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RESEARCH ARTICLE

EARLY BONE MARROW RESPONSE IN ACUTE LYMPHOBLASTIC LEUKEMIA

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ABSTRACT

Background: Evolution of risk-adapted therapies has improved our ability to treat Acute lymphoblastic leukemia. This study was planned to evaluate prognostic factors for disease remission, including age, gender, leukocyte count and blasts percentage at presentation, immunophenotype and early bone marrow response. **Methods:** Thirty-seven newly diagnosed cases of Acute Lymphoblastic Leukemia, aged 14 years and above were recruited for the study. The patients were diagnosed based on cytological and immunophenotypic criteria. Results were analyzed using the chi-square test and Fisher's exact test. RESULTS: The mean age at diagnosis was 32.48±14.39 years and females were predominant (56.76%). The most common presenting features were fever and generalized weakness. The most frequently observed clinical signs were pallor and organomegaly. B-ALL was more common (78.38%) than T-ALL. The most common CD markers expressed were CD34, CD19 & CD79a in B-ALL and CD5 & CD34 in T-ALL. The remission induction rate was 70.27%. **Conclusion:** The prognostic factors observed are compatible with literature. It was observed that persistence of lymphoblasts in day 7 Bone marrow examination is prognostically significant. M1 Bone marrow response at day 7 is a strong predictor of prolonged complete remission and good clinical outcome as compared to M2 and M3 Bone marrow response. Addition of this clinical characteristic to the usual prognostic factors in ALL could better discriminate patients, especially among those initially thought to have a relatively favourable outcome.

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INTRODUCTION

Acute Lymphoblastic Leukemia (ALL) is a hematologic malignancy that results from the dysregulated proliferation of lymphoid progenitor cells in Bone marrow. Proliferation is primarily due to pathogenetically important, disease-specific mutations at various levels of development.[1]Acute Lymphoblastic Leukemia is primarily a disease of children and young adults. There is a slight male predominance with a male-to-female ratio of 1.2:1.0.The clinical presentation of ALL may range from insidious non-specific symptoms to life-threatening manifestations, reflecting the extent of bone marrow involvement and degree of extramedullary spread. Stratification into risk groups is based on a range of clinical, biological and genetic features, such as age, gender, race, degree of organomegaly and lymphadenopathy, initial haemoglobin level, initial platelet count, white blood cell (WBC) count, immunophenotypic, cytogenetic and molecular characteristics, Central Nervous System disease at diagnosis and Philadelphia chromosome, besides early medullary response to induction therapy (Friedmann, 2005). Improved stratification of risk groups, identification of prognostic factors, and survival analysis has made it possible to identify favourable and unfavourable presenting features of the disease and to evaluate treatment outcome (Stock, 2008). Early bone marrow response to therapy has also been used widely to assign treatment. Identification of prognostic factors permits the more efficient and effective design of future protocols. The present study was conducted with the aim to evaluate various presenting risk factors, early bone marrow response and their association with clinical outcome. Further, an attempt had also been made to assess the correlation between early response to chemotherapy in patients of ALL and high-risk factors. The aim was to refine the risk without using modern minimal residual disease (MRD) techniques that might not be available

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in less affluent countries because of cost. A relevant predictive test might allow intensification of a subgroup of patients and could lead to better results with a clinically efficient strategy.

METHODS

This prospective study was conducted at the Department of Medicine of Pt. B. D. Sharma PGIMS, Rohtak in which thirty-seven newly diagnosed cases of Acute Lymphoblastic Leukemia, aged 14 years and above were recruited. Ethical clearance for the study was obtained from the Institutional Ethics Committee of Pt B D Sharma Postgraduate Institute of Medical Sciences, Rohtak. Written consent was obtained from all participating patients. The patients were diagnosed by complete haemogram, bone marrow examination showing blasts >20% and flowcytometric confirmation of the lymphoid type of blasts by Immunophenotyping. Patients of primary malignancies other than Acute Lymphoblastic Leukemia involving Bone marrow secondarily, cirrhosis of the liver, chronic renal or any other severe illness, were excluded from the study.

