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Original Research Article

HEMATOPATHOLOGICAL PROFILE AND OUTCOME AFTER ALL- TYPE INDUCTION IN ACUTE LEUKEMIA OF AMBIGUOUS LINEAGE

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ABSTRACT

Background: Acute leukemia of ambiguous lineage (ALAL) is infrequent in occurrence with research data available only as small case series, thus leading to a diverse approach in the management. Using “Acute lymphoblastic leukemia (ALL)- type” induction therapy along with a tyrosine kinase inhibitor for t (9,22) has achieved higher remission rates with less toxicity compared with the more intensive AML induction chemotherapy in many case series. The role of immunophenotypic and genetic markers in directing chemotherapy and the utility of targeted therapy is still unknown.

In current study, 12 patients who were diagnosed with ALAL have been retrospectively analyzed for patient demographics, hematopathological profile and induction outcomes. Among 12 patients, there were 9 male and 3 female. 25% of the patients showed t (9,22) and 16.6% showed other cytogenetic abnormalities. 5 patients showed remission after induction, 5 failed after induction, 1 expired before induction and 1 deferred chemotherapy. 50% of the patients who were started on ALL- type induction chemotherapy have shown good outcomes. Prospective studies are required to establish the best therapeutic approach in this heterogeneous disease.

Keywords: acute leukemia, ALL-type induction, ambiguous lineage, Acute leukemia of ambiguous lineage (ALAL).

INTRODUCTION

Acute leukemias of ambiguous lineage (ALAL) are defined as leukemias that either exhibit signs of commitment to more than one lineage, myeloid, B-, or T-lymphoid lineage. ALAL accounts for <3% of all cases of acute leukaemia.[1] ALAL is difficult to diagnose and treat since acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) have separate treatment regimens.

The expression of certain sets of markers that determine lineage is linked to the maturation and differentiation of blood cells during the process of hematopoiesis. This is a multistep, hierarchical, and strictly controlled process that is powered by a transcription factor network. Although some transcription factors are assumed to have key functions in directing hematopoietic progenitors toward a specific lineage (eg, CEBPα in myeloid cells or PAX-5 in B lymphocytes), this interaction in vivo is significantly more complex, context-dependent, and controlled at several cellular levels.[2,3,4] It has previously been demonstrated that early hematopoietic multipotential progenitors’ express markers from trilineages. The precise fate selection is dependent on intricate interactions that simultaneously enhance a certain lineage phenotype and block alternative programming, a process known as "lineage priming."[5] The determination of lineage may be impacted by the expression level and timing of a particular transcription factor. To favor the expression of one lineage over the other, competing transcription factors interact and counteract one other's actions.[3]

Acute leukemia of ambiguous lineage (leukemias that show no clear evidence of differentiation along a

single lineage) consists of Acute undifferentiated leukemia, Mixed phenotype acute leukemia (MPAL) with t (9,22) (q34.1; q11.2): BCR: ABL1, MPAL with t(v:11q23.3); KMT2A rearranged, MPAL, B/ myeloid, NOS, MPAL, T/ myeloid, NOS.[6] The European Group for the Immunological characterization of leukemias (EGIL)criteria is used to diagnose biphenotypic leukemia (BAL)when the scores are >2 for the myeloid and one of the lymphoid lineages (Table 1).[7,8]

Table 1: EGIL Criteria

	B-lineage	T-lineage	Myeloid lineage
2 points	CD79	CD3	MPO
	cμ	TCR	(lisozyme)
	cCD22		
1 point	CD19	CD2	CD13
	CD10	CD5	CD33
	CD20	CD8	CDw65
		CD10	CD117
0.5 point	TdT	TdT	CD14
	CD24	CD17	CD15
		CD1a	CD64

OBJECTIVES

To study the Hematopathological profile and outcomes after ALL-type induction in acute leukemia of ambiguous lineage.

MATERIAL AND METHODS

Once Acute leukemia of ambiguous lineage is identified, patients are usually treated according to an ALL–type induction regimen followed by allogeneic stem-cell transplant (alloSCT) in responding patients if feasible.[9] Philadelphia chromosome, with occurrence rates around 20% to 40%, represents the most common cytogenetic abnormality in cases of Acute leukemia of ambiguous lineage.[10] The overall survival (OS) of ALAL is known to vary from 9 months to 3.5 years based on published data, and it is generally acknowledged that the clinical outcomes is significantly poor.[11,12] The current study sought to investigate data on instances of ALAL in India because there is a dearth of information in the literature regarding diagnosis, treatment, and outcomes in this population. Here in the present study, the Heamatopathological profile and outcome after ALL-type induction in acute leukemia of ambiguous lineage in 12 patients are discussed.

Methodology

All the cases with acute leukemia of ambiguous lineage that came to the cancer institute in Eastern India for a period of three years were taken into the study and analyzed. This was an observational retrospective study and permission from the IRC (Institutional Review Committee) and ethical committee was taken for the study.

