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Original Research Article

Study of Clinical Profile and Post BFM-90 Induction Outcome of Adult Acute Lymphoblastic Leukemia (ALL)

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Conflict of interest: Nil

Abstract:

Introduction: Acute leukemias are classified into Acute Myeloid Leukemia (AML) and Acute Lymphoid Leukemia (ALL). India has the highest population of adolescent and young adults globally, and most centers see a significant proportion of patients in this age group.The proportion of ALL among adult patients diagnosed with acute leukemia reporting at Indian institutions are ranged from 7.3% to 57.8%. There are Different protocols used for the treatment of Adult ALL, among adults with ALL, although the complete remission rates (CR) have approached to 74% to 93 %, the overall survival rate has only approached to 27% to 54%. The present study has analyzed the response rates of the adults treated by the BFM-90 protocol.

Material and Methods: This was a prospective, observational and descriptive study conducted in tertiary care centre & teaching institute during the period from December 2019 to July 2021. Total 50 patients of ALL were included in this study as per Guidelines after satisfying inclusion and exclusion criteria.

Results: This study shows 54% of cases were < 20 yrs of age. There were 60% of males. Most of the patients had fever (86%), pallor (100%) and 06% cases showed CNS involvement. In the present study mean HB (g/dl), Total TLC (cells/cu.mm) and platelet count (cells/cu.mm) was 7.124 ± 1.58, 106831.4 ± 49328.32 and 78880 ± 77303.18. In this study 34 cases were of B-cell type of adult ALL whereas 16 cases were of T-cell type of adult ALL. The present study showed that before induction of BFM-90 protocol Bone marrow Blasts were > 20% in all cases of ALL. Post induction at Day 35 showed remission in 72% of cases. Also there was significant association between pre and post induction BFM-90 (p=0.0001). On multivariate analysis it had showed significant association between TLC (p=0.0001) and platelets counts (p=0.003) with Bone marrow Blasts (%).

Conclusion: Our study data supports that BFM-90 Protocol is feasible chemotherapy regimens for adult patients with ALL, with efficacy that appears comparable to outcomes observed with other regimens used in the treatment of adult ALL.

Keywords: Acute Leukemia, Adult, Bone marrow Blasts, Flowcytometry, ALL, BFM-90 induction, Remission.

Introduction:

Leukemia is characterized by neoplastic proliferation of hematopoietic stem cells and accumulation of blasts and immature cells in the bone marrow. Leukemia is classified as lymphoid or myeloid depending on the lineage of the progenitor cells involved. Depending on the natural history, leukemia is again classified into acute leukemia and chronic leukemia. Acute leukemia's are classified into acute myeloid leukemia (AML) and acute lymphoid leukemia (ALL) [1].

The classification of acute leukemia is based on the cellular involvement of the primary stem cell defect. Defect in the maturation and differentiation of common myeloid progenitor cells produces acute myeloid leukemia. Acute myeloid leukemia is characterized by clonal expansion of myeloid blasts. On the contrary acute lymphoblastic leukemia is due to the defect in the maturation and differentiation of common lymphoid progenitor cell. Acute lymphoblastic leukemia is characterized by clonal expansion of lymphoid blasts in peripheral blood, bone marrow and other tissues [1].

It has been reported as one of the most common malignancy of the childhood, accounting for almost 25% of all pediatric tumours and about 80% of pediatric leukemia [2]. Its incidence shows a bimodal peak, with the initial and the highest peak seen between 2 to 5 years of age and then a continues to decline in the incidence with increasing age till the age of 50 years, following which it again shows a second peak[3].

India has the highest population of adolescent and young adults globally, and most centers see a significant proportion of patients in this age group. The proportion of ALL among adult patients diagnosed with acute leukemia reporting at Indian institutions ranged from 7.3% to 57.8%. Most studies had a male preponderance (57%-80%), and had a predominance of B-ALL (65.2%-75.9%). The treatment protocols used for ALL includes MCP-841, BFM (Berlin-Frankfurt-Munster)-90, chemotherapy plus a tyrosine kinase inhibitor, GMALL (German multicenter study group for adult acute lymphoblastic leukemia), and hyper-CVAD (cyclophosphamide, vincristine, doxorubicin (Adriamycin), dexamethasone).

