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To Analyze the Impact of Prognostic Factors on Remission Induction in Acute Lymphoblastic Leukemia-A Tertiary Care Centre Study

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Abstract: ***Objective: To analyze the impact of prognostic factors on remission induction in acute lymphoblastic leukemia-A tertiary care centre study. Study Design: Prospective and Cohort. Place and Duration of Study: Aga Khan University Hospital, Karachi, data collected from March 2005 to February 2006. Materials and Methods: 36 patients were evaluated to analyze the impact of prognostic factors on remission status after receiving 04 weeks of induction chemotherapy. Patients with acute lymphoblastic leukemia of all ages and gender were included and all other lymphoproliferative disorders, refractory and relapsed acute lymphoblastic leukemia were excluded in the study. A proforma was filled for each patient at the time of presentation. These patients were followed at the end of induction chemotherapy and remission status is assessed by bone marrow examination. Tests Performed on the Blood Samples. Chi-square test was applied to determine the significance. The P value <0.05 was taken as significant. Results: The disease was observed more in males but the remission was found to be independent of gender (P>0.23). Although more cases were found in remission among ages between 1-20 years but the result was not statistically significant probably due to sample size. The remission is dependent of WBC count with a cutoff range ≥50x10^9/L (P<0.005). The remission is independent of FAB classification (P>0.23) and regarding immunophenotyping the remission is independent on immunophenotype seen on flow cytometry (P<0.07). Conclusion: WBC count at diagnosis is highly associated with long-term survival in ALL. Remission was not found dependent on age in our study. Probably larger sample size is required for it. Other prognostic factors defined in the present study were found consistent to those identified by previous studies.***

Keywords: Prognostic factors, acute lymphoblastic leukemia, Remission induction

1. Introduction

Acute lymphoblastic leukemia (ALL) is a malignant disorder that originates in a single B- or T-lymphocyte progenitor. The proliferation and accumulation of blast cells in the marrow result in suppression of hematopoiesis and thereafter anemia, thrombocytopenia and neutropenia. Extra medullary accumulation of lymphoblasts may occur in various sites, especially meninges, gonads, thymus, liver, spleen or lymph nodes[1].Clinical manifestations at the time of presentation include constitutional symptoms like fever, weight loss and night sweats, , dyspnea, dizziness, easy bruising or bleeding, and infections. Joint pain and pain in the extremities may be the only presenting symptoms. Symptomatic central nervous system (CNS) involvement may be found in less than 10% patients, although the frequency is higher in patients with mature B-cell ALL[2]. In recent years the therapy of acute lymphoblastic leukemia (ALL) with chemotherapeutic agents has resulted in longer remissions and possible cures in many patients. However, still a large number of patients do not respond to therapy. Efforts have been made over the last decade to identify this group who do not respond well to usual therapies. Factors such as age, sex, FAB classification, initial white cell count have been reported to be useful prognostic factors.

Current cure rate are nearly 80% in children, in contrast only 30-40% adults with ALL are cured[3]. 20-25% of patients still experience relapse[4].The prognostic factors of ALL are age, sex, FAB classification, time to achieve remission, white cell count and cytogenetic abnormalities. The most important bad prognostic factor is high white cell count above 50x10^9/L, which is more common in T-ALL than B-ALL. Prognosis is worse in males. Adults have L2 blast morphology more frequently than children and this seems to influence the remission induction particularly in adults. Treatment of ALL is generally divided into three phases that is induction, intensification and maintenance. The goal of induction is remission and eradication of all microscopically detectable leukemia[5].

There are constellations of clinical and laboratory features to distinguish patients who likely will be cured with conventional therapy from those whose outcome is likely to be less favorable. The prognostic factors are age, sex, WBC, time to remission, Mediastinal mass, Hepatosplenomegaly, lymphadenopathy, central nervous involvement, French American British (FAB) classification, immunophenotyping and cytogenetics.[6]

The total white cell count is the single most powerful determinant of remission induction.[7] Counts in excess of 100x10^9/L are devastating

The hemoglobin level appears to be an indirect gauge of the biologic aggressiveness of leukemia. With explosive disease, symptoms evolve before anemia has time to develop, whereas with indolent leukemia, disordered bone marrow function becomes clinically apparent before anemia.

