tumor suppressor genes [5]. T cell receptor (TCR) loci translocations, translocations involving *MLL*, the *SIL-TAL1* fusion gene, the *CALM-AF10* fusion gene, the *NUP214-ABL1* fusion gene, and del(6) q are also commonly reported cytogenetic abnormalities [6]. Analysis of adult Philadelphia chromosome (Ph)-negative ALL (both B-ALL and T-ALL) patients enrolled on MRC UKALL XII/ECOG E2993 identified t(4;11), *KMT2A* translocation, t(8;14), complex karyotype (⩾ 5 chromosomal abnormalities), and low hypodiploidy (30–39 chromosomes)/near triploidy (60–78 chromosomes) as aberrations with inferior outcomes. Patients with hyperploidy and del(9p) had improved outcomes [7]. However, given increased identification of specific molecular aberrations in T-ALL and the role of measurable residual disease (MRD) status, the prognostic impact of cytogenetics has become less apparent.

Notch1 is a ligand-activated transcription factor that directly influences gene expression within the nucleus, and greater than 50% of T-ALL patients have an activating mutation in *NOTCH1* [8–10]. Normal Notch1 signaling is essential for directing hematopoietic stem cells to a T cell fate; knockout of *NOTCH1* leads to early T cell arrest and accumulation of B cells [11]. Constitutive Notch1

Table 1. Common molecular aberrations in adult T-ALL

Gene	Type of genetic aberration	Frequency in adult T-ALL (%)
NOTCH1 signaling pathway		
	NOTCH1	Activating mutations
57		
FBXW7	Inactivating mutations	14
Cell cycle		
	CDKN2A	9p21 deletion
55		
	CDKN2B	9p21 deletion
46		
Transcription factors		
TAL1	Chromosomal rearrangements/super-enhancer mutations/deletions/expression	34
LMO2	Chromosomal rearrangements/deletions/expression	21
TLX1	Chromosomal rearrangements/deletions/expression	20
MYB	Chromosomal rearrangements/duplications	17
ETV6	Inactivating mutations/deletions	14
WT1	Inactivating mutations/deletions	11
RUNX1	Inactivating mutations/deletions	10
Signaling		
DNM2	Inactivating mutations	13
JAK3	Activating mutations	12
IL7R	Activating mutations	12
Epigenetic factors		
PHF6	Inactivating mutations/deletions	30
DNMT3A	Inactivating mutations	14
EZH2	Inactivating mutations/deletions	12

Genetic aberrations reported in greater than 10% of adult T-ALL patients were included. Adapted from Girardi et al. [4•]

activation leads to T cell development with a failure to produce B-lymphocytes, which is thought to be the reason for the high prevalence of activating mutations in T-ALL [12]. Acquisition of aberrations in pathways downstream of *NOTCH1* or genes implicated in T cell development can further contribute to leukemogenesis [10, 13]. Alternatively, mutations in genes such as *FBXW7* that lead to constitutive Notch1 signaling can drive leukemogenesis as well [14].

Other commonly found molecular aberrations in T-ALL include mutations resulting in activated kinase signaling within the JAK/STAT, PI3K-AKT, and RAS-MAPK pathways [4•]. Molecular aberrations in genes responsible for epigenetic

changes are also found in greater than 50% of adult T-ALL cases [15]. Trinquad and colleagues found that activation of the Notch1 pathway via mutations in *NOTCH1* or *FBXW7* was associated with better overall outcomes in T-ALL patients. This benefit was abrogated, however, if a concurrent *PTEN* or *RAS* mutation was present. The mutational status of these genes retained prognostic significance even with multivariate analysis incorporating traditional high-risk factors [16]. Beldjord and colleagues confirmed the presence of this high-risk genetic profile in T-ALL, which is defined by the absence of a *NOTCH1/FBXW7* mutation and/or the presence of a *RAS* mutation and/or a *PTEN* alteration [17].

Others have also evaluated gene expression signatures to describe aberrantly expressed genes important to leukemogenesis in T-ALL. Ferrando and colleagues described 5 oncogenes that are frequently aberrantly expressed in the absence of chromosome abnormalities: *HOX11*, *TAL1*, *LYL1*, *LMO1*, and *LMO2*. They identified gene expression signatures that corresponded with stage arrest within thymocyte development: *LYL1*+ signature (pro-T), *HOX11*+ (early cortical thymocyte), and *TAL1*+ (late cortical thymocyte). The HOX11+ signature was associated with a favorable prognosis, while the other expression signatures correlated with a poorer prognosis [8].

Coustan-Smith and colleagues identified an additional T-ALL subtype via gene expression profiling, early T cell precursor ALL (ETP-ALL). This subtype is characterized by pluripotency and shared features with both hematopoietic stem cells and myeloid progenitor cells. The characteristic immunophenotype for ETP-ALL is CD1a-, CD8-, CD5 (weak), and positive for 1 or more stem cell or myeloid antigens [18]. In contrast, Pro-T-ALL is typically CD7+ and precursor T-ALL typically is either CD2+, CD5+, and/or CD8+ [2]. Some, but not all, pediatric studies suggest that the ETP phenotype may have slower disease clearance and adverse outcomes [19]. In an adult cohort of patients with T-ALL/lymphoblastic lymphoma treated at the MD Anderson Cancer Center, 17% had the ETP subtype. In their study where the hyper-fractionated cyclophosphamide, vincristine, adriamycin, and dexamethasone (Hyper-CVAD) regimen was used, the ETP-ALL/lymphoblastic lymphoma (LBL) patients were found to have significantly lower complete remission rates (73% versus 91%, $p = 0.03$) and poorer median overall survival (20 months versus not reached, $p = 0.008$) in comparison with other T-ALL/T-LBL patients [20••]. Mutational analysis of ETP-ALL has identified that greater than 60% of ETP-ALL cases have genetic mutations leading to dysregulation of the JAK/STAT pathway [21], which may serve as a potential therapeutic target.