The complete remission rates and median overall survival for these protocols ranged from 46.7% to 91.4% and 7 to 46 months, respectively. The overall relapse rates were 24.3% to 57.1% within median time of 9 to 24 months, with bone marrow being the most frequent relapse site [4]. Among adults with ALL, although the complete remission rates (CR) have approached 74% to 93%, the overall survival rates has only approached 27% to 54% [5].these response rates are much lower than the response rates achieved in children, which is close to 80 % [6].there are multiple reasons for these differences, though they have been mainly attributed to the higher occurrence of poor risk cytogenetics, along with a reduction in incidence of the favorable cytogenetics and a poor tolerability to chemotherapy with increasing age. Also, the adult leukemic blasts have been shown to be more resistant to chemotherapy [7]. Survival gains in adult ALL have been more modest and confined to the adolescent and young adult population. Age is an important factor in determining outcomes in ALL. Additional factors like adverse biology, less treatment regimens, and poorer tolerance to therapy contribute to inferior survival among adults. Indian physicians face unique challenges while managing these patients. There are high infection rates, limited access to high-end investigations, and newer drugs. In this context, the management decisions in individual patients are highly nuanced [8].

The challenges faced in achieving better response rates in the developing countries include limited government funding considering its other urgent health priorities and more importantly the poor family resources and its associated high dropout rates [9].

Since mid-2017, there have been major modifications in the treatment protocols of the population in our institute with a switch from MCP 841 to BFM-90.

These changes were implemented in an effort to improve the clinical outcomes and achieve results on par with those achieved in developed countries. Since the introduction of these changes, no systematic analysis has not been done to assess if the anticipated improved clinical outcomes were achieved at the end of day 35 induction. The present study had analyzed the response rates of the adults treated by the BFM-90 protocol and assessed the morphological remission at the end of day 35 induction. Through this study we had discussed clinical scenario in adult ALL where we detailed our current approach i.e. Post BFM-90 effectiveness in the treatment of adult ALL cases in the context of available evidence.

Material and Methods:

This was a prospective, observational and descriptive study conducted in tertiary care centre & teaching institute during the period from December 2019 to July 2021.

This study was started after getting valid written Permission from institutional ethical committee; Total 50 patients of adult Acute Lymhoblastic leukemia (ALL) were included in this study.

A)**Inclusion criteria:** 1) Patient diagnosed to have adult acute lymphoblastic leukemia 2) peripheral blood smear and flow cytometry evidence of adult acute lymphoblastic leukemia 3) Patient of either sex with valid consent 4) Patient having age more than or equal to 12 years.

B) **Exclusion criteria:** 1) Patient having age less than 12 years 2)Patients denying consent for the study 3) Chronic leukemia patients which have transformed to acute leukemia 4) Patients who have received steroids or any other chemotherapeutic agents outside of this Hospital.

Detail Procedure of study:

Selected 50 patients of adult Acute Lymhoblastic leukemia (ALL) were enrolled in this study as per inclusion and exclusion Criteria. Selected patients were admitted to medical Oncology wards and intensive care unit if needed. After admission detailed clinical history was taken from each and every case, detailed clinical examination was done and routine blood investigations were done as per preformed proforma. Vitals were taken on admission and regularly during the course of treatment. After admission following investigations were done for the diagnosis and management of