Time of remission is an independent prognostic factor and it is the time required to achieve remission after the start of

treatment. Children in whom bone marrow or blood is cleared of blast cells within 14-15 days have significantly longer remissions and fewer late relapses than those responding more slowly. In adults it is longer and undoubtedly contributes to the adverse effect of increasing age on prognosis.[8]
The present study focuses the impact of prognostic factors on remission induction in acute lymphoblastic leukemia.

2. Objectives of the Study

To analyze the impact of prognostic factors on remission induction in ALL

3. Materials and Methods

a) Study Design
The study was a prospective and cohort, conducted from March 2005 to February 2006 at Aga Khan University Hospital, Karachi.

b) Sample Size
Sample size is 36 patients.

c) Sample Technique
It is convenient sampling.

d) Sample Selection

Inclusion Criteria
Patients with acute lymphoblastic leukemia of all ages and gender, were included.

Exclusion Criteria
All other lymphoproliferative disorders, refractory and relapsed acute lymphoblastic leukemia, were excluded.

e) Study Design
This is a prospective cohort study.

4. Research Strategy and Methodology

4.1 Data Collection Procedure

A proforma was filled for each patient at the time of presentation. These patients were followed at the end of induction chemotherapy and remission status is assessed by bone marrow examination (Annex-1).
Tests Performed on the Blood Samples and their Principles

Complete Blood Count: Performed by running the blood sample in EDTA tube on Coulter STKS. Blood counts including hemoglobin, WBC and Platelets counted by light scattering technology. A dilute cell suspension flows through an aperture so that the cells pass in single file, in front of a light source; light is scattered by the cells passing through the light beam. Scattered light is detected by a photo-multiplier which converts it into electrical impulses and are counted.[9]

4.2 Bone Marrow / Bone Trephine

Bone marrow (BM) and bone trephine (BT) performed by using Salah and Islam's needles respectively. Staining performed by Leishman stain, morphology was according to FAB classification and cytochemistry by means of Periodic Acid Schiff (PAS), Sudan black-B (SBB).[10]

Bone marrow aspiration or biopsy is mandatory for diagnosis of ALL. In <15% of patients, the bone marrow cannot be aspirated and a biopsy must be performed. Dry taps are due to densely packed blast cells, fibrosis, or inadequate technique. Most patients have >50% or even >90%, of blast cells in the marrow. In <3% of cases, the blast cells constitute <50% of the nucleated marrow cells.[11]

4.3 Immunophenotyping

Performed by flowcytometry on FAC Scan (Becton Dickinson, USA).[12]

5. Statistical Analysis of the Data

The statistical significance of differences of various quantitative data were evaluated by chi-square test. The numerical data was subjected to SPSS software for statistical analysis. The difference was regarded as statistically significant if the P value was equal to or less than 0.05.

6. Results

During the period of one year, from March 2005 to February 2006, 36 patients were evaluated to analyze the impact of prognostic factors on remission status after receiving 04 weeks of induction chemotherapy. The prognostic factors evaluated were age, sex, WBC count, FAB classification, and immunophenotyping.

Among 36 patients, 20 received UKALL-XII protocol and 16 patients received BFM protocol.

After 04 weeks of therapy on bone marrow examination, out of 36 patients, 29 patients were in complete remission and 07 patients, who were all males, were found not in remission. Twenty-four male patients found in remission and all 05 female patients were in remission.

Although the disease was observed more in males than in females, i.e. 31 of 36 were males and 05 of 36 were females. The remission was found independent of gender. Statistically, result is insignificant (P>0.23) (Table-1).Out of 29 cases who were in remission, 23 were found between ages 1-20 years. Only 6 cases were in remission between ages 21-40 years and no case was in remission between ages 41-50 years. Although there were many cases reported in remission between ages 1-20 years but the results were statistically insignificant (P=0.14) (Table-2).

Out of 07 patients who were not in remission, 06 had WBC count >$50x10^9$/L and only one patient had WBC count <$50x10^9$/L. Thus remission is dependent of WBC count with a cutoff range ≥$50x10^9$/L. The results are highly significant (P<0.005**) (Table-3).

Bone marrow morphology showed L1 FAB type in 05 (13.9%) patients and L2 in 31 (86.1%) patients and all 07 patients who were not in remission had L2 FAB morphology. So remission is independent of FAB classification on bone marrow examination. The results are insignificant (P>0.23) (Table-4).

