Poor Response to Standard Chemotherapy in Early T-precursor (ETP)-ALL: A Subtype of T-ALL Associated with Unfavourable Outcome: A Brief Report

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Abstract Early T-precursor (ETP)-ALL, a type of T-ALL, is a new pathobiologic entity with distinct immunophenotype (CD1a[−], CD8[−], CD5^{weak/absent} with stem-cell/myeloid markers) and genetic expression, poor response to standard intensive chemotherapy and very high risk of relapse. The genetic mutations typically associated with the pathogenesis of acute myeloid leukemia are seen with increased prevalence in ETP-ALL. No Indian data exists regarding this rare entity. Recently we have seen six cases of ETP-ALL and hereby reporting their clinical characteristics and treatment outcome. All patients were given induction chemotherapy according to standard protocols. Only one out of six patients could achieve remission after induction therapy. Rest five patients died because of their leukemia. This reflects the aggressive biology of this disease and its poor response to standard chemotherapy regimens generally used in T-ALL. The limited experience with ETP-ALL reflects whether rarity of this condition or failure to recognize this is not clear at this time. More studies are required to understand the basic biology of this disease and new therapeutic strategies need to be devised.

Keywords T-acute lymphoblastic leukemia · Early T-precursor ALL · Poor response

Introduction

T-acute lymphoblastic leukemia (T-ALL) constitutes about 15 % of all ALL in children and about 25 % of adult ALL [1]. Recent studies have identified a subtype of T-ALL termed “early T-precursor” (ETP) ALL that comprises up to 15 % of T-ALL, and is associated with a high risk of treatment failure. This entity was first described at St. Jude Children’s Research Hospital based on the findings of the flow cytometric analysis and gene expression profiling [2]. ETPs (early T-precursors) are a subset of thymocytes representing recent immigrants from the bone marrow to the thymus; they retain multilineage differentiation potential, suggesting their direct derivation from hematopoietic stem cells. These thymocytes retain the ability to differentiate into cells of both the T cell and myeloid, but not B-cell, lineages [3]. ETP ALL is characterized by aberrant expression of myeloid and haematopoietic stem cell markers (for example, CD13, CD33, CD34 and CD117), weak or absent expression of CD5, lack of expression of the T-lineage cell surface markers CD1a and CD8, and a gene expression profile reminiscent of the murine early T-cell precursor [4].

Genetic instability in ETP-ALL is among the highest yet recorded for any type of ALL [5]. Most recently, for the group of ETP-ALL a mutational spectrum similar to acute myeloid leukemia (AML) was observed [6, 7]. ETP-ALL patients show less frequent NOTCH 1 mutations (15 %) [8, 9] and a high rate of FLT-3 mutations (35 %). Even among ETP-ALL patients, patients with a FLT3 mutation show a distinct immunophenotype with positivity for CD117, CD34, CD13 and CD2. In contrast, ETP-ALL patients with a FLT3 wild-type status have more often positivity for CD5 and CD33 [9, 10].

At molecular level, the expression of stem cell-associated genes (BAALC and IGFBP7) and genes known to be

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of prognostic significance in AML (BAALC, MN1, WT1) are underlining the immature nature of ETP-ALL, which have been correlated with the poor outcome [11, 12]. The multilineage potential is further strengthened by the over-expression of the molecular marker WT1 in ETP-ALL which confers poor prognosis in AML as well as ETP-ALL [13, 14].

Patients with ETP-ALL have a particularly poor response to chemotherapy, very high risk of remission failure and subsequent relapse indicating the need for alternative approaches to treatment. On the basis of this, ETP-ALL is regarded as a high-risk subgroup and allogeneic hematopoietic SCT is recommended in first complete remission (CR) [2, 15, 16].

The incidence of T-ALL is higher (21–41 %) in India as compared to West (11–25 %) [17]. No data exists regarding ETP-ALL from Indian Sub-continent due to either rarity or non-recognition of this entity.