Acute Lymhoblastic leukemia (ALL) patients i.e. Complete Blood Count, Peripheral blood smear, Serum electrolytes, Serum Calcium level, Serum uric acid level, Serum LDH Level, Serum phosphorus level, Random blood sugar, Arterial blood gases as and When required, Electrocardiogram, Liver function tests, Kidney Function Tests, Bone marrow aspiration and biopsy, Radiological investigations (X-ray,CT scan, PET-CT, USG), HIV, HBsAg, HCV, Prothrombin Time, CSF cytology & culture, Flow cytometry, Cytogenetic analysis, Fluorescence in situ Hybridisation (FISH), FISH for BCR-ABL ,Polymerase chain reaction (PCR), Immunophenotyping, and other relevant Investigations were done as per need and diagnosis, co-morbidities and clinical condition of patients as and when required. Along with BFM-90 protocol regimen all adult acute lymhoblastic leukemia (ALL) patients were given standard treatment and care including IV fluids, antibiotics, blood products, G-csf therapy and other required medicines as and when required as per guidelines**.** After the all necessary examinations and investigations, the data was entered in master chart in MS-excel on regular intervals. Data of selected patients was analyzed with the help of SPSS software version 20. On analysis of data observations were noted and results were formulated.

Level of significance "P" value was evaluated, where P value < 0.05 was considered statistically significant.

Results

A total 50 ALL cases were taken during the study period and Results were analyzed in detail.in the present study maximum number of cases (54%) were in the age group of < 20 yrs, followed by 31-35 yrs having 16%, 21-25 yrs. & 26-30 yrs. having 12% of cases each and > 35 yrs having 06% cases. Mean age was found to be 22.98 yrs and standard deviation was 7.52.

In the present study maximum numbers of cases 60% were males, while 40 % cases were females. The M:F ratio was 1.5:1. There was male predominance in the present study. at the time of admission 86% cases were having history of fever whereas 14% cases were Afebrile. 46% cases showed signs of weight loss and 54% had no signs of weight loss. All (100%) the patients had pallor (Anemia), 06% cases showed CNS involvement whereas 94% did not showed any CNS involvement. 96% cases were having pulse in the range of 60-100/min, 4% cases had tachycardia. The blood pressure of patient classified by ICMR guidelines 2017 which showed that most of cases 90% had ideal blood pressure whereas 10% had satisfactory blood pressure. In the present study HB level ranges from 4-10 g/dl with mean ± SD 7.124 ± 1.58. TLC values ranges from 3800-2,45,000 cells/cu.mm with mean ± SD of 106831.4 ± 49328.32. Platelet value ranges from 9000-5,70,000 cells/cu.mm with mean ± SD of 78880 ± 77303.18.

The spleen size of cases ranged from 04 - 19 cm with mean ± SD of 12.92 cm ± 2.62 whereas liver size of cases ranged from 11 – 17 cm with mean ± SD of 13.28 cm ± 1.40.In the present study at the time of diagnosis Bone marrow blast % level ranged from 24-91 with mean ± SD 63.73 ± 18.65. Further data revealed that after BFM-90 induction protocol Bone marrow blast % level ranged from 01-48 with mean ± SD of 10.80 ± 14.26.In the present study 68% cases were of B-cell type of adult acute lymphocytic leukemia whereas 32% cases were of T-cell type of acute lymphocytic leukemia. In our study 52% cases showed remission in B-ALL followed by 20% in T-ALL. Further data revealed that the comparison of bone marrow blast percentage after 35 days of BFM-90 induction protocol with type of adult ALL showed that there was no significant correlation found as $p>0.05$. our study data shows that there was significant correlation between bone marrow blast % before and after 35 days of BFM-90 induction protocol as $p<0.05$. There was significant correlation found between TLC ($p=0.0001$) and platelet count ($p=0.003$). Whereas no correlation was found between age, sex, hemoglobin level and type of ALL with bone marrow blast % (day 35 BFM-90 protocol) as $p>0.05$.

Discussion

Significant strides have been made in the management of adult ALL and clinical outcomes have steadily improved over the last few decades. Many of these advances involve intensification of therapy, allogenic SCT, improved molecular risk stratification and measurable residual disease (MRD) directed therapy.

However in the developing world and low middle income countries (LMIC) there are significant challenges in implementing or access to such advances. Additionally, in the absence of large collaborative research groups in LMIC, as has been developed in most developed economies, it is difficult to handle the magnitude of the problem and develop strategies to overcome them. Clinicians are depend on the newer diagnostic modalities to diagnose and recognize the association between the morphology and immuno-phenotype and specific cytogenetic abnormalities. This has led to the development of added treatment modalities based upon specific genetic defects [11].

