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Improvement in Survival Outcomes of Acute Lymphoblastic Leukemia Patients Treated With Berlin-Frankfurt-Munster 76/79 Protocol

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ABSTRACT

Introduction: Acute lymphoblastic leukemia (ALL) is a malignancy of the white blood cells and lymphoid lines of hematopoietic cells in the blood and bone marrow while lymphomas mostly involve the lymph nodes. This study showed the response rate of ALL treated with BFM (Berlin-Frankfurt-Munster) 76/79 protocol. **Aims & Objectives:** To study the effects of WBC (White Blood Cells), age, and treatment protocols on the survival of ALL patients to BFM 76/79 protocol and other chemotherapy protocol. **Place and duration of study:** 6 months retrospective study on 2015-2017 indoor patient data from INMOL Hospital Lahore, Pakistan. **Material & Methods:** Data of 129 patients was assessed for eligibility, and 84 patients of ALL selected. Clinical information of patients regarding Gender, Age, WBC, Fever, Hepatosplenomegaly, Lymphadenopathy, Bleeding, Bone Pain, Immunophenotype, Relapse, Death, and survival rates were recorded. Patients were grouped according to Age, WBC, Gender, and Immunophenotype. Patients were treated with BFM 76/79 Protocols and the remaining patients were treated with other protocols (CALGB, FLAG-TDA, Hyper-CVAD, EURO, COG, T-Cell ALL protocol, and ALL protocol 9111). **Results:** Out of 84 patients, 55 (65.5%) patients were treated with Berlin-Frankfurt-Munster 76/79 protocol and the remaining 20 (23.81%) patients with other protocols. After the end of induction 64 (73.8%) patients achieved complete remission and 5 (5.95%) patients did not achieve Remission. **Conclusion:** Response rate of ALL (Acute Lymphoblastic Leukemia) patients treated with BFM 76/79 protocol was better than other protocols and possibly when risk adapted for male gender, WBC > 50 x 10^9/L and age> 30 years.

Keywords: Acute Lymphoblastic Leukemia (ALL), BFM protocols, Acute Myeloid Leukemia (AML), Non-Hodgkin Lymphoma (NHL)

INTRODUCTION

Acute Lymphoblastic Leukemia is a cancerous disease of the bone marrow where immature leucocytes and lymphoid precursors proliferate and replace the normal hematopoietic cells and immune system B and T cells. Whereas lymphatic tissue and lymph nodes malignancy is preponderant in lymphomas. Research has revealed that most of the deaths and poor outcomes of leukemia and lymphoma patients were due to many reasons i.e. lack of awareness about the disease, lack of early treatment of disease, the toxic effect of protocol or chemotherapy treatment, and poor socioeconomic condition of patients. Studies have shown that major risk factors involved in poor outcomes of Leukemia patients were, WBC > 50 x 10^9/L, Male Gender, Age, and poor socioeconomic condition.[1,2] Heredity may also play a role as a leukemic gene ETV6-RUNX1 could arise in one of the twins in the womb and twins can develop ALL.[3] Following chemotherapy the rate of Induction Remission varies with different ALL protocols. In case of the BFM protocol it was found to be 86.6% which is greater than as compared to the outcome of 85% of UKALL-X protocol.[2] 86% patients, when treated with BFM protocol, showed complete remission, in comparison to 62% overall survival for T-Cell ALL patients and 38% B-Cell ALL patients using CALGB.[4] Risk-adapted therapy for Pre B-Cell and T-Cell ALL Children showed 86% of 5-year Event-free survival rates and low relapse rate.[5] Mitoxantrone is an effective drug for relapse patients of ALL then "idarubicin".[6] Fever, weakness were considered the commonest symptoms for

Leukemia patients.[7] Toxicity is a major risk for long-term event-free-survival outcomes, so a balance in therapeutic treatment is required.[8] It is suggested that Risk adapted therapies are beneficial for good outcomes of patients in ALL.[5,9] Classification of Acute Leukemia according to FAB classification and World Health Organization was described so that the treatment should be given according to the diagnosis of a particular subtype.[10] Proper treatment should be given to ALL patients to attain improvement in survival rates and to decrease the rate of deaths due to infectious diseases.[11] High Relapse rate is a major problem in previous studies. In the present study, the relapse rate was controlled by risk adapted therapy.