Therapeutic approach

Combined chemotherapy treatments of ALL have historically focused on pediatric populations, and they have not distinguished between T- and B-immunophenotypes of ALL. Treatment regimens in pediatric populations of ALL achieve great success with 5-year survival rates among the 80–90% range [22], compared with much lower historical overall 5-year survival rates of 30–40% among adults [23, 24]. In addition to this discrepancy by age, very few studies to date have sought to distinguish T-ALL from B-ALL when evaluating the impact of particular components of a treatment regimen.

As previously mentioned, T-ALL occurs more commonly in AYAs; therefore, a directed focus on T-ALL may be particularly important in this population. Retrospective analyses of treatment of the AYA population—defined broadly as ages 15–39 years—demonstrated that patients treated with a classically pediatric chemotherapy regimen fared better in long-term survival rates as compared with contemporary older adult regimens [25]. The historical differences in observed outcomes are thought to be multifactorial—less favorable underlying genetic differences of AYA B- and T-ALL [26], less frequent clinical trial enrollment in the AYA population, and differences in the intensity of treatment between pediatric and AYA populations [25, 27]. Pediatric regimens contain significantly higher cumulative doses of asparaginase [28–30]; however, T-lymphoblasts may be more resistant to asparagine depletion in comparison to B-lymphoblasts [31, 32].

Several prospective studies addressed the feasibility and efficacy of using pediatric-inspired regimens to treat ALL in AYA populations, administered in adult treatment settings. These landmark studies showed acceptable tolerability of these pediatric regimens in AYA patients and are discussed in further detail below [33–37]. All of these studies enrolled ALL patients regardless of B or T cell immunophenotype, with each of them having a minority of T-ALL patients. The backbone of the non-myelosuppressive drugs used in pediatric induction regimens include glucocorticoids, vincristine, and asparaginase, along with early and prolonged CNS prophylaxis [25]. Given the focus of this review, we describe below those studies where evaluation of outcome by T- versus B-immunophenotype was included in the publication.

The PETHEMA ALL-96 trial sought to evaluate a pediatric-based regimen in the AYA population with newly diagnosed ALL. The regimen was well tolerated in this population, with a 6-year overall survival (OS) of 69%, but outcomes were not specifically reported for T-ALL patients within this study [38]. The Augmented Berlin-Frankfurt-Münster (ABFM) regimen has also been studied in the AYA population. Rytting and colleagues treated 106 newly diagnosed ALL patients ages 12–40 with the ABFM regimen and compared them with 102 historical AYA patients treated with Hyper-CVAD. The 5-year OS was 60% for both treatment regimens; however, outcomes specific to T-ALL patients treated with ABFM were not reported [39]. Multiple other studies evaluating AYA patient outcomes, however, have specifically reported on outcomes in T-ALL patients.

The GRAALL-2003 study evaluated 225 patients with previously untreated ALL from 2003 to 2005; 33% of these patients had T-ALL. Their regimen used a modified pediatric backbone with intensified asparaginase, vincristine, and prednisone—as well as shortened interval treatment times, intensified CNS prophylaxis, but with retention of cranial irradiation as part of the protocol. There was a trend toward better outcomes for T-ALL, with EFS at 3.5 years at 62%, compared with 52% in B-ALL ($p = 0.09$). Notably, a poor early response to therapy did not have a negative impact on the disease-free survival (DFS) of patients with T-ALL as it did in patients with B-ALL [37].

The Dana-Farber Cancer Institute study also set out to determine whether pediatric regimens were well tolerated and effective in adults aged 18–50 with new diagnoses of ALL. They enrolled 92 patients between June 2002 and February 2008, with 20% subtyped as T-ALL. The 4-year OS was 67%, with a 4-year DFS of 69% in patients that achieved a complete remission (CR).

Additionally, this regimen used a 30-week asparaginase regimen, with 72% of adults completing it in the study, with similar toxicity rates as compared with children. An important additional contribution of this study was that it showed improved outcomes for T-ALL patients, with 89% achieving a CR, 4-year DFS of 87% (versus 64% in B-ALL), and an OS of 76% (versus 53% in B-ALL), although these improved survivals compared with B-ALL were not statistically significant ($p = 0.20$) [34].

The Cancer and Leukemia Group B (CALGB) 10403 study likewise investigated the feasibility of employing a pediatric regimen in AYA ALL patients and recruited newly diagnosed precursor B or T cell ALL, without prior non-emergent treatment, for ages 17–39 between 2007 and 2012 [35••]. The treatment regimen used was identical to that of the Children's Oncology Group (COG) AAL0232 study [40]. They recruited 295 patients, of whom 24% were T-ALL. There were no significant differences in treatment outcomes between T and B cell immunophenotypes, with a 3-year OS of 68% in T-ALL patients versus 74% among B-ALL patients ($p = 0.40$), and 67% 3-year DFS in T-ALL versus 68% in B-ALL ($p = 0.94$) [35••].

The Nordic Society of Pediatric Hematology and Oncology (NOPHO) ALL2008 study was the first population-based study of newly diagnosed Ph-negative B-ALL patients as well as T-ALL patients, enrolling a total of 1509 patients aged 1–45 between 2008 and 2014, with 18% of these being T-ALL. They showed a statistically significant increasing incidence of T-ALL with age and a 5-year event-free survival (EFS) of 74% in T-ALL as compared with 86% in B-ALL ($p < 0.001$), despite risk group-adapted therapy [33]. In a subsequent sub-analysis of the T-ALL patients, relapse risk and MRD rates were similar among children and adults, whereas the treatment-related death rate was increased in adults. The OS of the entire cohort at 5 years was 74%, but only 65% in the high-risk group ($p = 0.01$), which was defined by biological risk stratification [41••].