Our Experience with ETP-ALL

We hereby are briefly reporting the initial presentation, diagnostic challenges and outcome of six cases of ETP-ALL seen at our centre between 2009 and 2012.

The baseline characteristics, flow cytometry findings, treatment regimens used and response to therapy is shown in Table 1. Three patients (patient 1, 2 and 6) were initially diagnosed as T-ALL but later on found to have ETP-ALL after the retrospective analysis of 65 T-ALL patients diagnosed between 2009 and 2012. Four were young adult males (between 20 and 27 years) whereas (patient 4) was 12 years old girl and (patient 6) was 53 years old. Five out of six patients were males. Four patients (patient 1, 3, 5 and 6) had $TLC < 4 \times 10^9/L$ at baseline. Organomegaly in the form of lymphadenopathy was present in all six cases. Mediastinal mass was present in two patients (patient 1 and 4). Baseline CSF examination was normal in all patients. The flow cytometric analysis of bone marrow of all four patients showed expression of T-cell markers except for CD1a, CD8 and CD5 and aberrant expression of myeloid markers (CD13, CD33, CD34 and CD117) which was consistent with the diagnosis of ETP-ALL. FLT3 mutation analysis which could be done in patient 3 and 4 was negative. All patients were given intensive ALL induction protocols. Two patients received induction according to INCTR protocol [18], three received BFM-90 ALL protocol [19] and one received HyperCVAD protocol [20]. Only one patient (patient 4) who received HyperCVAD protocol achieved remission and is currently on maintenance. The rest five patients did not achieve remission at 4 weeks of diagnosis and died of various infectious complications of leukemia. Overall, the response to treatment was very poor in this subset of patients.

Discussion

ETP-ALL is a strong negative predictor of outcome in T-ALL patients [2]. Since this is a newly recognized entity of T-ALL with limited literature and no Indian data, we decided to share our experience.

Coustan-Smith et al. [2] first described this entity in 2006 at St. Jude Children's Research Hospital. Out of 139 cases of T-ALL studied, ETP-ALL was found in 17 (12.2 %) patients on the basis of typical immunophenotype and gene expression profiling. These cases had highly variable karyotypes. No significant associations between a diagnosis of ETP-ALL and clinical features were found. Thirteen of 17 patients had detectable minimal residual disease after the first phase of remission induction as compared to 55 of the 91 patients having typical T-ALL. The 2-year EFS of ETP-ALL patients was 22 versus 71 % for those with typical T-ALL.

Neumann et al. [9] studied a total of 178 patients with early T-ALL (enrolled in the GMALL trials (05/93, 06/99, 07/03) between 1993 and 2008) out of which 57 patients were identified as ETP-ALL on the basis of immunophenotype. There was no difference in the clinical characteristics between the group of ETP-ALL and non-ETP early T-ALL except that a lower frequency of patients with a mediastinal mass at diagnosis was found among patients with ETP-ALL. Patients of both groups were treated similarly in this series. Seventy-nine percent patients with ETP-ALL achieved CR after induction therapy compared to 82 % with non-ETP early T-ALL. The probability of survival at 10 years was slightly poor in patients with ETP-ALL and non-ETP early T-ALL (35 vs 38 %). Notably 10 year survival of 38 % in early T-ALL is not considered very impressive. In patients with early T-ALL, more patients remained in CR in the group of non-ETP early T-ALL than in the group of ETP-ALL (57 vs 46 %) with a follow-up of 9 years.

Neumann et al. [10] in another study analysed 68 patients of ETP-ALL out of which data on clinical follow-up was available in 52 patients. Forty-five patients were treated according to a GMALL-like protocol, three patients to an AML-like protocol. Fifty-eight percent of patients achieved a complete remission (CR) after induction therapy. The cumulative 3-year OS was 60 %. ETP-ALL patients who received an alloSCT had a favorable outcome ($n = 20$; 3-year OS: 74 %) compared to ETP-ALL patients treated with chemotherapy only ($n = 19$; 3-year OS: 37 %, $P = 0.006$).

