Early precursor T-cell acute lymphoblastic leukemia: current paradigms and evolving concepts

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Abstract: Early precursor T cell acute lymphoblastic leukemia (ETP-ALL) is a rare entity characterized by chemo-resistance and a paucity of data regarding optimal management. We review here the literature regarding the management of ETP-ALL and focus on the recent, emerging data, regarding the potential role of molecularly targeted approaches with a focus on venetoclax.

Keywords: early precursor T cell acute lymphoblastic leukemia, ETP-ALL

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Introduction

T-cell acute lymphoblastic leukemia (T-ALL) is a rare hematologic malignancy in adults. A particular challenging subgroup is early precursor T cell (ETP)-ALL. ETP-ALL has distinct characteristics compared with other subtypes of T-ALL, and has attracted attention given its refractoriness to chemotherapy. In this review, we will outline the features of ETP-ALL, diagnostic challenges, and treatment outcomes. We will also outline the emerging data for targeted treatments.

ETP-ALL: a distinct entity of T-cell ALL

ETP-ALL was recognized as a new provisional entity in the 2016 update to the World Health Organization (WHO) classification of acute leukemia, and is characterized by a unique immunophenotype and genetic profile. The origin of ETP-ALL is considered to involve the migration of cells from the thymus to the bone marrow (BM). These cells, although they have characteristics of T-cell lineage commitment, continue to have the potential for myeloid/dendritic cell differentiation. As such, ETP-ALL lymphoblasts have positivity for antigens such as CD7, CD2, and cCD3, but also positivity for antigens associated with myeloid lineage, such as CD34, CD117, CD13, CD11b, HLADR, and CD65, whereas MPO is negative and CD4 may be positive in some cases. On the other hand, CD5 is negative/weakly positive (expressed in up to 75% of blasts). Notably, CD1a and CD8 are not typically detected. The CD33 and CD123 may be positive and appear to be so more frequently compared with non-ETP-ALL. Interestingly, ETP-ALL with co-expression of B-cell markers has been reported, but the numbers of patients were small. The clinical significance of B-cell marker expression is unclear.

A study raised concerns if the ETP-ALL immunophenotypic signature may lead to underestimation of ETP-ALL cases. The authors of the latter study did not include CD5 and rather utilized CD7+, with CD34+ and/or CD13+/CD33+, whereas CD1, CD4, CD8 were negative. This immunophenotypic signature identified cases with ETP-ALL gene expression signature with 94% specificity.

Mutations uncommonly seen in other subtypes of ALL are enriched in ETP-ALL patients. Such mutations include EZH2, FLT3 ITD, RAS, and RUNX1. Recently, NPM1 deletions were found to be enriched in ETP-ALL patients. The ETP-ALL cases reported in the literature do not have a uniform or pathognomonic cytogenetic...
aberration profile. PICALM-MLLT10 fusion has been reported and was associated with dismal prognosis in the context of ETP-ALL. Similarly, HOXA gene activating mutations have dismal outcomes.

ETP-ALL cases may be challenging to diagnose. Exemplifying this difficulty, in a recent publication, the authors used flow cytometry to categorize cases as definite or probable. Scoring schemas based on immunophenotypic profiles have been reported in an attempt to distinguish ETP-ALL from other leukemias. Notably, it may be challenging to distinguish ETP-ALL from mixed phenotype acute leukemia.

ETP-ALL is uncommon (reports of ETP range from 5% to 36% in T cell ALL series/studies). Limited data point towards a higher prevalence in adults compared with the pediatric population. ETP-ALL is a relatively new entity as it was not discovered until the late 2000s, and literature, especially for adults, is limited.

The interplay of transcription factors to the development of ETP-ALL has been explored only partially. A seminal study revealed that the expression of FLT3 ITD modulated the down-regulation of EZH2 and RUNX1, leading to ETP-ALL features in a mouse model. Other studies have raised the possibility that an entity termed “near/close to ETP” has a gene expression signature that is distinct from non-ETP-ALL but does not have the typical immunophenotype of ETP-ALL. Of particular interest are the findings implicating EZH2 inactivation in murine models resulting in upregulation of genes expressed in ETP-ALL.