Finally, the COG AALL0434 study enrolled 1596 patients exclusively with T-ALL between the ages of 1–31, between 2007 and 2014, and aimed to compare outcomes between different styles of methotrexate intensification: Capizzi-style, intravenous methotrexate (C-MTX) and Berlin-Frankfurt-Münster high-dose intravenous methotrexate (HD-MTX). Although approximately 90% of patients in this study also received prophylactic or therapeutic cranial irradiation, they found significantly improved survival with the C-MTX regimen. In the C-MTX arm, there was a 5-year DFS of 91.5% versus 85.3% for HD-MTX ($p = 0.005$) and an OS of 93.7% in the C-MTX arm, versus 89.4% for HD-MTX ($p = 0.036$) [36••]. The 2 × 2 pseudofactorial design also studied the inclusion of nelarabine in the frontline setting and will be discussed later.

Overall, these studies have established the tolerability and efficacy of pediatric regimens despite the varying therapeutic backbones tested and have established the upper age limit of tolerability between 45 and 55 years. The data on efficacy of these regimens in T-ALL subtypes has been somewhat limited given the dominance of B-ALL in these studies, but overall, there have been no significant differences in outcomes between B-ALL and T-ALL with existing regimens (Table 2). Despite this, emerging evidence and studies may point toward unique therapies that are beneficial in T-ALL as a distinct disease entity, and forthcoming studies may shed new clinical light on improved outcomes for these patients.

Table 2. Multi-agent frontline regimens with outcome specific to T-ALL

Trial	T-ALL patients (n)	Disease-free survival	Overall survival	Comments	Reference
COG AALL0434	1596	91.5 versus 85.3, 5 years*	89.5%, 5 years	Enrolled T-ALL patients ages 1–30	[36••]
]UKALL XII/ECOG 2993	356	58%, 5 years	48%, 5 years	Enrolled Ph-negative ALL patients ages 15–59	[3]
NOPHO-ALL2008	278	74%, 5 years**	75%, 5 years	Enrolled Ph-negative ALL patients ages 1–45	[41••]
GRAALL-2003	76	63%, 3.5 years	60%***	Enrolled Ph-negative ALL patients ages 15–60	[37]
CALGB 10403	71	65%, 3 years (DFS)	68%, 3 years	Enrolled Ph-negative ALL patients ages 17–39	[35••]
MDACC Hyper-CVAD	38	55%, 5 years	48%, 5 years	Enrolled ALL patients ages 15–92	[42]
CALGB 8811	31	57%, 3 years	69%, 3 years	Enrolled ALL patients ages 16–80	[24]
DFCI 01-175	18	87%, 4 years	76%, 4 years	Enrolled ALL patients ages 18–50	[34]

*2 × 2 pseudofactorial design with patients randomized to high-dose methotrexate (HD-MTX) versus Capizzi methotrexate (C-MTX), and the addition of nelarabine to the frontline setting versus not. The reported DFS is C-MTX versus HD-MTX
**Event-free survival was reported but not disease-free survival
***Overall survival in all patients enrolled on study, specific T-ALL data not available

Older adults with T-ALL

Much like what has been seen in the AYA population, current treatment recommendations for older patients with T-ALL are based largely on studies conducted in ALL populations as a whole. Clinical trials specific to older adults with T-ALL have been rarely conducted. The decreased prevalence of T-ALL in older patients, and often exclusionary nature of clinical studies to this age group, is a potential reason for this paucity of evidence. In one study, for example, T-lineage was found in only 8% of ALL patients over the age of 60, compared with 29% for those under the age of 60 [43].

In comparison with younger patients with T-ALL, older patients have been shown to have decreased CR and OS rates. In the UKALL XII/ECOG 2993 trial, for example, CR rates for those with T cell disease were as follows: 98% at ages 15–19 and 20–29, 93% at ages 30–39 and 40–49, and 79% in those age 50 and older. OS ranged from 46 to 53% for those under the age of 50, but was 27% for those older than 50 ($p = 0.009$) [3].

While older patients typically fare worse than their younger cohorts, in some of the older clinical studies that included all adults over the age of 18 years, patients with T-ALL appeared to have equal or improved outcomes when

compared with B-ALL patients. In the CALGB 8811 study, high-intensity induction chemotherapy consisting of cyclophosphamide, daunorubicin, vincristine, asparaginase, and prednisone produced a CR of 97% in 31 patients with T-ALL. The 3-year survival rate for these patients was 69%, compared with 38% for those with B-ALL. Age-adjusted analysis of these T cell patients was not available [10]. Furthermore, in a meta-analysis of 11 studies in ALL patients with ages ranging from 15 to 92, T-ALL patients were found to have superior survival compared with B-ALL patients. The use of dexamethasone, higher total doses of methotrexate (MTX), and a higher total dose of L-asparaginase were also associated with improved outcomes in T-ALL patients compared with B-ALL patients [44].

Another regimen commonly considered for adults is Hyper-CVAD [31]. An analysis of outcomes of all adult patients treated with Hyper-CVAD at MD Anderson Cancer Center demonstrated a 95% CR rate in those with T-ALL, a 5-year continuous CR of 55%, and a 5-year OS of 48% [42]. However, when Hyper-CVAD has been studied at other centers, the outcomes have been poorer. Data from Sweden demonstrated a relapse rate of 83% in adults over the age of 35 that received hyper-CVAD and did not receive an allo-SCT in CR1 [45]. In addition, a multi-center retrospective study noted a relapse rate of 69.8% in adult T-ALL patients treated with Hyper-CVAD [46].