Regarding immunophenotyping, out of 36 cases, who were T-cell type, 06 were in remission, 16 cases who were B-cell type, 13 were in remission, and all 10 cases who were pre-B-cell type were in remission. The remission is independent of flow cytometry (P<0.07) (Table-5).

7. Discussion

The acute leukemias account for about one-third of childhood cancer and about three-quarters of these leukemias are ALL. The others being AML or acute undifferentiated leukemia. In general, ALL has a better outcome than AML. The prognosis in children with acute lymphoblastic leukemia has markedly improved during the past 30 years. Nevertheless, 25% of the children still suffer a relapse.[13]the chances of Survival in pediatric ALL has improved to roughly 90% in trials with risk stratification by features of leukemic cells and to treatment response, treatment modification based on patient's pharmacodynamics, and improved supportive care[14].

Older adults (55 years and above) are regarded as a prognostically unfavorable group, with a probability of survival of 20% at 3 years; while Adolescents and young adults (>25 years) behave extremely well if treated according to pediatric protocols.[15-22]

However, innovative approaches are needed to further improve survival while reducing adverse effects. However a study conducted by Joanne M et al signifies Infant acute lymphoblastic leukemia has a poor therapeutic outcome despite attempts to treat it based on prognostic factor–guided therapy. This study focuses the impact of prognostic factors on remission induction in acute lymphoblastic leukemia. The goal in the search for prognostic factors is to individualize the treatment in order to avoid both over and under treatment. Great efforts have been employed to define uniform prognostic criteria for childhood ALL. The criteria is essential when comparing the results of different treatment regimes in different study groups.

The Rome Workshop in 1985 was the first serious attempt to make recommendations for categorizing ALL.[23] After that an attempt was made in 1993 by U.S. National Cancer Institute. In the present study the mean age was 15.5 years. This is in favor of Rome/NCI risk classification. Again the present study is in agreement with the study of Wintrobe.In comparison with the present study, another study showed overall prognosis was better in patients younger than 25 years .A study conducted by Daniel Willian Lustosa de Sousa et al in the year 2015 reported the most prevalent age group was between one to nine years (75% of the sample size) [28].These findings may in part be related to the increased incidence of the Philadelphia chromosome in older ALL patients, a subgroup associated with poor prognosis.[24]

The sex difference in prognosis still persists but it may be explained in part by presenting risk features. The present study does not agree with the study conducted on B-cell precursor ALL by Pediatric Oncology group in which boys had a significantly lower 5-year event free survival than did girls.

Although in one randomized study, prophylactic testicular irradiation prevented overt testicular relapse but did not improve overall disease free survival.[25] consequently this mode of therapy is no longer in use in clinical trials. The poorer prognosis in boys overall can be attributed in part to a higher incidence (2:1) of T-cell ALL, as well as lower incidence of favorable DNA Index. In the United Kingdom the MRCC UKALL trials from 1970 to 1990 were analyzed and even the results of the latest protocols show a prognostic advantage of female gender.[25] However, comparing the present study with Athanassiadou et al[26], in which neither age nor gender had a significant influence on event free survival for the children suffering from ALL. They reported that their findings were consistent with the results reported by Steinherz et al and Gustafasson et al who found the gender had no significant impact on outcome. It might be due to the reason they reported that their patients were not treated uniformly.

The negative prognostic influence of an elevated WBC reflects a higher tumoral mass and proliferative rate.3-17 in many, but not all studies the cut point for high-risk (HR) ALL has been$30x10^9$/L for BCP and $100x10^9$/L for TCPALL, respectively.[29, 30]
Regarding WBC count at diagnosis, results of the present study are in favor of Rome/NCI risk classification. The cutoff point between the low and high risk differs in relation to the treatment protocol and its intensity includes children with WBC $>50x10^9$/L in the high risk group while Pediatric Oncology group and Dana-Fabric Cancer Institute employ 100 $x10^9$/L as the criterion for intensive high risk treatment. The age and WBC count at diagnosis are still included in the modern risk assessment. In future they may be possibly replaced by immunologic and genetic markers of the disease.