Outcomes of conventional chemotherapy are suboptimal in adult ETP-ALL patients

Few studies have examined the impact of chemotherapy and optimal treatment management of ETP-ALL. The optimal treatment regimen for ETP-ALL remains uncertain. Studies have reported using different regimens utilizing combinations of steroids, vincristine, methotrexate, cyclophosphamide, and anthracyclines. Notably, the majority of the reported studies included a relatively small number of patients.

A study reported outcomes of patients with ETP compared with non-ETP-ALL treated under GRAALL-2003 and GRAALL-2005 protocols. The study identified 47 patients with ETP and 166 with non-ETP-ALL. The majority of ETP-ALL patients were male and younger (median age 38.5 years old), with lower white blood cell (WBC) count (median WBC 13.2 × 10⁹/l) compared with the non-ETP patients. At the molecular level, the majority of patients harbored mutations, which were clustered in the RAS signaling pathway, and involved cytokine receptors and genes involved in histone modifications. Although patients with ETP-ALL attained morphologic complete remission (CR), a higher percentage had persistent minimal residual disease (MRD) as measured on days 42 and 84. When data were censored for allogeneic hemopoietic stem cell transplant (alloHSCT), the ETP-ALL group had an inferior overall survival (OS) (49.2% versus 67.4%) compared with non-ETP-ALL, whereas event free survival (EFS) was not different.

Data from three consecutive GMALL studies were reported in 2009. Further analysis identified 57 patients with ETP-ALL (defined as CD1a–, CD8–, CD5weak with co-expression of stem and/or myeloid markers). The ETP-ALL patients comprised a sizeable fraction (32%) of early T-cell ALL (defined as sCD3–, CD1a–). Of ETP-ALL patients, 79% achieved CR after induction and the probability of survival at 10 years was 35%; 46% of patients with ETP-ALL remained at CR at 9 years of follow up.

In another study for MD Anderson Cancer Center (MDACC), outcomes of 111 patients with T-cell ALL/lymphoblastic lymphoma (LBL) were reported. Notably, 15 patients had ETP-ALL and 4 ETP-LBL. The majority of patients were male, with chromosomal aberrations (37% having diploid karyotype); 16% of patients had CNS involvement. The majority of patients (79%) were treated with hyperCVAD +/− nelarabine. Patients with ETP-ALL had significantly worse rates of CR achievement and OS (median 20 months versus NR) but comparable EFS to that of non ETP-ALL patients (the latter likely impacted by the low number of patients). Prognostic markers were not identified likely given the low number of patients. Only three ETP-ALL patients underwent alloHSCT and one maintained long-term remission.

In a small series from India, outcomes of six patients were described, and only one responded to intensive chemotherapy. In another report,
four patients received FLAG-IDA [fludarabine, cytarabine (Ara-C), granulocyte-colony stimulating factor (G-CSF) and idarubicin] early on after induction, with three achieving CR without MRD.31 One patient had a reduction in leukemic burden and subsequently received high dose cytarabine with sorafenib. All patients were able to proceed to alloHSCT, but two succumbed to complications.

The use of asparaginase in the upfront setting in ETP-ALL patients was reported to be associated with improved progression-free survival.18 A recent publication reported a cryptic inversion [inv(7)(q22.3q21.3)] in patients with relapsed ETP-ALL that led to enhanced levels of asparagine synthetase (ASNS).32 Increased levels of ASNS may play a role in conferring resistance to asparaginase.33 The importance of this finding is hampered by the limited number of reported patients and the conflicting reports regarding the ASNS role in chemo-resistance.34

A case report described a 51-year-old man with ETP-ALL and monosomy 7 as well as mutations in KRAS and DNMT3A genes.35 The patient was treated initially with the HyperCVAD regimen without response. Clofarabine and cytarabine were used as salvage leading to profound hypocellularity, and fluorescent in situ hybridization (FISH) analysis for monosomy 7 was negative. The patient was able to proceed to alloHSCT.