Detailed history and physical examination were carried out on every patient: Routine investigations like complete hemogram, Kidney function tests, and Liver function tests were done. Flow Cytometric Analysis (FCA) using primary and/or a secondary panel of monoclonal antibodies was performed. Bone marrow aspiration and biopsy were performed and other special investigations like Cerebrospinal fluid analysis, Contrast-enhanced computerized tomography thorax/ abdomen, Philadelphia chromosome were also done. Individuals diagnosed with Acute Lymphoblastic Leukemia received Standard induction-remission therapy in the form of drugs (Daunorubicin, Vincristine, L-Asparaginase, Prednisolone and/or intrathecal Methotrexate) besides supportive care (Reiter, 1994). Bone marrow aspiration was again done on Day 7 of chemotherapy and marrow was rated M1 if % of blast cells is <5%, M2 for blast cells 5-25% and M3 if >25% blast cells. The clinico-haematological profile was followed up at end of induction- remission therapy i.e. day 28. At the end of the study, the data was collected and statistically evaluated using IBM SPSS version 23. Continuous data were presented as mean ±standard deviation and categorical data as count and percentage. All statistical assessments were 2 tailed and a p-value of <0.05 was considered significant. Quantitative data were analyzed using students t-test while qualitative data was analyzed by chi-square test and Fischer's exact test.

RESULTS

The mean age at diagnosis was 32.48±14.39 years with a range of 14-61 years. Majority of patients were in their 2nd decade of life (32.43%).Out of 37 patients, 21 (56.76%) were females & 16 (43.24%) males. In subgroups, it was observed that females 17 (58.62%) also predominated over males 12 (41.38%) in B-ALL group (Table 1). It was observed that fever in 13 (44.83%) cases was the most common chief complaint followed by generalised weakness in 6 (20.68%) cases of B-ALL, whereas fever and generalized weakness both were seen in 3 (37.5%) of cases of T-ALL. Pallor in 27 (93.1%)cases of B-ALL and in 8 (100%) cases of T-ALL was the most frequently observed clinical sign followed by organomegaly in 23 (79.31%) cases of B-ALL and 6 (75%)cases of T-ALL. Mean Hb 7.28±1.84 gm/dl was observed with B-ALL and 8.02±2.09 gm/dl levels were observed in T-ALL cases.

Mean TLC observed was 37.5±44.82 $x10^9$/L in B-ALL group and 84.625±53.689 $x10^9$/L in T-ALL. Blasts percentage on PBF ranged from 20%-95% and 50%-85% in B-ALL and T-ALL respectively. On FAB classification, It was observed that ALL L1 comprised of 26 (70.27%) cases and it was common than ALL L2 which comprised of 11 (29.73%) cases. No case of ALL L3 was detected. It was observed that B-ALL 29 (78.38%) cases were more common than T-ALL (21.62%). On flowcytometric analysis, CD45 Antigen showed dimorphic expression in 35(94.2%) cases and heterogenous expression in 1(5.4%) case of Acute Lymphoblastic Leukemia. In B-ALL, the most common CD markers expressed were CD34, CD19 and CD79a in 28 (96.55%), 27 (93.1%) and 27 (93.1%) cases, HLA-DR in 26 (89.66%) cases, Tdt and CD10 in 22 (75.86%) cases each & CD20 in 13 (44.83%) cases. In T-ALL, the most common CD markers expressed were CD5 and CD34 in 8 (100%) & 6 (75%) cases, CD3 in 5 (62.5%) cases & CD7 in 4 (50%) cases. In the present study, out of 37 ALL cases, 5 (13.51%) patients died, 26 patients went into complete remission and 6 patients relapsed during the study. In B-ALL, out of total 29 patients, 3 (10.34%) died, 23 (79.31%) entered into complete remission and 3 (10.34%) relapsed. Further, in T-ALL, out of 8 cases, 2 (25%) died, 3 (37.5%) entered into complete remission and 3 (37.5%) relapsed. M1 bone marrow response (Bone marrow blasts <5%) was most common response seen in 17 (45.94%) cases while M2bone marrow response (Bone marrow blasts 5-25%) and M3bone marrow response (Bone marrow blasts <25%) was seen in 10 (27.03%) cases each (Table 2).