For more than 20 years, cytomorphological response has been the leading criterion for stratifying patients into risk groups within the

ALL-BFM trials. Since the ALL-BFM-86 trial, cytomorphological response has been estimated very early during induction treatment. Cytomorphological treatment response in the Bone Marrow (BM), however, was evaluated only at the end of induction treatment (Day 33). Early marrow response has become an integral part of risk stratification in ALL treatment regimens. We tried to use risk criteria in ALL-BFM-90 without using modern minimal residual disease (MRD) techniques that might be not available in less affluent cohorts because of cost.

Early response to treatment can be an important alternative indicator of treatment outcomes. The purpose of our current study was to identify the prognostic value of the blast percentage of the induction interim bone marrow, which might predict Event free survival in patients with adult acute lymphoblastic leukemia. In our study we studied the clinical profile and post BFM-90 effectiveness after 35 days in treatment of adult ALL cases. We used bone marrow blast % as parameter to evaluate outcome after day 35 as a BFM-90 protocol in 50 selected cases during the study period. In our study most cases were in the 2nd and 3rd decade i.e. 54% & 24 % respectively. Also among adult ALL cases males accounting for 60% while females were 40% and also that of age and sex preponderance analysis did not show any statistical significance in the current study. This was correlating with the following studies and age is given in bracket, Ibrahim A.et.al [12] (17), Khan AH.et.al [13] (27.97), Aziz SA. Et.al [14] (15.9), Jain H. et.al [15](20).

In our study males were 60% and females were 40 %. Male to female ratio was approximately 1:5:1. In study of Aziz SA.et al [14] the ratio was found to be 1.17:1. Generally, the larger number of males is evident in previous studies. The findings are comparable with other studies as shown Bracket; Ibrahim A. et.al [12] (M-66.28%, F- 33.72%), Khan AH. et.al [13] (M-64%,F-36%), Muffly L. et al[16] (M-64.1% , F-35.9) Jain H. et.al[15] (M-76.4%,F-23.6%).

In the present study at the time of admission most cases 86% were having history of fever, 46% had signs of weight loss, 100% had pallor (Anemia), 06% cases showed CNS involvement. The findings are comparable with other studies as shown in table No.1

Table 1: Result

Result					
Clinical Features	**Present study**	**Khan AH. et. al. [13]**	**Shams SF et. al. [17]**	**Dai Q. et. al. [18]**	**Jain H. et. al. [15]**
Fever	86%	85%	38%	63.7%	25.53%
Weight loss	46%	-	-	-	-
Pallor (Anemia)	100%	72.5%	12%	42.5%	-
CNS involvement	06%	-	12.26%	1.4%	29.%

Investigations: In our study HB level ranged from 4-10 g/dl with mean ± SD 7.124 ± 1.58. TLC ranged from 3800-2,45,000 cells/cu.mm with mean ± SD of 106831.4 ± 49328.32. Platelet ranged from 9000-5,70,000 cells/cu.mm with mean ± SD of 78880 ± 77303.18. The findings are comparable with other studies as shown in table No.2

Table 2: Result (Mean)

Result (Mean)					
Investigations	**Present study**	**Khan AH. et. al. [13]**	**Danthala M. et. al. [19]**	**Shams SF et. al. [17]**	**Pandey A et. al. [20]**
HB (g/dl)	7.124	7.56	8.76	6.72	5.9
TLC (Cells/cu.mm)	106831.4	100849.8	73205	60776	69000
Platelet count (Cells/ cu.mm)	78880	45200	106600	81100	47000

Flowcytometry: In our study 32% cases were of T type of acute lymphocytic leukemia. An incidence of B-cell ALL and T- cell ALL comparable to three major Indian cancer centre's and has been reported as 75%, 60% and 45 % and 21 %, 32% and 43 % respectively [21].findings are comparable with other studies as shown in table No.3