Regarding the immunophenotyping the result of the present study is independent of flow cytometry. This might be due to small sample size. In order to get more precise conclusion a study with greater number of cases should be conducted. Although the present study is consistent with the results conducted by Athanassiadou et al[26] in which it was reported that the event free survival was significantly unfavorable among patients with T-cell lineage ALL than among patients with B-cell lineage ALL. Regarding cytogenetics, which is described as a single most important factor in a study conducted by Vinod Pullarkat et al [27] with the title," Impact of cytogenetics on the outcome of adult acute lymphoblastic leukemia: results of Southwest Oncology Group 9400 study" although it is an important prognostic factor but due to limited resources, socioeconomic burden, barriers in communication and low level of family awareness of the necessity of the intensive investigations it was not performed in most of the cases selected.

A co-relation between L2 morphology and a slow early response to treatment has also been described. Drug resistance is the main reason for unfavorable treatment results with intensive therapy. 95% of the patients achieve CR by morphologic criteria but in approximately 20% a relapse occurs later during or after treatment. The mechanism of drug

resistance is the P-glycoprotein mediated multiple drug resistance. This is caused by cross-resistance to several anti-cancer drugs. As the targets of MDR are widely used in the treatment of childhood ALL, P-gp expression might be assumed in future to be an important prognostic factor. The P-gp expression should be measured at diagnosis or at relapse in the lymphoblasts of the patients suffering from ALL and patients with P-gp positive cells should be dealt separately.

In contemporary studies intensification of therapy appears to abrogate the prognostic significance of many established factors. Future approaches will focus on better identification of biologically defined risk groups and their risk adopted treatment ultimately the emerging new data from pharmacogenomics and the field of molecular diagnostic techniques will be incorporated into ongoing clinical trials, providing more individualized and potentially less toxic treatment approaches.

Further modification of contemporary treatment protocols, coupled with systematic evaluation of novel biologic strategies, may provide uniformly effective therapy for children with ALL and begin to improve the generally unfavorable outlook for adults with this disease.

8. Conclusion

The prognosis of patients with acute lymphoblastic leukemia, treated with modern chemotherapeutic regimens is dependent on a number of variables. These factors are highly associated with long-term survival. Prognostic factors defined in the present study were found consistent to those identified by previous studies. However, more prospective studies are required to define the occurrence of these factors in our population.

(Annex-1).

Proforma

Medical Record #:

Sex: Male / Female
Age:

Presenting Features
- White Cell Count at Presentation
- Bone Marrow at Presentation

FAB Classification
Immunophenotyping (by flowcytometry)

TREATMENT RECEIVED MEDICAL RESEARCH COUNCIL
UNITED KINGDOM ACUTE LYMPHOBLASTIC LEUKEMIA
(MRC UKALL XII) PROTOCOL / BERLIN-FRANKFURT-MUNSTER (BFM) PROCOL
BONE MARROW EXAMINATION
(4 Weeks after Induction Chemotherapy)

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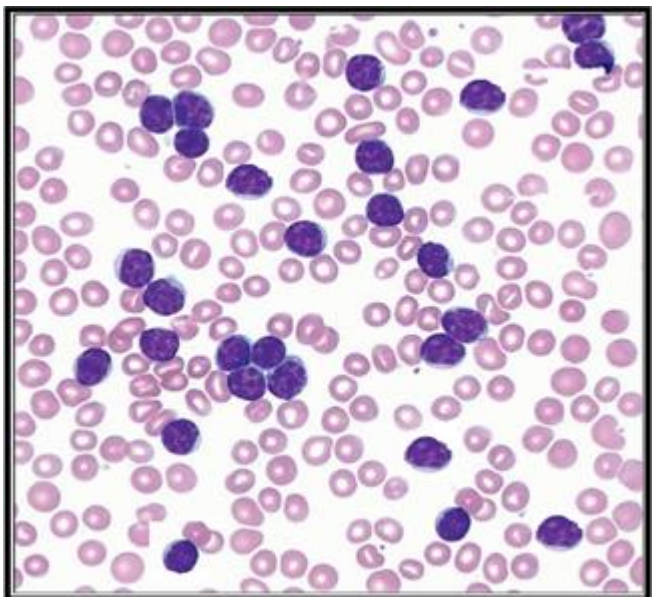

Figure 1: Peripheral film of Acute lymphoblastic leukemia with WBC count >50x109/L