The management of refractory/relapsed patients with ETP-ALL is challenging. ETP-ALL lacks the targeted, United States Food and Drug Administration (FDA)-approved therapies available for relapsed or refractory Pre-B ALL such as inotuzumab ozogamicin, blinatumomab, or CAR-T cells.36,37 Therefore, outside the context of clinical trials, chemotherapy is the backbone of the salvage treatments and may include peg-asparaginase-containing regimens (e.g., augmented HyperCVAD, MOpAD),38,39 alkylating containing regimens, liposomal vincristine,40 high dose cytarabine, or nelarabine.41,42 Notably, the combination of nelarabine with the hyperCVAD was reported not to improve outcomes, with the caveat of a low number of ETP-ALL patients.20 Data comparing the efficiency of different regimens are lacking.

In a case report, again from China, a patient with ETP lymphoblastic lymphoma did not respond to a five-drug regimen including anthracycline, cytarabine, steroids, pegasparginase, and vindesine.44 However, when the modified CAG regimen was combined with low dose decitabine the patient was able to achieve CR and proceed to alloHSCT.

Notably, encouraging treatment outcomes for ETP-ALL in children have been reported. The COG AALL0434 trial included 130 ETP-ALL and 195 near-ETP-ALL patients (~28% of the 1144 patients with T-ALL enrolled).45,46 Significantly, more patients with ETP or near-ETP ALL had induction failure compared with non-ETP-ALL patients. In addition, more patients with ETP and near-ETP-ALL had MRD on day 29 compared with non-ETP-ALL patients. However, EFS and OS were similar between the three subgroups.46

In this trial, the high and intermediate risk patients could receive through randomization six courses of nelarabine administrated for 5 days. Notably, the patients with induction failure were non randomly assigned to receive the nelarabine courses.47 In addition, high- and intermediate-risk patients received cranial irradiation.

On the UKALL 2003 trial, 35 and 17 T-ALL patients were classified as definite/probable and possible ETP-ALL respectively.48 Induction failures for ETP-ALL patients were rare in this trial (only two patients). With a median follow up of approximately 5 years, the EFS of ETP-ALL patients was not inferior (76%) to those with non-ETP-ALL (84.1%). There was a trend \( (p = 0.08) \) for inferior OS (84.1% versus 90.9%) for patients with ETP-ALL. Both protocols (AALL0434 and UKALL 2003) employed risk-stratified treatments.

In a recent retrospective analysis of 185 T-ALL patients recruited in the ALL-HR-2003 and LL-HR-11 trials was reported.49 Diagnosis of
ETP-ALL was based on the criteria proposed by Zuurbier and colleagues, and, notably, dim CD5 expression was not a criterion. A total of 34 patients met criteria for ETP-ALL, and their characteristics and outcomes were compared with those of 133 non-ETP-ALL patients. The authors reported that the median age for ETP-ALL patients was 39 years, and lymphadenopathy was common (79%). Compared with non-ETP-ALL patients, the ETP-ALL patients had inferior responses to chemotherapy, as manifested by persistence of blasts at day 14, administration of a second induction course. Overall, 77% of the ETP-ALL patients ultimately attained CR compared with 94% for non-ETP-ALL; 85% of ETP-ALL patients were MRD positive (level > 0.01%) compared with 37% for non-ETP-ALL patients. Moreover, the rate of alloHSCT was significantly higher in ETP versus non-ETP-ALL patients (70% compared with 21%, respectively). Despite performance of alloHSCT, the outcomes of patients with ETP-ALL were dismal.

The role of alloHSCT in the management of ETP-ALL

As noted above, ETP-ALL is a complex and aggressive neoplasm with multiple factors leading to poor outcomes. Over the past several years, we have seen significant progress in the management of ALL, including new therapies, better MRD assessment, and stratification tools that continue to refine the role of alloHSCT. Transplant outcomes continue to improve over time, and the use of reduced-intensity regimens offer the option of transplantation to less fit and older patients with ALL. In general, allograft for ALL in CR1 has been increasingly performed based on the presence of high-risk features, which includes the ETP-ALL phenotype. However, with the advent of pediatric-based chemotherapy protocols, some of the traditional high-risk features are being brought into question. In addition, some of the accepted indications for alloHSCT may need reevaluation in the light of outcomes with intensive regimens, the more widespread use of MRD status, and the use of oncogenetics for risk stratification.