A total of 12 patients who were newly diagnosed with acute leukemia of ambiguous lineage were analyzed in this study. In all cases, the diagnosis was established according to the WHO 2016 or EGIL criteria (Table 1) based on morphological, immunophenotypical, and cytogenetic/molecular data. The patient demographics, hematopathological profile, and outcomes of each case were examined. Ten of the twelve patients had ALL-type induction chemotherapy, and the results were examined. A statistical analysis was done by using IBM SPSS 16, Chicago, United States and MS Excel 2010, Qualitative variables were expressed as frequencies and percentages.

RESULTS

In the current study, 12 patients were analyzed. The immunophenotypical markers were used to classify into ALAL subtypes as shown in Table 2.

The various subtypes of acute leukemia of ambiguous lineage in this study were B myeloid (66.6%), T myeloid (16.6%), B/T MPAL (8.3%), and Acute Undifferentiated Leukemia (8.3%) as depicted in Figure 1.

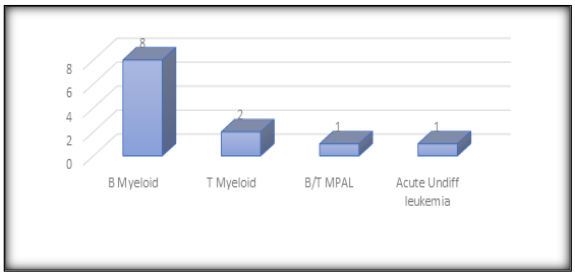

Figure 1: ALAL subtypes

Table 3 depicts the patient demographics, hematopathological profile and induction outcomes of total 12 ALAL patients. Of these, 9 were male and 5 were female. Age group stratification shows, 41.5% were below 15 years, 16.6% were in between 16-30 years, 33.2% were in between 31-45 years and 8.3% were above 45 years. The cytogenetic characteristics of this study showed t (9,22) translocation among 25% of the patients.16.6% of the patients showed other cytogenetic abnormalities. Haemoglobin was <8gm/dl in 50% of patients. Total Leukocyte count was > 50000 cumm in 33.6% of the patients and platelet count was < 1 lakh/cumm in 66.6% of the patients. All patients were planned for ALL- type induction chemotherapy, out of which 1 patient expired before induction, and 1 patient deferred induction. Of 10 patients who received ALL- type induction, 5 were in remission and 5 were in failure after induction (Figure 2).

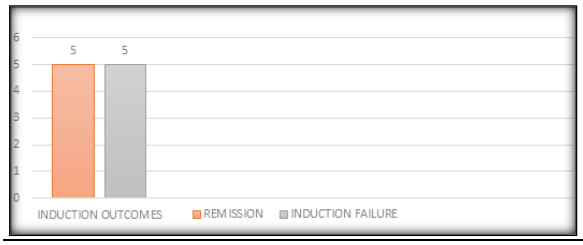

Figure 2: Induction outcomes

Table 2: Immunophenotypical markers of 12 patients

Cases	Myeloid markers				T cell marker	B cell marker		
	MPO	CD 11c	CD 64	CD 117	Ccd3	CD 19	CD79A	CD 10
1.	+	+	+	-	-	+	+	+
2.	-	-	-	+	+	-	-	-
3.	+	-	-	-	-	+	+	-
4.	-	-	-	+	-	+	-	-
5.	+	-	-	-	-	+	+	+
6.	+	+	+	+	-	-	-	+
7.	+	-	-	+	-	+	+	+
8.	-	+	+	-	-	+	+	-
9.	-	-	-	+/-	-	+	-	-
10.	-	-	-	+	-	-	-	-
11.	-	-	-	-	+	+	-	-
12.	+	-	-	-	+	-	-	-

Table 3: Patient demographics, Haematopathological profile and induction outcomes

		Number of patients
Acute leukemia of ambiguous lineage	B- myeloid (B MPAL)	66.6% (8)
	T- myeloid (T MPAL)	16.6% (2)
	B/T MPAL	8.3% (1)
	Acute undifferentiated leukemia	8.3% (1)
Age	0-15 years	41.5% (5)
	16-30 years	16.6% (2)
	31-45years	33.2% (4)
	>45 years	8.3% (1)
Sex	Male	75% (9)
	Female	25T% (3)
Cytogenetics	Fish t(9,22)	25% (3)
	Other cytogenetic abnormalities	16.6% (2)
Haemoglobin	Hb<8gm/dl	50% (6)
	Hb>8gm/dl	50% (6)
Leukocyte count	TLC<50000 cumm	66.4% (8)
	TLC>50000 cumm	33.6% (4)
Platelet count	Platelets <1 lakh/cumm	66.6% (8)
	Platelets >1 lakh/cumm	33.3% (4)
Induction Outcomes	Remission after Induction	50% (5)
	Failure after Induction	50% (5)

