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Clinical characteristics and outcomes of previously untreated patients with adult onset T-ALL and T-lymphoblastic lymphoma (T-LL) with Hyper-CVAD based regimens

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Keywords

T-ALL; T-LL; Acute lymphoblastic leukemia; Hyper-CVAD

Adult onset precursor T-cell acute lymphoblastic leukemia (T-ALL) and T-cell lymphoblastic lymphoma (T-LL) are considered as different spectra of the same neoplastic process. T-ALL and T-LL are differentiated on the basis of the extent of bone marrow involvement by the clonal T cell blasts i.e. <25% in T-LL while ≥ 25% in T-ALL. They are both similar in morphology and in phenotype profiling, however the initial clinical presentation of T-ALL is characterized by extensive marrow and peripheral blood involvement while in T-LL, localized mediastinal or nodal involvement is common.[1,2]

Traditionally, in clinical trials of adult onset acute T-cell ALL, patients with T-ALL and T-LL are combined for the analysis of treatment response and survival outcomes. Clinical trials with HCVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high doses methotrexate and cytarabine)-based regimens[3,4] or with intensive chemotherapies combined the patients with T-ALL/T-LL.[5] Jabbour et al[6] reported that patients with T-LL have superior response and outcomes after treatment with the LMT-89 protocol compared to patients with T-ALL. Here, we have analysed our data on

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Authorship Contributions

P.J., E.J. and H.K. contributed to the study design, data collection (S.P. and P.J.), P.J., E.J., N.J.S, and K.S., wrote the paper and analyzed results. R.K-S., K.S., C.Y. and R.G. analyzed molecular data, Z.E., F.R., J.C., N.S., T.K., M.K., S.O.B., W.W., F.R., E.J. contributed patient samples.

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the initial presentation, treatment response, and survival outcomes of adults with T-LL and T-ALL treated with frontline HCVAD-based regimens.

One hundred and fifty previously untreated patients with T-LL (n=54; 36%) and T-ALL (n=96; 64%) who were treated with HCVAD-based regimens (1992–2016) were included in this analysis. Of patients with T-LL, 31 (57%) were treated with HCVAD and 23 (43%) with nelarabine-HCVAD. Of those with T-ALL, 72 (75%) were treated with HCVAD and 24 (25%) with nelarabine-HCVAD. All patients signed a consent form in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of The University of Texas MD Anderson Cancer Center. Patient charts were reviewed for initial clinical characteristics, treatment responses, and survival outcomes; event-free (EFS) and overall survival (OS) were analysed. Outcome differences between T-LL and T-ALL were assessed using log-rank test.

Clinical characteristics of patients with T-LL versus T-ALL at the initial presentation are summarized in Supplemental table-1. Among patients with available immunophenotype data (n=104), early T precursor (ETP) phenotype was significantly more frequent among patients with T-ALL compared to patients with T-LL (44% versus 19%; p=0.006) while cortical immunophenotype was significantly higher in T-LL compared to patients with T-ALL (49% versus 31%; p=0.03). The patients with T-ALL were slightly older at presentation (median age 37 years [range, 18–67] versus 31 years [range, 17–78]; p=0.07) and had significantly higher serum LDH levels compared to patients with T-LL (p=0.001). Not surprisingly, distribution of chromosomal aberrations was significantly different among the two groups: diploid karyotype was more commonly encountered in patients with T-LL (91% versus 56% in T-ALL; p <0.0001). Among the 146 evaluable patients for response, complete remission (CR) rates were significantly higher in T-ALL 95% (87/92) vs 85% (46/54) in T-LL (p=0.002), respectively.

Overall the median follow up times were 74 months (range, 5–243) for T-LL and 122 months (range, 1–267) for T-ALL. Thirty nine (72%) patients with T-LL and 43 (45%) with T-ALL were alive at the last follow-up. The 5-year EFS rates were 78% and 48% p=0.005) and 5-year OS rates were 69% and 40% in patients with T-LL and T-ALL, respectively (p=0.001) Figure-1A–B. In a subset analysis, we noted that survival was not significantly different within patients with T-LL when analyzed according to the presence (83%) or absence (17%) of mediastinal involvement at initial presentation (not shown). As previously reported, patients with ETP-ALL had a worse outcome compared to non-ETP-ALL (p=0.01). In addition, there was no difference in outcome between patients with non-ETP and ETP-LL, although the number of patients with ETP-LL was small (n=9). Finally no difference in outcome between T-LL and T-ALL was observed when only accounting for non-ETP cases (Figure-1C).