High-intensity upfront alloHSCT in CR1 for ALL has been justified historically by a post-relapse 5-year survival of less than 10%. The largest randomized study comparing post-remission therapies in adults with ALL in CR1 (MRC/ECOG trial) demonstrated a significant survival advantage for alloHSCT in adults with standard-risk disease when performed in CR1. However, this was not the case for high-risk patients; the discordance may have been due to the significantly higher non-relapse mortality (NRM) in the latter group. A Cochrane systematic review and meta-analysis by Pidala and coworkers that included a total of 14 trials consisting of 3157 patients, supported the use of matched sibling donor alloHSCT as optimal post-remission therapy in ALL patients aged 15 years or over. In this patient population, this approach offered a superior OS and disease-free survival (DFS) at the expense of increased NRM. A European Society for Blood and Marrow Transplantation (EBMT) analysis has concluded that alloHSCT outcomes for adults with ALL in CR1 have improved significantly over time in regards to reduced NRM, relapse, treatment failure, and overall mortality despite the use of myeloablative conditioning regimen.

Bond and colleagues examined whether alloHSCT influenced the prognosis of adult ETP-ALL using data from the GRAALL studies suggesting that alloHSCT directly affected the outcome of patients in the ETP cohort. Patients were more likely to receive transplantation in first CR because of the frequently poor initial treatment response. The analysis showed that alloHSCT correlated with a trend toward better OS in this high-risk population. Taken together, these findings suggest that implementation of alloHSCT in first CR confers a survival benefit that may abrogate the negative effects of intrinsic therapeutic resistance in ETP-ALL.

As noted previously, a recent retrospective analysis by Genescà and colleagues included 34 patients with ETP-ALL, and, despite treatment intensification with alloHSCT, a significant improvement on OS was not attained. The 4-years OS was 36% for ETP-ALL patients when censoring occurred at alloHSCT and 33% without censoring for alloHSCT. On the other hand, non-ETP-ALL patients exhibited a 4-years OS 49% when censoring at alloHSCT and 51% without censoring for alloHSCT. The cumulative incidence of relapse at 3 years for the ETP-ALL patients was 24% versus 11% for the rest of the patients, but it did not reach statistical significance. The authors pointed out that the OS for the patients who
underwent alloHSCT was lower compared with other studies, and that the inferior outcomes of ETP-ALL patients may be secondary to lower CR rates.49

Another recent report by Zhu and colleagues (based on abstract available in English) explored the efficacy and outcomes of alloHSCT in 23 patients with ETP-ALL from 2010 to 2018.59 The patients were diagnosed following WHO criteria. Of the 12 patients who received HaploHSCT, 7 had matched sibling donor alloHSCT, and in 4 patients matched unrelated donors were utilized. Out of the 23 patients, 19 were in CR at the time of alloHSCT. After the alloHSCT, 22 patients engrafted, and 1 died due to infection on day +14 post-transplantation.

The estimated 18-month OS and relapsed-free survival (RFS) rates were 55.0 ± 14.4% and 48.1 ± 14.7%, respectively. The median OS of patients proceeding to alloHSCT at CR was 20 months. The OS and RFS between HaploHSCT and match-sibling alloHSCT were comparable (p = 0.460 and 0.420 respectively). The transplant-related mortality (TRM) was 4.3%.

Four patients received alloHSCT as salvage and achieved CR. Three patients relapsed within a year post-transplant, with median OS of only 13 months. Although limited by the small number of patients, it appears that salvage alloHSCT may not be associated with favorable long-term outcomes in ETP-ALL patients.

In summary, alloHSCT remains an important part of the therapy for ALL including high-risk subgroups as ETP-ALL, with the caveat that the indication for alloHSCT in CR1 may change in the future. For example, MRD negative status may be attained by other means, including adoptive cell therapy, which could be an effective bridge to alloHSCT.

**Novel treatment and approaches**

The dismal outcomes of ETP-ALL with standard chemotherapy have led others to explore the use of different approaches including tyrosine kinase inhibitors (TKI), monoclonal antibodies, and inhibitors of anti-apoptotic pathways. Adoptive immunotherapies are a field with potentially great promise, and we will discuss recent developments.