As noted above, there is little specific evidence for treatment outcomes in older adults with T-ALL. The optimal intensity of induction therapy in these patients should consider the risk of toxicity while not forfeiting clinical effectiveness. An individual's performance status and overall level of functioning should also be considered. While there is no general consensus, a moderate- to high-intensity regimen with specific dose modifications for some of the agents that have significant increases in toxicity with age (glucocorticoids, asparaginase, vincristine) may be the most likely to result in high CR rates with improved DFS [47]. Newer approaches to treatment of T-ALL that are being tested in early-phase trials may be important steps to the development of less toxic, more effective approaches for these older patients.

Allogeneic stem cell transplantation in the era of MRD

A number of factors should be considered when recommending allo-SCT in T-ALL patients; these include the presence of high-risk disease at diagnosis, achievement of a second complete remission (CR2) or later, and the presence of MRD. High-risk factors at diagnosis of T-ALL include white blood cell (WBC) count over 100,000/μL, age greater than 35 years, CNS involvement, complex karyotype, residual disease at day 15 post-induction, and the need for more than one induction regimen to achieve a CR [48, 49, 50•]. However, the MRD status of T-ALL patients as they approach allo-SCT is taking on growing significance in comparison with these other risk factors.

A number of studies have evaluated the role of allo-SCT in T-ALL without incorporation of MRD data. Marks and colleagues prospectively evaluated 356 T-ALL patients on the UKALL XII/ECOG 2993 trial, of which 107 received an allo-SCT while in a CR. They found that 5-year OS in patients with a matched sibling donor compared with those without donors was 61% versus 46%, respectively ($p = 0.02$). This survival benefit was primarily driven by lower rates

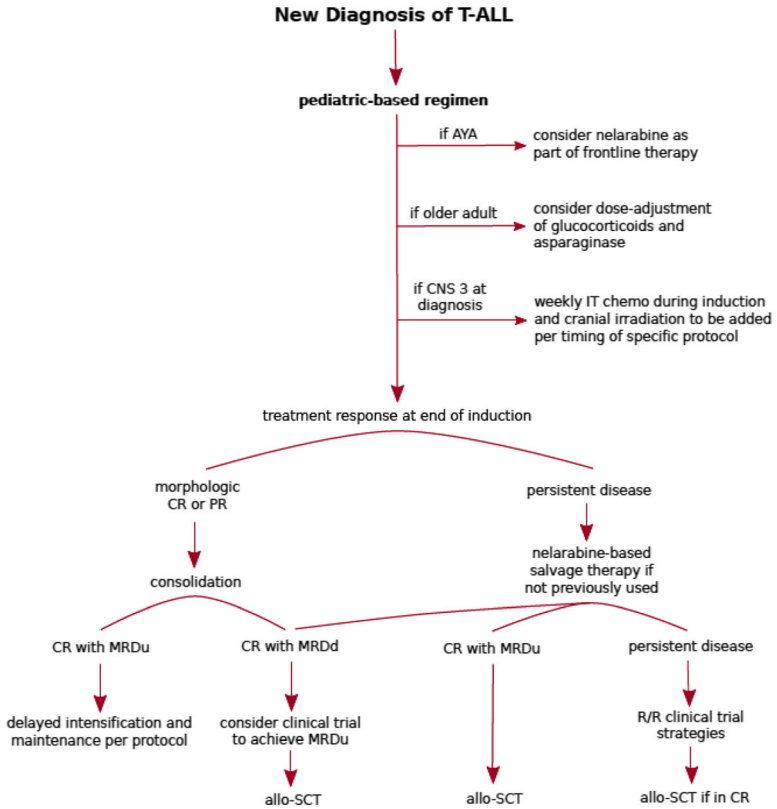

Fig. 1. Treatment considerations in T-ALL. T-ALL, T cell acute lymphoblastic leukemia; AYA, adolescent/young adult; CNS, central nervous system; IT, intrathecal; CR, complete remission; PR, partial response; MRDu, undetectable measurable residual disease; MRDd, detectable measurable residual disease; R/R, relapsed/refractory; allo-SCT, allogeneic stem cell transplant.

of relapse [3]. Bakr and colleagues reported on allogeneic transplantation outcomes in high-risk T-ALL patients. Of those who underwent allogeneic transplantation in CR1, 5-year OS was 53.5% with 5-year DFS of 52.0%. In comparison, those patients in CR2 or later had 5-year OS of 31.9% and 5-year DFS of 29.4% ($p < 0.001$ for both DFS and OS) [49]. Hamilton and colleagues retrospectively evaluated 208 adult T-ALL patients who underwent allo-SCT at 13 North American centers; 1-year OS across the entire cohort was 58%, and 5-year OS was 34%. Utilization of total-body irradiation (TBI) regimens was associated with improved OS. Risk factors for poorer survival on multivariate analysis included relapsed or refractory (R/R) disease at time of allo-SCT and age 35 years or older [50•]. A retrospective analysis by the European Society of Blood and Marrow Transplantation (EBMT) of 601 T-ALL patients undergoing allo-SCT found a leukemia-free survival benefit of a TBI conditioning regimen in patients under the age of 35 [51].

The role of allo-SCT has been studied in ETP-ALL as well. Of the 213 T-ALL patients treated on the GRALL-2003 or GRALL-2005 clinical trial, 47 were classified as ETP-ALL. Patients could be considered for allo-SCT if they had CNS involvement at diagnosis, corticosteroid resistance, early bone marrow chemotherapy resistance, or failure of remission induction [52]. Due to these criteria, a greater percentage of ETP-ALL patients (48.9%) received an allo-SCT in CR

compared with other T-ALL patients (28.3%). Despite higher rates of treatment resistance in ETP-ALL, 5-year OS was not statistically different in the ETP cohort (59.6%) compared with the non-ETP cohort (59.6% versus 66.5%, $p = 0.33$). When censoring for allo-SCT, however, the 5-year OS in the ETP-ALL cohort was significantly inferior to the non-ETP cohort (49.2% versus 67.4%, $p = 0.02$) [52]. This suggests that allo-SCT in CR1 for ETP-ALL may result in similar long-term outcomes compared with non-ETP patients. Of note, ETP-ALL patients were significantly more likely to have detectable MRD post-induction in comparison with non-ETP patients (71.4% versus 20.9%, $p < 0.001$) [52].