Overall, in our analysis, we have shown that the patients with T-LL had better outcomes than patients with T-ALL after treatment with HCVAD-based regimens as a frontline therapy. One possible explanation for better outcome in T-LL as compared to T-ALL could due to the preponderance of cortical immunophenotype in T-LL which overall has better prognosis then other immunophenotype of T-ALL[7], as overexpression of CD1a has been associated

with better survival and treatment response.[8] We also observed that the proportions of patients harboring early T cell precursor immunophenotype were significantly higher in T-ALL as compared to T-LL and ETP immunophenotype may be associated with poor outcomes in adult T-ALL. Furthermore, gene expression studies in samples from pediatric patients has revealed some differences in T-LL and in T-ALL[3], with T-LL being associated with the down-regulation of genes involved in chemotaxis such as ARRB[2,4] and up-regulation of genes promoting cell adhesion and angiogenesis in local tissues. The degree of bone marrow infiltration is considered as a poor prognostic factor in T-LL, therefore this factor also could explain the difference in outcomes since the extent of marrow infiltration is used to differentiate between T-LL and T-ALL. It could well be that T-LL represents the localized form of T-ALL akin to lymphoma without a leukemic phase. Of interest, we did not observe a difference in clinical outcome according to the presence or the absence of ETP immunophenotype in patients with T-LL in contrast to T-ALL where ETP had poor outcome. Moreover, survival was similar in non-ETP T-LL and T-ALL suggesting that the survival in T-ALL was dependent upon immunophenotype. Furthermore, it is possible that there is preponderance of NOTCH1/FBXW7 mutations without any RAS/PTEN mutations in T-LL as compared to T-ALL which can confer better prognosis, however, precise molecular events which can explain the differences in clinical outcomes and treatment response are still not fully defined in adult T-LL/T-ALL.

In summary, despite lower CR rates, adults with T-LL have better survival outcome than patient with T-ALL after treatment with HCVAD-based regimens. Furthermore, the worse outcome of patients with T-ALL is mostly driven by a higher incidence of ETP immunophenotype. Additional studies to characterize the genomic profile in tumoral tissues, as well as the pattern of relapses in patients with adult T-LL and T-ALL are ongoing.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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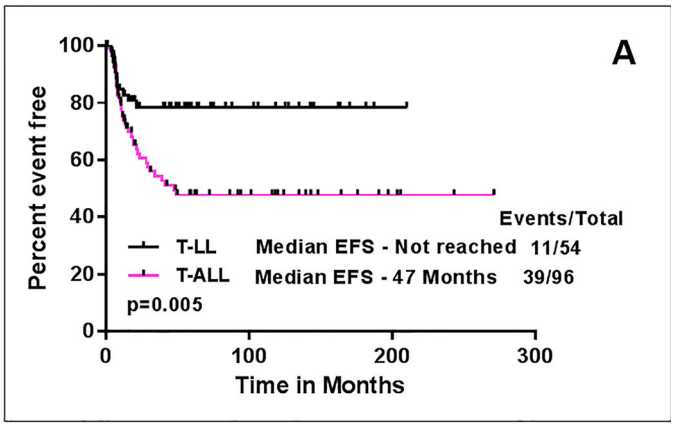

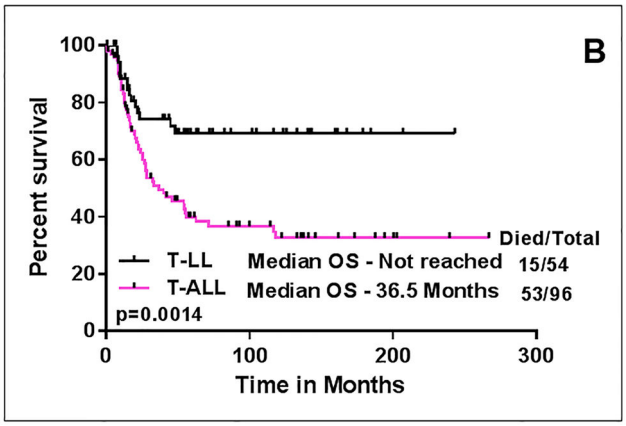

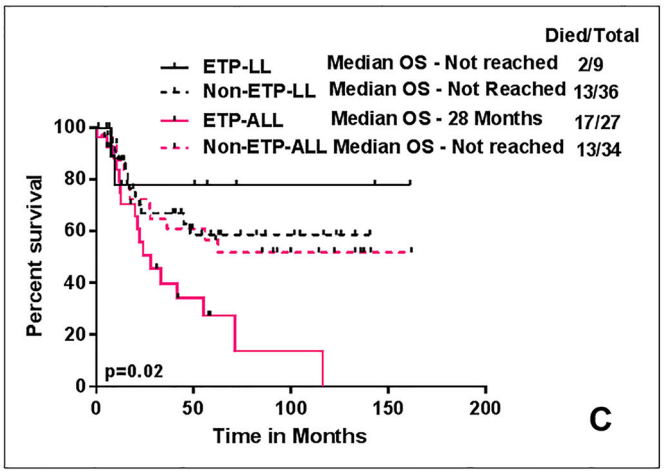

Figure-1. (A–B) – Survival outcomes of patients with T-LL vs T-ALL

A) Event free survival (EFS) is significantly longer in patients with T-LL. Median EFS not reached vs 47 months (p<0.0005). **B)** Overall survival (OS) is significantly longer in patients with T-LL. Median OS not reached vs 36 months (p=0.001). **C)** Survival in early T precursor (ETP) vs non-ETP immunophenotype according to the diagnosis of T-LL and T-ALL. ETP-ALL had an inferior outcome compared to other groups.