MATERIAL AND METHODS

A 6 months retrospective study was conducted on 2015-2017 indoor patient data from INMOL Hospital Lahore, Pakistan. Data of 129 patients aged from 2-54 years (83.0% patients between age 11 to 30 years) were assessed for eligibility on the basis ALL (n= 84), AML (n=9) and NHL (n=35) patients. 84 patients with ALL were selected for this study. Patients enrollment, allocation, follow up and analysis are detailed in the Patients Consort E Flow (Fig-1).

Complete information of patients containing their physical examination, biological and clinical features as well as the family history was recorded for analysis. clinical information of patients regarding Gender, Age, WBC, Fever, Hepatosplenomegaly, Lymphadenopathy, Bleeding, Bone Pain, Immunophenotype, Relapse, Death, and survival rates were recorded.

Patients were grouped according to the Age, Gender. WBC, and Immunophenotype and Treatment protocol. Patients were grouped for age (1-10 years, 11-20 years, 21-30 years, and greater than 30 years). Patients having WBC > 50 x 10^9/L, age > 30 years, male gender, and T Cell ALL patients were considered in a High-Risk group, and patients having WBC < 50 x 10^9/L were in a Low-Risk Group. Immunophenotyping and FAB classification Leukemia subtypes were used for determining morphology and immunophenotype of patient's blood and Bone marrow samples. Grouping according to immunophenotyping e.g. Pre B-Cell and T-Cell patients were done separately. Due to meagre data on Philadelphia +ve chromosomes in these patients, it was excluded from analysis, and no risk assessment was done on it.

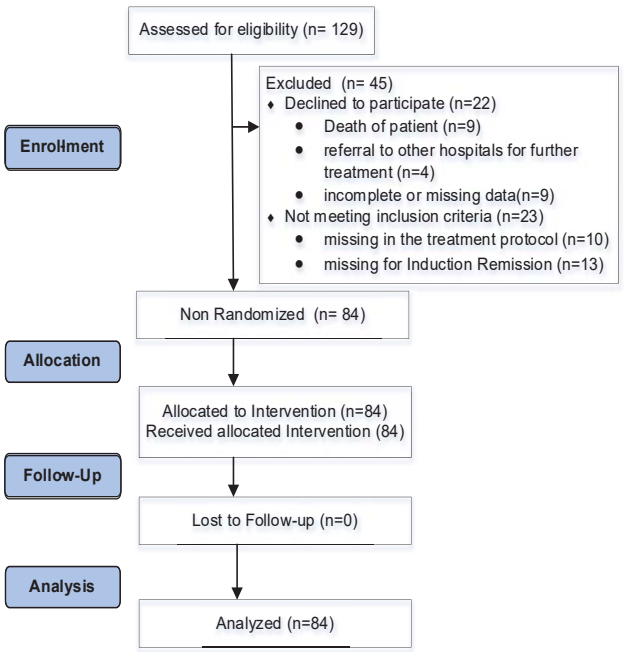

Fig-1: Patients Consort E chart

Treatment: Most of the patients were treated with BFM 76/79 Protocols and the remaining patients were treated with other protocols (CALGB, FLAG-TDA, Hyper-CVAD, EURO, COG, T-Cell ALL protocol, and ALL protocol 9111).

Statistical analysis:

The data was analyzed statistically using MS Excel and SPSS 16.0 software Characteristics of patients were calculated and analysis of risk patients was done. Risk directed therapy protocols were used to analyze the survival rates of patients. Overall 4 year survival rate of leukemia patients was determined using MS Excel line charts after analyzing the deaths and relapse rates.

RESULTS

Out of 84 patients 65 (77.3%) males and 19 (22.6%) were females. The male to female ratio was 3.4:1. Clinical features of 84 patients with Acute Lymphoblastic Leukemia are shown in Table-1. The most common feature among patients was Fever; this was also proved by another study.[7] The characteristics of patients are shown in Table-3.