DISCUSSION

Myeloid lineage-derived disease (AML) or lymphoid lineage-derived disease (ALL) are the two main classifications for patients diagnosed with acute leukemia (>20% blasts in blood or marrow, or fewer in the case of certain chromosomal translocations or an extramedullary presentation). Depending on the diagnostic criteria (EGIL or 2016 WHO), there are differences in the incidence of BAL or ALAL. According to the EGIL criteria, ALAL is estimated to make up 2-5% of all Acute leukemias, whereas ALAL accounts for 1-2.5% of Acute leukemias according to the WHO criteria.[8,16]

In the current study, 66.6% patients were B Lymphoid and Myeloid,16.6% were T Lymphoid and Myeloid ,8.3% were T/B MPAL and 8.3% were acute undifferentiated leukemia according to the EGIL criteria and WHO 2016 classification. The percentage of ALAL subtypes have been found to be comparable to that of prior research. Xiao-Qian Xu et al,[13] study shows 21 cases with BAL. Among them, B Lymphoid and Myeloid were 14(66.7%), T Lymphoid and Myeloid were 5(23.8%), T/B Lymphoid were 1(4.8%) and trilineage differentiation were 1(4.8%). The B-lymphoid/myeloid phenotype cases were more than the T-lymphoid/myeloid phenotype cases in the studies done by Rubnitz. et al. and Al- Seraihy et al.[17,18] In a study done by Carbonell et al., 69% of the cases were B/myeloid and 23% were T/myeloid, 3.8% with trilineage differentiation and 3.8% with B/T lymphoid phenotype.[19] Owaidah et al. study results show 74% of cases with B/ myeloid and 24% were T/ myeloid.[20]

In this study, BCR-ABL 1(Philadelphia chromosome-Ph+)) rearrangements were seen in 25% and abnormal cytogenetics in 16.7%.In literature review, philadelphia chromosome abnormalities were the most common, accounting

for 17–41% of cases in BAL and MPAL patients with almost entirely B-lymphoid/myeloid phenotype, even though MPAL was not consistently associated with cytogenetic/molecular abnormalities.[14,21,22] Matutes E et al,[14] research in patients with MPAL showed t (9,22) translocation in 20% of the patients, 11q23/MLL rearrangements in 8% of the patients, complex cytogenetics in 32%, aberrant cytogenetics in 27% and normal in 13% of the patients. Tyrosine kinase inhibitors (TKI) may be beneficial for all Ph+ patients, just as they are for those with Ph+ ALL, hence it is important to identify them in all cases of ALAL,[9,22]

Compared to other forms of leukemia, ALAL may have a worse prognosis. The following were the suggested explanations: The delayed replication of the mixed-phenotype leukemic stem cells makes them resistant to chemotherapy; additionally, the blasts can change their phenotype in response to treatment; and some MPALs exhibit high levels of multidrug resistance proteins.[9,23] The classification of a case as myeloid or lymphoid largely influences the choice of an anti-leukemic chemotherapy strategy and the presence of markers for both lineages may have important treatment implications for acute leukemia of ambiguous lineage. Therefore, established chemotherapy regimens for ALAL patients do not yet exist.[9,24]

In the current study, the ALL-type induction therapy was started in 10 patients as 1 patient deferred chemotherapy and one expired before starting induction. Out of 10 patients, 5 patients (50%) achieved remission and 5 patients (50%) failed after induction. Pomerantz et al,[15] in their study showed a significantly worse disease-free survival and overall survival (OS) in MPAL patients as compared to other acute leukemias and better OS in patients treated with ALL-type chemotherapy compared to AML-type regimens. According to Rubnitz et al.25 study results, the complete remission rate for ALL-type therapy was greater than that of AML-type induction therapy (83% vs. 52%, respectively). In a study done by Gerr et al.26, patients who underwent ALL-type induction therapy had a considerably higher survival rate than those who underwent AML-type induction therapy (81% vs. 41%, P=0.0009).

The study's retrospective, observational design and small sample size are its main limitations, but the findings will undoubtedly add to the existing pool of literature on ALAL patients

CONCLUSION

Acute leukemia of ambiguous lineage is rare and regarded as high-risk. Results for this patient subgroup may be enhanced by therapy targeted at ALL-type induction, enhanced supportive care, and measures to prevent chemotherapy discontinuation. Consolidation with allogenic Hematopoietic stem cell transplant in complete remission provides a favorable disease control to patients with acute leukemia of ambiguous lineage. Multicentric and prospective studies are required to establish the best therapeutic approach for this heterogeneous disease.

In summary, the consensus is to treat pediatric and adult ALAL with ALL-type induction therapy, considering the limitations of the available retrospective evidence. The fraction of ALAL patients that respond best to an AML-versus an ALL-type strategy has to be validated by prospective studies.

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