MRD status has been well-established as having prognostic significance in ALL with MRD-detectable (MRDd) patients having poorer OS [17, 53]. Gokbuget and colleagues specifically looked at ALL patients enrolled on German Multicenter Study Group for Adult ALL (GMALL) 06/99 and 07/33 and achievement of MRD after induction therapy. MRD assessment was done by real-time quantitative PCR (RT-PCR) with a sensitivity of 0.01%. A total of 89% of ALL patients achieved a cytologic CR. Of the patients in a CR with evaluable MRD at day 71, 79% of T-ALL patients were MRD-undetectable (MRDu) compared with 66% of B-ALL patients ($p < 0.0001$). When analyzing OS in all enrolled patients, those who were MRDu at week 16 had a 5-year OS of 81% versus 43% in patients with detectable MRD ($p < 0.0001$). Furthermore, multivariate analysis of multiple high-risk prognostic factors showed MRD as the only factor having significant prognostic effect upon continuous CR at 5 years. Age and MRD were the only factors with significant prognostic effect on 5-year OS [53]. MRD assessment has also been shown as a means of categorizing T-ALL patients as high-risk if they have detectable disease 6 weeks after initiation of induction. Interestingly, genetic profile appears to have a larger impact on prognosis than MRD status [17].

Brammer and colleagues analyzed 102 T-ALL patients who underwent allo-SCT, of whom 84 were MRD-assessable while in a CR. MRD determination was made via flow cytometry immunophenotyping with a sensitivity of 0.01%. Patients who were MRDd at time of transplant had significantly higher rates of 3-year progression (76%) compared with those who were MRDu (34%) with a hazard ratio (HR) of 2.8 ($p = 0.006$). There was no significant difference in OS or PFS between subtypes, including ETP [54•].

Given the importance of MRD assessment in T-ALL, it is essential to identify a means of monitoring MRD for all patients. Flohr and colleagues reported that 16% of T-ALL patients did not have a sensitive target via RT-PCR in comparison with 8% of B-ALL patients [55]. With this in mind, Modvig and colleagues sought to establish MRD assessment via flow cytometry as a reliable methodology in T-ALL. Of the 274 T-ALL patients evaluated as part of the NOPHO-ALL2008 study, 93% of patients had a flow cytometry marker appropriate for MRD monitoring and 84% had an appropriate RT-PCR marker, with only 0.7% of patients having no flow markers or RT-PCR markers appropriate for MRD monitoring. Furthermore, MRD assessment by flow cytometry was shown to have strong correlation with RT-PCR. Assessment of MRD by flow cytometry was done at day 29; those with MRDu had a 5-year EFS of 86%, those with MRD levels between 0.01–0.1% had a 5-year EFS of 83.6%, and those with MRD levels between 0.1–1.0% had a 5-year EFS of 70.2% [56]. Given the prognostic significance of MRD, ensuring that all T-ALL patients have a reliable means of undergoing assessment will be essential in appropriate management of this

patient population. In addition, as MRD continues to be incorporated into clinical trial protocols, it may become the factor that dictates pursuing allo-SCT as opposed to the traditional high-risk prognostic factors. Beyond MRD, other management decisions regarding allo-SCT may play a role in outcomes as well.

When considering allo-SCT for T-ALL, a number of factors should be taken into consideration in the current treatment era. Well-established high-risk factors include MRDd disease and patients that have R/R disease. There may be a benefit to pursuing allo-SCT in CR1 for ETP-ALL patients; however, it is unclear if that is necessary in those that are MRDu. In addition, converting MRDd disease into MRDu prior to allo-SCT may offer improved progression-free survival. While a high-risk genetic profile based upon *NOTCH1*/*FXBW7*/*RAS*/*PTEN* mutational status has prognostic value, its relevance in a transplant population has not yet been established. Other transplant-related factors associated with improved outcomes include having a matched sibling donor, being transplanted in CR1, being under the age of 35, and receiving a TBI conditioning regimen if one undergoes allo-SCT under the age of 35.

Management considerations in T-LBL

The 2016 WHO classification places T-LBL in the same category as T-ALL due to the overlapping morphology and immunophenotype [57]. Despite these similarities, gene expression analysis and whole-exome sequencing have identified aberrations specific to T-LBL [58, 59]. T-LBL is typically treated in a very similar fashion to T-ALL; however, some additional considerations in diagnosis and management are generally recommended. Greater than 90% of adult T-LBL patients will have a mediastinal mass, and only a minority of patients will have bone marrow involvement [60]. If a patient has 25% or less blasts in the bone marrow with extramedullary involvement, a diagnosis of T-LBL is made. In adult patients with T-LBL, staging workup should include imaging (either CT or PET-CT) to identify all sites of disease. In addition, cerebrospinal fluid (CSF) analysis is performed to rule out CNS involvement [61].