Features	YES	NO
Fever	70 (83.3%)	5 (5.95%)
Bleeding	33 (39.3%)	10 (11.9%)
Hepatomegaly	22 (26.2%)	26 (31%)
Splenomegaly	36 (42.9%)	18 (21.4%)
Lymphadenopathy	30 (35.7%)	5 (5.95%)
Bone Pain	32 (38.1%)	6 (7.14%)

Table-1: Clinical features of ALL Patients

Patient's record	Complete Remission	Incomplete Remission	No Record
No. of patients	64	5	13
%age	73.8%	5.95%	15.5%

Table-2: Remission status of ALL patients

Groups	No. of patients (n=84)	Percentage of patients (%)	P-value
Gender			
Male	65	77.4	}
Female	19	22.6	}< 0.05
WBC			
> 50 x 10^9/L	26	30.9	}
< 50 x 10^9/L	58	69.0	}N.S
Age			
1-10	9	10.7	}
11-20	50	59.5	}
21-30	20	23.8	}< 0.05
>30	5	5.95	
Immunophenotype			
Pre B-Cell ALL	49	58.3	}
B-Cell ALL	2	2.38	} N.S
Pre T-Cell ALL	10	11.9	}
T-Cell ALL	3	3.57	
FAB Classification			
L1	2	2.38	}
L2	16	19.0	}
L3	2	2.38	}N.S
Treatment Protocol			
BFM 76/79	55	65.5	}< 0.05
CALGB	7	8.33	}
ALL Protocol 9111	1	1.19	}
FLAG TDA	1	1.19	}
Hyper-CVAD	1	1.19	}
T-Cell Protocol	4	4.76	}
EURO Protocol	2	2.38	}
COG Protocol	4	4.76	}
Risk Group			
Low Risk Patients	58	69.0	}
High Risk Patients	26	30.9	}N.S
Overall Survival	75	89.9	
N.S=Not Significant			

Table-3: Characteristic of ALL Patients

DISCUSSION

Clinical features of ALL patients were taken after the CBC report before Induction. A complete history of the patient as well as their physical condition, blood, and bone marrow examination was recorded. 83.3% of patients have a fever, a common clinical feature found in most of the patients, 39.3% had bleeding, (26.2%) hepatomegaly, (42.9%) Splenomegaly, (35.7%) lymphadenopathy and (38.1%) bone pain (Table-1). In our study 26 (30.9%) patients had WBC > 50 x 10^9/L were at high risk and 58 (69.0%) patients had WBC < 50 x 10^9/L and were at low risk. 55 (65.5%) patients were treated with BFM protocol and an improvement was seen in overall survival of patients which was 89.9%. After the end of induction 64 (73.8%) patients achieved complete remission, 5 (5.95%) patients did not achieve remission and there was no record of 13 (15.5%) patients about remission shown in Table-2. FAB classification and immunophenotyping determine the prognosis and treatment of patients having ALL. According to FAB classification, ALL is divided into three subtypes L1, L2, and L3. L1 comprises of small uniform cells and is common in children. L2 comprises small and large cells and is mostly found in adults and L3 comprises varied cells with vacuoles. L3 is called Burkitt's lymphoma /Leukemia. 2 patients had FAB L1, 16 patients had FAB L2 and 2 patients had FAB L3. Immunologically ALL is classified into the categories, 58.3% of patients had Pre B Cell ALL, (2.38%) B Cell ALL, (11.9%) Pre T Cell ALL and (3.57%) T Cell ALL. Most of the patients had B Cell ALL while T Cell ALL was rare in patients. B Cell ALL have a better prognosis in childhood and those patients are at a low-risk rate while T Cell ALL patients tend to relapse due to high WBC rate and considered at the high risk (Table-3). BFM-95 protocol was effective in highrisk T-Cell ALL patients as compared to UKALL-XI, MLP-841, and Interfant-99.[13] Our results were better as compared to results in which high dose of L-asparaginase addition to BFM protocol gave no advantage to ALL patients.[12] Our findings showed that even though T-Cell ALL are considered high-risk patients, timely treatment with BFM76/79 protocol was effective. BFM 76/79 treatment protocol was offered to 55 patients while 19 patients were treated with different other protocols as shown in Table-3. In terms of percentage 66% patients were treated with BFM76/79 protocol, 19 patients were treated with different other protocols while 12% data was missing for ALL patients (Fig-2).

Previous studies exhibited that risk adapted therapies are beneficial for good outcomes of patients in ALL.[14,15] In the present study, we also attained positive results with the usage of Risk adapted therapy for ALL patients. One patient who was initially treated with BFM 76/79 relapsed in 2nd year of maintenance and then treated with FLAG-TDA had completes remission. Another patient who was initially treated with BFM 76/79 protocol had 44% blast cells after consolidation, so was treated with HD-MTX (high dose of Methotrexate) and then with FLAG-TDA resulted

in remission. Nine patients died out of which the death of one patient was due to relapse after the consolidation phase.