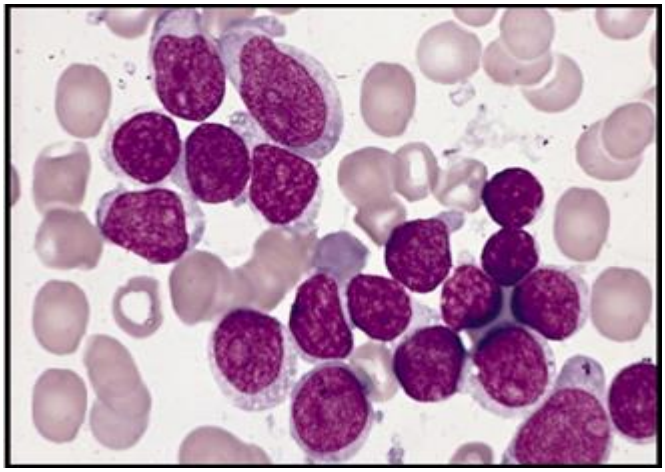

Figure 2: Bone marrow Acute Lymphoblastic Leukemia with FAB L2

Table 1: Statistical Analysis of Gender on Remission Induction in all

Bone Marrow	Sex		Total
	Male	Female	
Remission	24	05	29
No remission	07	--	07
Total	31	05	36

Chi-square = 1.40; P>0.23 Insignificant

Chi-Square Tests					
	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	1.402[a]	1	.236		
Continuity Correction[b]	.331	1	.565		

Likelihood Ratio	2.350	1	.125		
Fisher's Exact Test				.559	.315
Linear-by-Linear Association	1.363	1	.243		
N of Valid Cases	36				
a. 2 cells (50.0%) have expected count less than 5. The minimum expected count is .97.					
b. Computed only for a 2x2 table					

Table 2: Statistical Analysis of Age on Remission Induction in all

Age (Years)	Bone Marrow		Total
	Remission	No Remission	
1-10	11	02	13
11-20	12	01	13
21-30	03	02	05
31-40	03	01	04
41-50	--	01	01
Total	29	07	36

Chi-Square=6.85, P=0.14

Insignificant

Chi-Square Tests			
	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	6.854[a]	4	.144
Likelihood Ratio	6.025	4	.197
Linear-by-Linear Association	2.832	1	.092
N of Valid Cases	36		
a. 8 cells (80.0%) have expected count less than 5. The minimum expected count is .19.			

Table 3: Statistical Analysis of WBC Count at Presentation on Remission Induction in all

WBC Count	BONE MARROW		Total	P Value
	Remission	No Remission		
<50x10^9/L	21	01	22	Chi-square= 8.01 P<0.005**
≥50 x10^9/L	08	06	14	
Total	29	07	36	

Chi-square= 8.01P<0.005**

**Highly Significant

Chi-Square Tests					
	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	8.017[a]	1	.005**		
Continuity Correction[b]	5.758	1	.016		
Likelihood Ratio	8.210	1	.004		
Fisher's Exact Test				.008	.008
Linear-by-Linear Association	7.794	1	.005		
N of Valid Cases	36				
a. 2 cells (50.0%) have expected count less than 5. The minimum expected count is 2.72.					
b. Computed only for a 2x2 table					

Table 4: Statistical Analysis of Fab Classification on Remission Induction in all

FAB CLASS	BONE MARROW		TOTAL
	Remission	No Remission	
L1	05	--	05
L2	24	07	31
Total	29	07	36

Chi-square = 1.40; P>0.23

Insignificant

Chi-Square Tests					
	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	1.402[a]	1	.236		
Continuity Correction[b]	.331	1	.565		
Likelihood Ratio	2.350	1	.125		
Fisher's Exact Test				.559	.315
Linear-by-Linear Association	1.363	1	.243		
N of Valid Cases	36				
a. 2 cells (50.0%) have expected count less than 5. The minimum expected count is .97.					
b. Computed only for a 2x2 table					

Table 5: Statistical Analysis of Immunophenotyping on Remission Induction In All

Immuno-Phenotype	BONE MARROW		Total
	Remission	No Remission	
T-cell	06	04	10
B-cell	13	03	16
Pre-B-cell	10	--	10
Total	29	07	36

Chi-square = 5.11; P<0.07

Insignificant

Chi-Square Tests			
	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	5.116[a]	2	.077
Likelihood Ratio	6.565	2	.038
Linear-by-Linear Association	4.966	1	.026
N of Valid Cases	36		
a. 3 cells (50.0%) have expected count less than 5. The minimum expected count is 1.94.			