Treatment regimens are very similar to those used for T-ALL. Hoelzer and colleagues reported outcomes on 45 adult patients treated on the GMALL 04/89 and GMALL 05/93 ALL protocols. A total of 93% of patients achieved a CR, with a 51% 7-year OS [62]. The Swedish Lymphoma Registry identified 39 adult T-LBL patients; the CR rate was 97% in those that received ALL-based induction regimens [63]. The role of mediastinal irradiation in T-LBL is somewhat unclear. A single-center retrospective analysis of 47 LBL patients treated with systemic chemotherapy was performed; 19 patients received mediastinal irradiation while 24 patients did not. While rates of mediastinal recurrence were significantly lower in the patients that received irradiation (0% versus 33%, $p = 0.01$), the systemic freedom from progression rate and OS rate was not significantly different [64]. All T-LBL patients treated on GMALL 04/89 and GMALL 05/93 received mediastinal irradiation; 7 of 15 patients that relapsed within 12 months had mediastinal relapses [62].

The GRAAL-LYSA LL03 study enrolled 148 patients with LBL, of which 131 had T-LBL. These patients were treated with a pediatric-based ALL induction regimen with a 2-year maintenance phase, and mediastinal irradiation was not included. A total of 90.8% of T-LBL patients achieved a CR or unconfirmed

complete remission (CRu), and 3-year OS was 69.2%. Of the 34 patients that relapsed, 14 had mediastinal relapses. CT imaging was utilized as the primary means of response assessment. Sixty-eight T-LBL patients received PET scans at the end of induction in addition to CT imaging; however, PET results did not offer additional information regarding EFS, DFS, OS, or mediastinal relapse [65•]. A post-hoc analysis only identified initial standard uptake value (SUV) ≤ 8.76 as a statistically significant PET parameter predictive of inferior outcomes [66].

When considering CNS prophylaxis strategies in T-LBL, there has been considerable heterogeneity in what has been evaluated prospectively. GMALL 04/89, GMALL 05/93, and COG AALL0434 utilized intrathecal therapy alone, while the GRAAL-LYSA LL03 study treated patients with both intrathecal chemotherapy and cranial irradiation for CNS prophylaxis [62, 65].

In summary, utilization of pediatric-based ALL regimens in T-LBL has led to favorable outcomes in the adult population. The role of mediastinal irradiation and which CNS prophylaxis strategy to recommend remain somewhat unclear, although prophylactic cranial irradiation is now avoided and the period of long-term maintenance therapy in pediatric trials in the USA and Europe has been limited to approximately 2 years. Regarding response assessment, CT imaging has been traditionally incorporated into prospective trials and PET imaging seems to not offer additional information regarding outcomes.

CNS disease in T-ALL

Studies of adult ALL patients have shown that about 5% of patients have CNS disease at diagnosis, with a higher proportion of T-ALL patients (9.6%) being affected than B-ALL (4.4%) [67]. Comparing again the treatment of pediatric populations of T-ALL with older patients, children received more CNS prophylaxis, earlier treatment, and more maintenance intrathecal (IT) treatment than typical adult regimens [25]. The determination of CNS involvement is made at diagnosis based on the number of blasts and WBC count in the CSF [68].

From the earliest studies of ALL particularly in children, a significant risk of disease relapse with CNS involvement was observed, and marked improvements in relapse rates were seen with the introduction of CNS-targeted treatment—initially with cranial irradiation; however, the adverse long-term side effects of extensive radiation prompted the evaluation of less extensive radiation and, eventually, the complete omission of radiation from many pediatric regimens. Importantly, several early studies in children demonstrated that IT treatment was non-inferior to cranial irradiation among all ALL patients [69], but when subgrouped to T-ALL patients, there remained concern that the occurrence of CNS events and relapse was higher in patients who were not irradiated [70].

St. Jude Total Therapy Study 15 and Study 16 both evaluated treatment of children with ALL without cranial irradiation, with appropriate intensification of systemic treatment compared with historical treatments. In Total Therapy Study 15, 498 children aged 0–18 were enrolled between 2000 and 2007 and 15% of cases were T-ALL. The investigators found significantly longer rates of continuous complete remission when compared with 56 historical controls that

received cranial irradiation ($p = 0.04$). Overall, the 5-year EFS was 85.6% and 5-year OS was 93.5% for the 498 patients enrolled on the study. The 5-year cumulative risk of isolated CNS relapse was 2.7% and that of any CNS relapse was 3.9%. Of note, inferior outcomes were noted among T-ALL patients in comparison with B-ALL patients, with worse 5-year EFS (78.4% versus 86.9%, $p < 0.001$) and 5-year OS (87.6% versus 94.6%, $p = 0.013$) [71]. In addition, the T cell immunophenotype was more associated with CNS relapse in comparison with the B cell immunophenotype (HR 2.1, $p = 0.07$). Study 16 also evaluated a regimen without cranial irradiation; the T cell immunophenotype was the only independent risk factor for CNS relapse (HR 5.15, $p = 0.021$) [72•]. Overall, this pediatric work established the feasibility of systemic treatment without cranial irradiation, particularly as newer targeted therapies for systemic treatment emerge.

Of the studies discussed above in treatment of AYA patients, only one of these included prophylactic CNS irradiation [73] with 37 out of 723 patients (5.1%) experiencing CNS relapse, while other studies that only used IT treatment for CNS prophylaxis had comparable isolated CNS relapse rates at 9 out of 295 (3.7%) in CALGB 10403 [35••] and 6 out of 278 (2.1%) in NOPHO2008 among T-ALL patients [41••]. Of note, patients enrolled on CALGB 10403 who had T-ALL or CNS involvement at diagnosis received cranial irradiation in the first cycle of maintenance therapy [35••].

These studies altogether suggest that reducing the risk of isolated CNS relapse can be achieved through risk-stratified and -intensified systemic treatments without using cranial irradiation in the AYA population, thus avoiding its long-term associated toxicities. Unfortunately, the same degree of prospective data in the older adult population is not present.