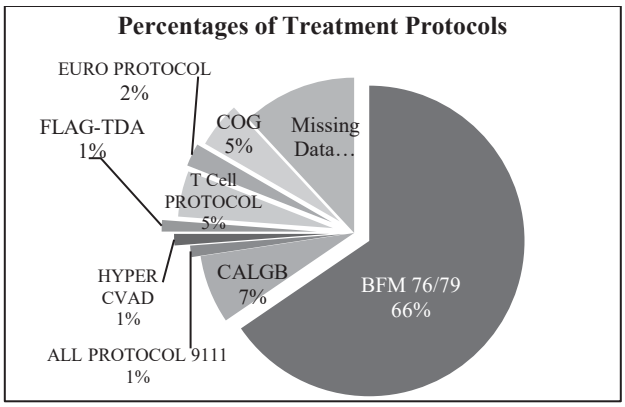

Fig-2: %age of patients treated with protocols

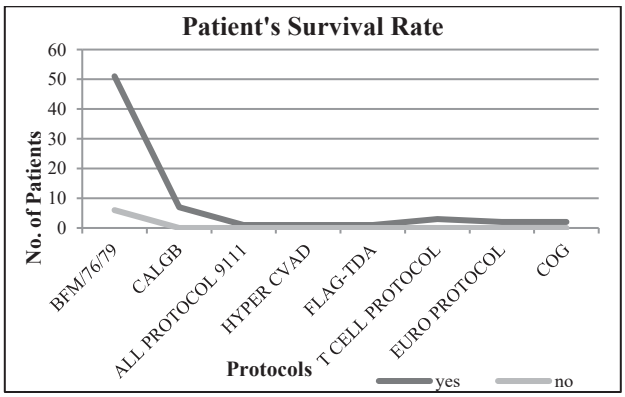

Fig-3: Survival of patients according to a treatment protocol

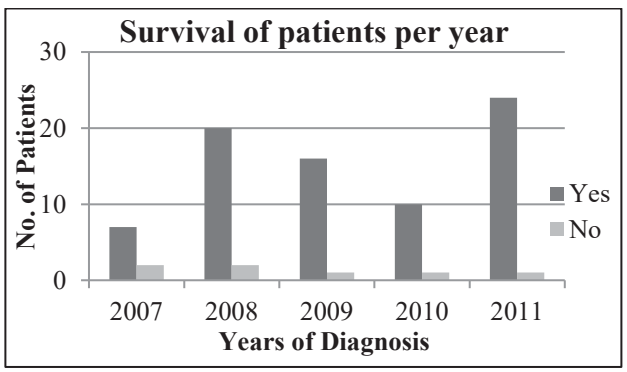

Fig-4: Survival outcomes of ALL patients

. Out of 84 ALL patients only 3 patients had strong leukemic history, so strong leukemic history was not considered as a high risk for leukemia patients. 51 (65.5%) patients survived treatment with BFM 76/79 protocol greater than outcomes of other treated protocols. The better outcome obtained was due to greater number of low-risk patients (Fig-3). Overall in our study the relative survival rate per year from 2007 to 2011 overcame the relapse rate and the death rate by treating the patients with risk adapted therapy. The survival rate was higher than the 2007 survival rate but the death rate was almost equal suggests that after treating the patients with risk adapted therapies and controlling the Relapse rate, the survival of patients was increased in 2011 and the death rate was reduced (Fig-4). Our findings concurred with data from other studies wherein the Risk adapted therapies are beneficial for good outcomes of patients in ALL.[11,16,17] Therefore choice of a protocol has a great impact on the outcome of patients.

Treatment of high-risk patients with suitable or risk directed therapies could result in better outcomes for ALL patients.

CONCLUSION

The response rate of ALL patients to different chemotherapy protocols was examined. The outcome of), BFM 76/79 protocol was higher than other protocols and possibly when risk adapted for male gender, WBC > 50 x 10^9/L and age> 30 years.

Limitations:

Clearer results could have been obtained from larger data set of patients treated with risk adapted therapies.

Recommendations:

We can further work on the survival outcomes of different protocols on AML patients.

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