**Dasatinib**

In one case report,60 a young adult patient with ETP harboring the NUP214-ABL1 aberration was treated with a combination of vincristine, idarubicin, cyclophosphamide, and prednisone as well as dasatinib 100 mg/day for the first 2 weeks. The rationale for the use of dasatinib was that the NUP214-ABL1 fusion protein had been demonstrated to be sensitive to dasatinib. The fusion protein contains the N-terminal part of the NUP214 protein, while the C-terminal part is derived from the ABL1 protein. The patient rapidly cleared lymphoblasts from the BM and attained CR. The patient proceeded to receive consolidation with cytarabine, cyclophosphamide, and 6-mercaptopurine (6-MP). *In vitro* assays demonstrated that the patient lymphoblasts underwent apoptosis in the presence of dasatinib or selinexor (the combination has led to a more pronounced effect). Although this case report is encouraging, the prevalence of this particular aberration in ETP-ALL patients is unknown; it has been reported to occur in 6% of T-cell ALL patients.

**CD123 targeting approaches**

The interleukin-3 receptor (CD123) has attracted attention in the context of hematological malignancies, with several ongoing clinical trials.61,62 CD123 has been reported to be expressed in patients with T-cell ALL (and especially ETP-ALL) and with a higher prevalence in adults compared with children. It should be noted that reports regarding the pattern of expression of CD123 in hemopoietic stem cells and T-cell ALL have been conflicting,8,63 possibly due to different cut-offs for the relative fluorescence intensity.

Pre-clinical models have shown the activity of an immunoconjugate targeting CD123 blasts.8

**Ruxolitinib**

The JAK2 inhibitor ruxolitinib has been approved for patients afflicted by myelofibrosis. It has attracted attention in the context of ETP-ALL given that the JAK/STAT pathway may be affected.64 In xenotransplant models, ruxolitinib demonstrated activity as monotherapy but did not eradicate ETP-ALL blasts.64 A clinical trial for relapsed/refractory ETP-ALL patients combines ruxolitinib with vincristine, prednisone and
Asparaginase [ClinicalTrials.gov identifier: NCT03613428].

**Daratumumab**

Daratumumab is a monoclonal antibody against CD38, which is approved for use in patients with multiple myeloma. Preclinical data demonstrated that, in ETP-ALL with xenotransplants, daratumumab demonstrated activity. Reports of Daratumumab use for ETP-ALL are scarce. In one report, experience with daratumumab is described in two patients. One patient had refractory disease following the UKALL-XII protocol. Moreover, the patient was not deemed a candidate for intensive salvage chemotherapy given comorbidities and fungal pneumonia. To this end, the patient was treated with daratumumab monotherapy, and achieved morphological remission rapidly. Further administration of daratumumab led to MRD negativity. Notably, multiple administrations of daratumumab were not associated with significant toxicities, and the patient was able to undergo alloHSCT. Unfortunately, the patient died from infectious complications. The second patient had refractory disease after induction and with MRD positivity after alloHSCT. Daratumumab was able to eradicate MRD positivity. In another report, daratumumab was used for a heavily treated patient who had relapsed after a second alloHSCT. Daratumumab was well tolerated, and the patient achieved MRD negativity.

It is important to note the activity of daratumumab in the above case reports. Post-alloHSCT relapse and persistent disease coupled with fungal infections, are very challenging cases with a dismal prognosis. The reported – albeit limited in number – activity of daratumumab in ETP-ALL is very encouraging. A clinical trial using daratumumab for patients with T-ALL is underway, and the outcomes of ETP-ALL patients that may be enrolled would be of interest. Therefore, CAR-T cells may attack lymphoblasts, normal T-cells, and CAR-T cells (fratricide). Furthermore, strategies to circumvent fratricide such as targeting CD1a cannot be used in ETP-ALL as the latter does not express CD1a. Despite these challenges, CAR-T cells targeting CD5 and CD7 have been reported and are in clinical trials. The progress in this field, although slower compared with B-cell ALL, is encouraging. It is currently unclear what impact CAR-T cells will have on ETP-ALL, and what would be the optimal target given its distinctive immunophenotype.

