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# Comparison of Outcome of Induction Chemotherapy In Pediatric Acute Lymphoblastic Leukemia Between Standard Risk and High Risk Group

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## ABSTRACT

***Objective:*** To compare the outcome of induction chemotherapy in paediatric acute lymphoblastic leukaemia between standard risk and high-risk groups.

***Study Design:*** Prospective Comparative study

***Place and Duration of Study:*** Paediatric Oncology Department, Combined Military Hospital, Rawalpindi Pakistan from Sep 2018 to Aug 2020.

***Methodology:*** All cases of paediatric Acute lymphoblastic leukemia, who completed induction chemotherapy were included in the study. They were divided into two groups on the basis of National cancer institute criteria. Standard risk group received dexamethasone, vincristine and peg-asparaginase while high-risk group received dexamethasone, vincristine, peg-asparaginase and daunorubicin. Bone marrow examination was carried out at day 8 and 15 and then at the end of induction to document remission status.

***Results:*** A total of 233 patients of Acute lymphoblastic leukemia were included in the analysis. One hundred and twenty (51.51%) patients were in standard risk group and 113(48.49%) were in high-risk group. Remission after initial marrow was significantly higher in standard risk group as compared to high-risk group 101(90.17%) vs 58(55.77%), *p*=<0.001). However remission after day 29 marrow was higher, but not statistically significant, in the standard risk group than the high-risk group 93(97.89%) vs 77(92.77%) group (p = 0.185).

***Conclusion:*** Patients in standard risk group have high remission after induction chemotherapy as compared to high-risk group. Patients in high risk group have more complications and higher treatment related mortality as compared to standard risk group.

**Keywords:** Acute lymphoblastic leukemia; high-risk; remission; standard risk

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## INTRODUCTION

Acute lymphoblastic leukemia (ALL) is defined as malignant changes and multiplication of lymphoid progenitor cells in the bone marrow, blood and extramedullary sites.[1,2] Individuals from all age groups can suffer from these malignant disorders but for some conditions a distinct age pattern has been noted. Acute lymphoblastic leukemia is found more in young age group and considered as a common childhood malignant condition.[3]

Various treatment strategies have been used to manage the children suffering from acute lymphoblastic leukemia.[4] Children affected with ALL have higher than 80% overall long-term survival rates in high-income countries, while survival rates are much lower in low-income countries.[5,6] ALL treatment is divided into different stages of chemotherapy i.e induction, consolidation and long-term maintenance phases.[7] Corticosteroids, vincristine, anthracycline,and methotrexate are used in induction therapy.[8] In general, chemotherapy has significant adverse effects and toxicity along with the resistance of malignant cells to therapy.[9] Although higher percentage of recovery has been achieved but still relapsed or refractory cases are challenge for the current treatment.[10]

Limited local data is available regarding difference in outcome among standard risk and high-risk ALL patients. We therefore planned this study with the rationale to compare the outcome of induction chemotherapy in pediatric acute lymphoblastic leukemia patients between standard risk and high-risk group.

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## METHODOLOGY

This prospective comparative study was conducted at the Pediatric Oncology Department, Combined Military Hospital Rawalpindi from September 2018 to August 2020. All patients of ALL diagnosed on basis of National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines11 between the age of 1 and 18 years were included in this study using non probability consecutive sampling technique. Sample size was calculated by WHO sample size calculator by using population prevalence proportion of response rate in ALL as 80%.[12]

This study was conducted at the Combined Military Hospital Rawalpindi form September 2018 to August 2020.

**Inclusion Criteria:** Children of age 1 to 18 years who were diagnosed with ALL.

**Exclusion Criteria:** Cases of paediatric ALL younger than one year of age; those who left treatment before completion of induction chemotherapy; refused treatment

Ethical approval from IREB committee (via letter noA/28/EC/206/2020) and consent from parents of children were taken before the start of study. The diagnosis of standard and high risk was made according to NCI criteria on the basis of age, WBC count and cytogenetic abnormalities.[13] Standard risk group received dexamethasone, vincristine and peg-asparaginase while high risk group received dexamethasone, vincristine,peg- asparaginase and daunorubicin as per the UK ALL protocol.[14] Bone marrow examination was done on day 8 and 15 of induction in high-Risk and standard risk groups respectively to see the remission status. End of induction remission was documented by performing bone marrow examination on day 29. A good response was represented by < 5% blasts present on bone marrow and >5% blasts on bone marrow or any adverse event during the 29 days of therapy was taken as poor response.[15] Age, gender, presence of anemia and CNS involvement were correlated with outcome of treatment in our study population.