Our experience with ETP-ALL is very limited. Only six patients were diagnosed with ETP-ALL in recent years after the discovery of this entity. We tried to study the clinical features, immunophenotypic characteristics, FLT3 mutation status and treatment outcome in these six patients. Similar to the original report four of the six patients were

Table 1 Baseline characteristics and treatment outcome of six patients with ETP-ALL

Parameter	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age (in years)	21	21	22	12	27	53
Sex	M	M	M	F	M	M
Lymphadenopathy	Yes	Yes	Yes	Yes	Yes	Yes
Hepatosplenomegaly	No	Yes	Yes	Yes	No	No
Mediastinal mass	Yes	No	No	Yes	No	No
CNS involvement	No	No	No	No	No	No
Baseline						
Hemoglobin (g/dl)	14.3	5.6	8.4	10	7	11.4
TLC (/L)	1.6×10^9	123×10^9	3.4×10^9	130×10^9	1.4×10^9	1.42×10^9
Platelet count (/L)	195×10^9	2.9×10^9	200×10^9	30×10^9	14×10^9	222×10^9
BMA	60–70 % blasts	95 % blasts	80–85 % blasts	96 % blasts	98 % blasts	70 % blasts
Flow cytometry	Positive for cCD3, CD45, CD34, CD33, CD117, CD44, CD56, CD7 and CD11b Negative for CD5, CD1a and CD8	Positive for CD45, CD117, CD13, CD34, cCD3, CD7 and CD44 Negative for CD5, CD1a and CD8	Positive for CD45, CD34, cCD3, CD13, CD117, CD7 and TDT Negative for CD5, CD1a and CD8	Positive for cCD3, CD45, CD7, CD2, CD117, CD33 and cCD79a Negative for CD5, CD1a and CD8	Positive for cCD3, CD7, CD117 ^{dim} , CD11b ^{htg} Negative for CD5, CD1a, CD8, HLA-DR, cMPO, CD33, TDT	Positive for CD45, CD34, cCD3, TDT, CD2, CD7, HLA-DR ^{dim} , CD117, CD13 Negative for CD5, CD1a, CD8, cMPO
FLT3	ND	ND	Negative	Negative	ND	ND
Treatment protocol	BFM-90 [19]	INCTR [18]	HyperCVAD [20]	INCTR [18]	BFM-90 [19]	BFM-90 [19]
Remission status	NA	NA	IR	NA	NA	NA
Final event	D	D	A	D	D	D
Time from diagnosis to death (in months)	one	One and a half	–	One and a half	One	One and a half
Time from diagnosis to last follow up (in months)	–	–	18	–	–	–

CNS central nervous system, TLC total leucocyte count, BMA bone marrow aspirate, FLT3 Fms-related tyrosine kinase, ND not done, NA not achieved, IR in remission, D died, A alive

young adults. Organomegaly particularly lymphadenopathy which was seen in all six cases hasn't been described. Only one out of six patients entered into remission with standard chemotherapy protocols. Allogeneic hematopoietic SCT was planned for this patient but there was no matched sibling donor. So he was started on maintenance therapy as per ALL protocol. Currently, this patient is on maintenance therapy with disease in remission after 18 months from diagnosis. Rest five patients died because of infectious complications of leukemia within 2 months of diagnosis. Our small observation study is consistent with that in Western literature confirming the poor response of ETP-ALL to chemotherapy and high rates of induction failure. The major limitation of this study was a very small sample size. To draw conclusions with this small sample size is not justifiable and we do not intend to do so. The main purpose of this report is to make physicians aware about this entity and its poor prognosis. We

also expect that by extensive flow cytometric analysis in near future more and more cases will be diagnosed and then it will be possible to have more robust studies from various centres to know the exact biology of this leukemia and to devise new chemotherapy protocols to overcome high resistance to treatment in ETP-ALL.

Conflict of interest Authors declare no conflict of interests.

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