The field of cancer immunotherapy has further expanded with the advent of CAR-natural killer (NK) cells. Off-the-shelf CAR-NK cells have attracted attention as the risk of graft versus disease is diminished, and these cells have a relatively short life span. CAR NK cells recognizing CD7 have been described and may offer a novel treatment approach. Another emerging technology is the use of CAR modified γδ T cells, which may offer another avenue for targeting difficult to treat diseases such as refractory/relapsed leukemias.

**Targeting CD33**

ETP-ALL may express CD33, and, in one report, more frequently than non-ETP-ALL (63% versus 17.9%) using 20% of blasts as the cut-off for positivity. In a pre-clinical model, the use of an immunoconjugate targeting CD33 leads to increased apoptosis. The use of gemtuzumab ozogamicin has been anecdotal in ETP-ALL.

**Venetoclax**

Venetoclax is an oral inhibitor of the Bcl-2 family of proteins and is used in patients with lymphoid malignancies such as CLL, and non Hodgkin’s lymphoma. Venetoclax was also recently approved for AML, and, thus, exhibits a broad anti-leukemic effect. A few reports have indicated that Venetoclax can exhibit activity in ETP-ALL.

In a case report series published from MDACC, two elderly patients received venetoclax for ETP-ALL. The first was refractory to HyperCVAD, nelarabine, and liposomal vincristine. The patient was treated with miniCVD and venetoclax. The initial dose of venetoclax was 400 mg daily after a ramp-up phase, and then 100 mg daily when azole antifungal prophylaxis was added. The patient...
achieved morphological remission with a low level of MRD by flow cytometry. The course was complicated by cytopenias, and, ultimately, the patient was transitioned to venetoclax mono-therapy. The second patient was diagnosed with secondary AML initially and failed remission-induction chemotherapy. Upon evaluation at MDACC, the diagnosis of ETP-ALL was made; monosomy 7 was also observed amongst other cytogenetic aberrations. The use of miniCVD and venetoclax had a transient response only. Notably, the best response achieved was without evidence of ETP-ALL by morphology but with MRD by flow cytometry.

The use of venetoclax in combination with decitabine was reported by Rahmat and coworkers. The patient was initially diagnosed with AML NOS and achieved CR with a combination of daunorubicin and high-dose cytarabine. The patient then received then cytarabine consolidation and sorafenib (given the presence of a FLT3 mutation). The patient relapsed after alloHSCT, and flow cytometry revealed positivity for CD34, TdT, CD5, and CD7 markers. Mutation analysis revealed aberrations in FBXW7, NOTCH1, and EZH2 genes. Retrospective analysis using clonoSEQ revealed that the same lymphoid population was present at diagnosis. Hence, there is a possibility that the AML NOS was in fact T-ALL.

Venetoclax was used in a dose of 800 mg daily reduced to 400 mg subsequent to given azole anti-fungal prophylaxis. The patient also received decitabine 20 mg/m² for 5 days every 28 days. The patient achieved CR within two cycles without MRD. Eventually the patient underwent a second alloHSCT. The case highlights the diagnostic challenges that aberrant myeloid markers may pose in the diagnosis of ETP-ALL, but also the potential sensitivity of ETP-ALL cells to venetoclax.

One of the authors (NP) also treated a patient with refractory ETP-ALL utilizing venetoclax and miniCVD. The patient received HyperCVAD at diagnosis and eventually achieved CR without MRD by flow cytometry. While on maintenance, the patient was diagnosed with relapsed disease. The patient achieved CR with nelarabine, but this was short-lived. The patient was treated with multiple regimens as remissions were short-lived or there was no response. Given the multiple lines of treatment previously received, the treatment plan was based on venetoclax (100 mg daily given concurrentazole anti-fungal prophylaxis) and miniCVD based on the experience described by MDACC. The patient tolerated miniCVD plus venetoclax without significant toxicities, and achieved CR with MRD by multi-color flow cytometry. The patient was transitioned to maintenance with monthly steroids and vincristine without antimetabolites; venetoclax was continued. The patient received prophylaxis with voriconazole as well as acyclovir and fluoroquinolone while neutropenic. G-CSF support was also provided with each cycle of miniCVD/methotrexate and cytarabine. The patient remained on CR (albeit with MRD) for more than 8 months with the described treatment schema.