None of the variables such as age<35 years, gender, the presence of organomegaly & lymphadenopathy and the presence of bony tenderness were significantly associated with remission failure. Total leukocyte count at presentation ≥50($x10^9$/L) was associated with poor treatment response with a statistically significant p-value (0.038). In B-ALL, Total leukocyte count of ≥30($x10^9$/L) at presentation was associated with poor treatment response with a statistically significant p-value (0.034). In T-ALL, Total leukocyte count ≥100($x10^9$/L) at presentation was associated with poor treatment response with a statistically significant p-value (0.018). T Cell lineage was having a poor treatment response with a statistically significant p-value (0.035) (Table 3). It was observed that M1 bone marrow response on Day 7 was associated with a good treatment response as compared to M2 & M3 combined (p=0.028). M3 (Bone marrow blasts >25%) response was associated with the worst treatment response as compared to M1 & M2 combined (p=0.003). (Table 4)

DISCUSSION

According to the analysis based on cytomorphology and immunophenotyping, Acute Lymphoblastic Leukemia cases were classified as B-ALL and T-ALL. In this study, out of a total of 37 cases of Acute Lymphoblastic Leukemia, B-ALL 78.38% of cases contributed more than T-ALL 21.62% cases which were consistent with other studies. Majority of Acute Lymphoblastic Leukemia cases belonged to age group 15-20 years of age followed by 41-50 years of age. Females 56.76% predominated over males 43.24% in ALL patients. These findings were in contrast to other studies. In the study conducted by Venkateswaran *et al*. male population constituted 58%.[6]In studies conducted by Bhattacharya *et al*. and Laishram *et al*. all age groups were included and maximum patients were males which constituted 81.7% & 62.1% respectively (Bhattacharyya, 2014; Laishram, 2013).

Table 1. Baseline characteristics of study population

		ALL (n=37)		
		B-ALL (n=29)	T-ALL (n=8)	Total (n=37)
Gender distribution	Male	12 (41.38%)	4 (50%)	16(43.24%)
	Female	17 (58.62%)	4 (50%)	21(56.76%)
Age distribution	14-20	11 (37.93%)	1 (12.5%)	12 (32.43%)
	21-30	3 (10.34%)	2 (25%)	5 (13.51%)
	31-40	5 (17.24%)	1 (12.5%)	6 (16.22%)
	41-50	9 (31.03%)	2 (25%)	11 (29.74%)
	51-60	0 (0%)	2 (25%)	2 (5.4%)
	>60	1 (3.46%)	0 (0%)	1 (2.7%)

Table 2. The cytomorphological response in day 7 bone marrow

Day 7 Bone marrow	B-ALL (n=29)			T-ALL (n=8)			Total
	Complete Remission	Remission failure		Complete Remission	Remission failure		
		Relapse	Died		Relapse	Died	
M1	14	1	0	1	1	0	17(45.94%)
M2	7	0	1	1	1	0	10 (27.03%)
M3	2	2	2	1	1	2	10 (27.03%)
	23	3	3	3	3	2	37

Table 3. Association of patient laboratory characteristics with treatment response

Variable			Remission failure	Complete Remission	p-value
Hemoglobin (gm/dL)		<7.0	3	13	0.285
		≥7.0	8	13	
Total Leukocyte Count ($x10^9$/L)	Overall	<50	5	22	0.038
		≥50	6	4	
	B ALL	<30	2	19	0.034
		≥30	4	4	
	T-ALL	<100	0	3	0.018
		≥100	5	0	
Platelet ($x10^9$/L)		<100	9	21	1.0
		≥100	2	5	
Immunophenotype		B cell	6	23	0.035
		T cell	5	3	

Table 4. Association of cytomorphological response in Day 7 bone marrow with treatment response

Day 7 Bone marrow response	Remission failure	Complete Remission	p-value
M1 (Marrow blasts <5%)	2	15	0.028
M2+M3(Marrow blasts ≥5%)	9	11	
M1+M2 (Marrow blasts ≤25%)	4	23	0.003
M3(Marrow blasts >25%)	7	3	