Treatment of relapse in T-ALL

The goal of treatment of relapsed disease is to induce a remission (optimally MRDu) that would then permit patients to proceed safely and rapidly with potentially curative allo-SCT. Historically, treatment in relapsed/refractory (R/R) T-ALL has been characterized by short responses and high treatment-related mortality. Combination cytarabine-based chemotherapy in R/R T-ALL achieved remission rates ranging from 34 to 56%; however, toxicities were significant and ability to proceed to allogeneic transplant was relatively low [74–76]. A retrospective single-center study reported 1-year survival of 24% in this patient population [75].

In 2007, the CALGB reported on the use of nelarabine, a T cell-specific purine nucleoside analog, in patients with R/R T-ALL/T-LBL in patients over the age of 16. Thirty-nine patients who were either refractory to induction treatment or in first or later relapse were ultimately treated on protocol. None had active CNS disease at the time of study enrollment. The overall response rate with single-agent nelarabine was 41%, with 31% of patients achieving a CR or CR with incomplete hematologic recovery (CRi). For the entire treated cohort, 1-year survival was 28%. Seven patients who achieved a response ultimately went on to allo-SCT [77]. This resulted in approval of nelarabine for treatment of relapsed T-ALL in 2005—to date, this remains the only agent specifically approved for relapsed T-ALL. The efficacy of nelarabine in R/R T-ALL

has been demonstrated in other studies as well. GMALL enrolled 126 adults with R/R T-ALL onto a prospective phase II study evaluating single-agent nelarabine. A total of 32% of patients achieved a CR following one cycle of nelarabine, with an additional 19% achieving a partial response (PR). The CR rate increased to 36% in patients who received up to 3 cycles of nelarabine, and 36 of 45 patients in a CR went on to allo-SCT. In the entire cohort, 1-year OS was 24% and 3-year OS was 12%; for the patients who received transplant, 1-year OS was 49% and 3-year OS was 36% [78]. Luskin and colleagues reported on the administration of nelarabine in sequential combination with cytarabine and etoposide (NCE) in adults with R/R T-ALL based upon the experience of this regimen in the pediatric population [79, 80]. Five patients were treated and three achieved a CR, two of whom went onto allo-SCT and the third progressed during the third cycle of NCE while awaiting allo-SCT. However, the two other patients treated with NCE died due to treatment-related toxicity. Additional combination therapies with nelarabine are being actively researched in the R/R setting, particularly given in vitro synergy between nelarabine and PI3K inhibitors [81].

Given the approval of nelarabine and its efficacy as a single agent for patients with relapsed disease, nelarabine has been studied recently as a component of therapy for newly diagnosed T-ALL. The COG AALL0434 trial enrolled newly diagnosed T-ALL patients from ages 1–31 [36••, 82••]. As part of its 2 × 2 pseudofactorial design, patients were randomized to receive a pediatric-based induction regimen with or without nelarabine. In the nelarabine-treated group, 4-year DFS was 88.9% versus 83.3% in the arm without nelarabine ($p = 0.0332$) [82••]. While this suggests a benefit of the addition of nelarabine to induction therapy in the AYA population, the utility of doing so in an older population remains unclear and additional outcome analysis of the AALL0434 study awaits formal publication.

Abaza and colleagues studied the addition of nelarabine to Hyper-CVAD in the frontline setting, and while it was safely tolerated, there was no significant improvement in OS rates and CR duration among treatment-naive/minimally treated adult T-ALL and T-LBL patients [83]. A phase II study evaluating the role of nelarabine in frontline treatment of adults aged 25–65 years old with T-ALL aims to answer questions of efficacy more definitively (NCT01085617) [84].

Currently, treatment strategies in the R/R setting remain quite limited with nelarabine serving as the backbone. However, with studies evaluating nelarabine in the frontline setting, additional therapeutic options need to be established for those that progress after exposure to nelarabine in the future.

Novel therapies

Discovery of novel agents with efficacy in treating R/R ALL is an area of active research. Developing such new therapies relies upon expanding the knowledge we have about the genetic landscape of T-ALL and includes inhibition of aberrant transcriptional activation, BCL, and the proteasome. There are also preclinical and early-phase studies to evaluate the impact of antigen targeting with anti-CD38 antibodies and chimeric antigen receptor (CAR) T cellular therapy directed to other T cell surface proteins.

As previously discussed, more than 50% of T-ALL cases have a *NOTCH1* mutation [8–10]. Gamma-secretase inhibition has been demonstrated to inhibit the activation of Notch1, making it an intriguing therapeutic target [85]. The gamma-secretase inhibitor PF-03084014 was studied in a phase I trial in 8 patients with either T-ALL or T-LBL. Patients were enrolled independent of *NOTCH1* mutational status. The most significant toxicities noted were gastrointestinal adverse effects with the dose-limiting toxicity being elevated liver enzymes [86]. Ultimately, gamma-secretase inhibition has not been pursued in later-phase trials due to systemic toxicities from treatment; however, recent work by Habets and colleagues regarding inhibition of the presenilin-1 class of gamma-secretases may spark renewed interest in this drug class [87]. Preclinical studies of the proteasome inhibitor bortezomib have identified its ability to repress transcription of Notch1 in addition to synergizing with dexamethasone, doxorubicin, and cyclophosphamide [88]. Given these findings, there are active studies investigating combination therapies with bortezomib. Horton and colleagues reported on the addition of bortezomib to an induction chemotherapy regimen in the phase II setting for patients with R/R B-ALL, T-ALL, and T-LBL. Patients were aged 1–31 years with 22 having R/R T-ALL and 10 having R/R T-LBL. A CR rate of 69% was seen in this subset of the study population, making it an appealing option to study as a bridge to transplantation [89]. There is also a limited experience with combination of bortezomib with the BCL-2 inhibitor venetoclax; three adult patients with R/R T-ALL were treated with bortezomib-venetoclax based on drug response profiling, and all three patients responded to and one patient achieved a CR [90].