Table 3: Result

Result					
Type of ALL	**Present study**	**Khan AH et. al. [13]**	**Shams SF et. al. [17]**	**Aziz SA et. al. [14]**	**Ganeshan P et. al. [22]**
B-cell ALL	68%	72%	91.6%	68.1%	56.80%
T-cell ALL	32%	28%	08.4%	31.9%	43.20%

Bone marrow blasts: Patients who went into a complete remission (no visible leukemia in the bone marrow) within 4 to 5 weeks of starting treatment tend to have a better prognosis than those for whom this takes longer. Patients who don't achieve a complete remission at all have a poorer outlook. This means the bone marrow contains fewer than 5% blast cells, the blood cell counts are within normal limits, and there are no signs or symptoms of the disease. The presence of minimal residual disease (MRD) after initial treatment also seems to affect prognosis, although this is still being studied. In our study after BFM-90 induction protocol Bone marrow blast % (BMB%) level ranged from 01-48 with mean ± SD of 10.80 ± 14.26. also Post induction < 5 BMB% seen in 36 (72.00%). Further in our study comparison of bone marrow blast percentage after 35 days of BFM-90 induction protocol with type of adult ALL shows that there was no significant correlation found as p>0.05. The findings are comparable with other studies as shown in table No.4

Table 4: Result: BFM-90 Post Induction

Result: BFM-90 Post Induction				
Blast Percentage (%)	**Present study**	**Sebban c. et.al. [24]**	**Park HS. et.al [25]**	**Rajendra A. et.al. [26]**
Blast % < 5	72%	65.4%	93.8%	61.39%
Blast % > 5	28%	34.6%	06.2%	38.61%
P value	0.0001	0.0001	0.006	0.074

Summary

This study was conducted on diagnosed 50 patients of adult acute lymphoblastic leukemia (ALL) and their day 35 post induction BFM-90 outcome was Analysed. Collected data was analysed meticulously and results were compared with other similar studies done across the world and following conclusions are drawn.

1. This study had shown maximum number of patients were in the age group of < 20 yrs which consist 54% of cases. There was male predominance in the present study as 60% were males and 40% females.(M:F Ratio of 1.5:1)
2. This study shows most of the patients had fever (86%) and pallor (Anemia) (100%). About 06% cases showed CNS involvement.
3. In the present study mean HB (g/dl), Total TLC (cells/cu.mm) and platelet count (cells/cu.mm) was 7.124 ± 1.58, 106831.4 ± 49328.32 and 78880 ± 77303.18 respectively.
4. In this study it was observed that significant number 68% cases were of B-cell type of adult acute lymphocytic leukemia whereas 32% cases were of T-cell type of adult acute lymphocytic leukemia and it was observed that there was no significant association between them (p=0.389).
5. The present study shows that before induction of BFM-90 protocol Bone marrow Blasts (%) were > 20% in all cases of ALL. BFM-90 Post induction showed remission in 72% of cases. Also, there was significant association between pre and post induction BFM-90 (p=0.0001)
6. In the present study it was observed that on multivariate analysis it had showed significant association between TLC (p=0.0001) and platelets counts (p=0.003) with Bone marrow Blasts (%).

Conclusion

BFM-90 chemotherapy was feasible in this adult ALL population and the majority of the patients were able to tolerate the full protocol treatment. This study has showed significant reduction in bone marrow blast percentage. Ultimately, our data supports that BFM-90 induction protocol is feasible chemotherapy regimens for adult patients with ALL, with efficacy that appears comparable to outcomes observed with other regimens used in adult ALL.

Limitations:

1. The Present study was done on 50 patients only, more number of sample size should be included to confirm the results of this study. In the present study adult acute lymphocytic leukemia was diagnosed by flowcytometry and day 35 post BFM-90 induction Response was evaluated by bone marrow blast % but further immunological test such as routine testing for specific cytogenetic abnormalities by FISH or PCR analysis was not obtained in our study and long term follow up was needed to know exact stages of remission. Also Minimal Residual disease (MRD) could not be done in this study because of financial constraints of patients involved in our study.
2. Analysis of toxicity due to induction therapy with BFM-90 needs to be carried out.

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