Fever in 44.83% cases and generalized weakness in 20.68% cases were the most common symptoms found in B-ALL group. Bhattacharya *et al*. and Naeem *et al*. also reported fever as the commonest presenting feature followed by bleeding manifestations (Chessells, 1997; Naeem, 2014). Pallor was the most frequently observed clinical sign followed by organomegaly, bony tenderness and lymphadenopathy. In a similar study, Bhattacharya *et al*. reported pallor as the commonest finding followed by organomegaly and lymphadenopathy which was consistent with our study (Sandlund, 2002). In a study by Naeem *et al*. lymphadenopathy was found in 63% of patients of B-all, hepatomegaly in 50% and splenomegaly in 36% of the patients at the time of presentation (Naeem, 2014). Majority of Acute lymphoblastic leukemia cases revealed anaemia, thrombocytopenia, and leucocytosis in peripheral blood. A high blast percentage was seen in PBF. All of these results were concordant with previous studies. Based on Flowcytometry, out of 37 cases, 78.38% and 21.62% cases of ALL were diagnosed as B-ALL and T-ALL respectively. The final outcome of follow up of ALL demonstrates that out of 37 ALL cases, 13.51% of patients died, 70.27% of patients went into complete remission and 16.22% patients relapsed during the study.

In B-ALL, out of a total of 29 patients, 10.34% died, 79.31% entered into complete remission and 10.34% relapsed. Further, in T-ALL, out of 8 cases, 25% died, 37.5% entered into complete remission and 37.5% relapsed. Sousa *et al*. observed that the remission-induction rate was 95%, the induction mortality rate was 2.6% and overall survival was 72% (Sousa, 2015). Monitoring of minimal residual disease (MRD) has been shown to be the most sensitive and specific predictor of relapse risk in several large studies. However, in developing countries with financial constraints and limited health care facilities, outcome prediction on basis of presenting features can be accepted. In this study, it was observed that Total leukocyte count at presentation ≥$50x10^9$/L was associated with poor treatment response (p=0.038). In B-ALL, Total leukocyte count at presentation, even ≥30 ($x10^9$/L) was associated with poor treatment response (p=0.034). T-cell lineage was associated with poor treatment response compared to B-cell lineage (p=0.035). Age at presentation, gender, organomegaly, lymphadenopathy, bony tenderness, haemoglobin concentration, and platelet count was not predictive of treatment response. This was in contrast to studies done before. Friedmann *et al*. observed that age and WBC at diagnosis, with infants (less than one year), adolescents (greater than nine

years), and children with WBC above 50,000/µl are at higher risk.[2]Jacob M. Rowe *et al*. noted that ALL patients who were older than 35 years and had WBC counts greater than $30X10^9$/L for B lineage or greater than $100x10^9$/L for T lineage had extremely poor prognoses (Jacob *et al*., 2005). M1 bone marrow response was the most common response seen at day 7. It was observed that M1 bone marrow response on Day 7 was associated with a good treatment response as compared to M2 & M3 combined (p=0.028). Also, M3 bone marrow response was associated with the worst treatment response as compared to M1 & M2 combined (p=0.003).

The rate of cytoreduction is a powerful, independent prognostic factor that can identify patients with a slow early response who are at risk for short remission duration. So, day 7 bone marrow response is a good predictor of treatment outcome. Sandlund *et al*. determined that persistence of lymphoblasts (even 1%-4%) on day 15 of remission induction was associated with a poor prognosis and on days 22 to 25 signified a particularly dismal outcome (Sandlund, 2002). Sebban *et al*. observed that the persistence of residual blast cells in the D15 bone marrow aspiration is strongly associated with a lower complete remission rate at D28 (Sebban, 1995). To conclude, it was seen that the persistence of lymphoblasts in day 7 Bone marrow examination is prognostically significant. M1 Bone marrow response at day 7 is a strong predictor of prolonged complete remission and good clinical outcome as compared to M2 and M3 Bone marrow response. Addition of this clinical characteristic to the usual prognostic factors in ALL could better discriminate patients, especially among those initially thought to have a relatively favourable outcome.

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Key points

- Day 7 bone marrow response provides prognostically relevant information and is a good predictor of treatment outcome.
- Treatment plan can be modified according to bone marrow response at day 7.
- Choosing proper path early in management of ALL has a bearing in long term in form of cost-effectiveness and good clinical outcome.

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