Given the particularly high incidence of relapse in ETP-ALL, much work has been done to better understand the aberrant pathways in this disease process. The high prevalence of genetic mutations causing dysregulation in the JAK/STAT pathway has inspired potential targeted therapeutic interventions. Patient-derived xenograft (PDX) models were generated from pediatric ETP-ALL samples, and JAK/STAT pathway activation was noted even in the absence of *JAK2* mutations. Five out of six PDX models responded to treatment with the JAK inhibitor ruxolitinib [91]. Work by Delgado-Martin and colleagues also provides preclinical evidence that JAK inhibition improves sensitivity to glucocorticoids in ETP-ALL PDX models [92]. However, these preclinical insights have not yet translated into prospective clinical trials specifically in ETP-ALL.

Another potential therapeutic strategy in R/R T-ALL is to target survival pathways via BCL inhibition. BCL-2, an anti-apoptotic protein, has been shown to be over-expressed in T-ALL with both in vitro and in vivo sensitivity to venetoclax [93]. Retrospective analysis of venetoclax combined with intensive chemotherapy in R/R T-ALL showed that of 13 patients analyzed, 10 were evaluable for bone marrow response, and three patients were noted to be in CR, one patient in CRi, and two patients in a morphologic leukemia-free state. Median OS was 7.7 months and median relapse-free survival was 4.0 months, suggesting a limited durability of response [94]. Venetoclax is currently being studied prospectively as well; one particularly effective combination appears to be venetoclax and the BCL-2/BCL-XL/BCL-W inhibitor navitoclax. Early-phase data presented by Lacayo and colleagues discussed the venetoclax-navitoclax combination in R/R ALL; 36 patients with a median age of 29 years old have been enrolled on protocol, 16 of whom have T-ALL. A total of 37.5% of T-ALL patients achieved a CR or CRi [95]. Additional work is needed to evaluate the

optimal dosing to prevent cytopenias, but this approach appears to be quite promising with complete responses reported in a heavily pre-treated patient population. Longer follow-up will be necessary to determine the durability of response.

Daratumumab is an anti-CD38 monoclonal antibody approved for treatment of multiple myeloma, and CD38 appears to be an excellent potential therapeutic target for T-ALL. Bride and colleagues evaluated expression of CD38 in 21 T-ALL patient samples and found that all 21 samples had robust expression that persisted even with exposure to cytotoxic chemotherapy, suggesting that it may be a useful target both at diagnosis and at relapse. They created 15 murine PDX models and observed robust antitumor activity in both standard precursor T and ETP PDX mice but noted significant toxicity in the non-ETP mice. The primary driver of toxicity was thought to be massive tumor lysis syndrome, suggesting significant anti-leukemia activity [96]. Daratumumab has also been established as a means of eradicating MRD in PDX T-ALL models [97]. A multi-center phase II trial evaluating daratumumab in children with R/R T-ALL is currently underway (NCT03384654) [98]. These early preclinical and clinical trials will provide insights on how daratumumab might be best incorporated into treatment trials for adults with T-ALL.

CAR T cell therapy is being developed in the setting of T cell malignancies as well. Cooper and colleagues discuss the generation of off-the-shelf CAR T cell therapy directed at the T cell marker CD7. Generation of CAR T cells deficient in CD7 was necessary to prevent "fratricide" of these cells. The activity of the CAR-T product was established both in vitro and in vivo in a PDX model [99]. A number of potential hurdles in using autologous CAR T cell therapy in R/R T-ALL exist, including heavy pre-treatment that may hinder separation of normal T cell effectors from malignant cells and generation of CAR T cells. This suggests that an off-the-shelf product may be of particular relevance in this T-ALL population. Hill and colleagues recently presented their early-phase clinical trial experience with an autologous CD5 CAR-T product in R/R T cell malignancies including T-ALL. Four heavily pre-treated T-ALL patients were enrolled on protocol with one of them achieving a CR [100]. These are the early days of T cell-targeted cellular therapies with a number of new clinical trials on the horizon. Given the tremendous activity with this exciting approach for B-ALL patients, there is a promise for similar efficacy in patients with advanced T-ALL, as this technology further develops and more trials are initiated.

Summary

Historically, we have treated T-ALL in much the same way as B-ALL despite significant differences in their biology and genetic landscape. This treatment strategy has been successful in the frontline setting, particularly with the use of pediatric-based regimens in the AYA population. In the older adult population, we have relied upon similar treatment techniques at the expense of higher toxicity. Allo-SCT continues to have a role in high-risk T-ALL treatment, with MRD status quickly becoming the dominant prognostic factor in long-term

outcomes. In addition to systemic therapies, CNS prophylaxis is essential given the higher rates of CNS disease in T-ALL, and IT therapy achieves CNS prophylaxis at similar rates to radiation-based therapies without the long-term toxicity risks of radiation (Fig. 1). Despite our success in the frontline treatment setting, the available therapies in the R/R disease are quite limited. Nelarabine has value as a single agent but may find a role within frontline therapies of younger adults with T-ALL. Fortunately, with our growing ability to target specific disease-related pathways and develop immune-mediated therapies, a number of novel therapies that utilize our understanding of genetic aberrations within T-ALL are being actively investigated. These include therapies that inhibit Notch1 activation, JAK inhibitors in ETP-ALL, BCL inhibitors, anti-CD38 therapy, and development of expanded CAR T cell therapies.

Compliance with Ethical Standards

Conflict of interest

Anand A. Patel declares that he has no conflict of interest.
Joseph Thomas declares that he has no conflict of interest.
Alexandra E. Rojek declares that she has no conflict of interest.
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