The results of use of venetoclax and an attenuated chemotherapy regimen such as miniCVD, or in combination with decitabine in the relapsed setting, are encouraging. However, more extensive series are needed to determine efficacy and any emergent toxicities.

In another report, a patient with ETP-ALL had refractory disease to HyperCVAD induction. ETP-ALL was noted to be sensitive to bortezomib and venetoclax. The use of venetoclax monotherapy (800 mg daily) was associated with leukemia burden decrease.
led to a further decrease in leukemia burden and the patient was planned to undergo alloHSCT.

A phase I clinical trial currently ongoing in MDACC is exploring the effect of venetoclax and miniCVD/methotrexate and cytarabine [ClinicalTrials.gov identifier: NCT03808610]. Another study is currently underway and combines liposomal vincristine with venetoclax [ClinicalTrials.gov identifier: NCT03504644], while a third combines navitoclax and venetoclax in patients with relapsed/refractory ALL [ClinicalTrials.gov identifier: NCT03181126].

The results of those early studies are eagerly awaited, especially in the ETP-ALL subgroup of patients and may provide more data regarding the possibility of treating ETP-ALL without intensive chemotherapy regimens associated with toxicities and prolonged hospitalizations.

Notably, the encouraging findings of venetoclax activity have led to the testing of molecules with activity against other proteins with anti-apoptotic activity. The S63845 is a potent inhibitor of MCL1 protein, and, in preclinical studies, it demonstrated activity against the Loucy cell line (resembling ETP-ALL).87

Tailored treatments (precision oncology)

Precision oncology has attracted attention as it offers the possibility to tailor treatment to the characteristics of the patient malignancy. A recent publication utilized computational biology modeling to identify synergic chemotherapy combinations for patients with ETP-ALL.16 In addition, ex vivo models were able to identify the sensitivity of ETP-ALL cells to venetoclax and other compounds.86,88 In another publication, patient derived xenotransplants were used to identify tyrosine phosphorylation pattern.89 Samples derived from ETP-ALL patients demonstrated an upregulation of JAK-STAT signaling cascade and phosphorylation of multiple residues in the tyrosine kinase ZAP70.89 In some cases, ruxolitinib had in vivo activity in the xenografted murine models. The authors of this study latter also reported the analysis of xenotransplants from a patient with refractory B-cell ALL that had also underwent alloHSCT.89 The patient had increasing MRD indicative of impending relapse. Analysis revealed augmented levels of LYN kinase phosphorylation compared with samples from the patient’s stored bone marrow. Dasatinib was able to effectively inhibit LYN kinase phosphorylation. This approach would be of further interest and may offer a novel platform for discovery of tailored treatments, especially for patients with refractory disease.

The field of in vitro drug sensitivity and resistance testing (DSRT) is expanding, and can include two-dimensional (2D) and three-dimensional (3D) cell culture systems.90 Such an approach has been used in hematological malignancies and has been reported in ALL.90,91 A small single-center study used ex vivo drug response profiling for patients with advanced hematological malignancies with a rapid turnaround time (5 days).92 The majority of patients had lymphoid malignancies, and have received multiple lines of treatment (2–7). Encouragingly, CR and partial responses were reported. Furthermore, a patient with T-ALL (who had received already four lines of treatment) had a partial response to bortezomib, cyclophosphamide, and dexamethasone. Although the study did not include ETP-ALL patients specifically, such an approach could be envisioned for such patients. Overall, tailored treatment approaches for patients with ETP-ALL may offer new treatment options.93

Concluding remarks

ETP-ALL is a complex disease that has recently attracted attention. The optimal management remains unclear. Our understanding of the molecular mechanisms of resistance may lead to more targeted and better tolerated treatments. Results of ongoing clinical trials may shape the future treatment paradigms for ETP-ALL.

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Conflict of interest

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