Participants were classed by standard and high-risk group. Descriptive statistics were used for analyzing the baseline data. Chi-square and t-test were used to evaluate the difference in outcome and other variables in standard and high-risk groups. Statistical Package for the social sciences (SPSS-24.0) was used to analyze the data for this study. Differences between groups were considered significant if *p*-values were ≤0.05.

## RESULTS

A total of 233 patients diagnosed as acute lymphoblastic leukemia at our department during the study period were included in analysis. One hundred and 44(61.8%) were male while 89(38.2%) patients diagnosed with this condition were female. One hundred and twenty (51.51%) patients were classed as standard risk group while 113(48.49%) were high-risk. The median ages were 4.2±1.2 and 7.2±4.2 years in standard risk and high-risk group respectively.

Table-I summarized the basic characteristics of study participants. Demographics, initial presentation and nutritional status were almost equal in both groups. WBC count was significantly higher in high-risk group as compared to standard risk group i.e 104.07±30.50 vs 13.59±27.4 with *p* value of <0.001. Most common presenting feature was pallor in 223(95.71%) patients followed by fever in 202(86.69%) patients.

**Table-I: Basic Characteristics of Study Participants**

| Variables | Standard risk n=120 (51.51%) | High risk n = 113 (48.49%) | *p*-value |
|---|---|---|---|
| Age in years | 4.2±1.2 | 7.2±4.2 | <0.001 |
| Age group | | | |
| <3 years | 27(22.5%) | 18(15.92%) | |
| 3-10 years | 93(77.5%) | 52(46.02%) | |
| >10 years | 0 | 43(38.05%) | |
| Gender | | | 0.536 |
| Male | 74(61.66%) | 70(61.94%) | |
| Female | 46(38.33%) | 43(38.05%) | |
| WBC count, 109/L | 13.59±27.4 | 104.07±130.50 | <0.001 |
| Hemoglobin g/dl | 7.08±2.47 | 7.97±2.36 | 0.537 |
| Platelets count 109/L | 65.53±79.04 | 67.13±97.66 | 0.562 |

There were more complications during induction chemotherapy in the high-risk group, but this difference was not statistically significant. The incidence of infection was 97(81.41%) in the high-risk group and 95(79.16%) in the standard risk group (*p*=0.395). The incidence of myopathy was 32(28.32%) in the high-risk group and 31(25.83%) in the standard risk group (p=0.749). CNS involvement was 3(2.7%) in high-risk group and 2(1.7%) in standard risk group (*p*=0.509). Testicular involvement was almost equal in both groups i.e. 43(38.1%) in high-risk group and 46(38.3%) in standard risk group (*p*=0.536).

Table-II summarized Treatment-related mortality (TRM) and other complications during induction chemotherapy. Mortality was 24(10.30%).TRM was greater, although not significantly in the high-risk group 14(12.39%) than in the standard risk group 10(8.33%), ($p$=0.211). After the induction chemotherapy, 178 patients underwent BM aspiration at day 29 to document remission status. Remission was higher, although not significantly in the standard risk group 93(97.89%) as compared to high risk group 77(92.77%), ($p$=0.185).

**Table-II: Presenting Features and Outcome of Induction Chemotherapy (n=233)**

| Variables | Standard risk n=120 (51.51%) | High risk n=113 (48.49%) | *p*-value |
|---|---|---|---|
| **Presentation** | | | |
| Pallor | 117(97.5%) | 106(93.8%) | 0.143 |
| Fever | 104(86.6%) | 98(86.7%) | 0.572 |
| Lymphadenopathy | 57(47.5%) | 57(50.42%) | 0.375 |
| Bruising | 28(23.33%) | 47(41.59%) | 0.002 |
| Bleeding | 09(7.5%) | 12(10.6%) | 0.274 |
| **Complications** | | | |
| Infections | 95(79.16%) | 92(81.41%) | 0.395 |
| Myopathy | 31(25.83%) | 32(28.31%) | 0.749 |
| Neuropathy | 4(3.3%) | 5(4.4%) | 0.362 |
| Mucositis | 2(1.66%) | 4(3.54%) | 0.314 |
| **Bone marrow status after induction chemotherapy** | | | |
| M1 | 93(97.89%) | 77(92.77%) | |
| M2 | 2(2.1%) | 4(4.8%) | |
| M3 | 0 | 2(2.4%) | |
| Treatment related mortality | 10(8.33%) | 14(12.39%) | 0.211 |

## DISCUSSION

Acute lymphoblastic leukemia (ALL) is common pediatric malignancy accounting for 70-80% of all leukemias.[14] The outcome of ALL in children has improved in the past

few years although no major change in chemotherapy medications.[15] We planned this study with the rationale to compare the outcome of induction chemotherapy in pediatric acute lymphoblastic leukemia patients between standard risk and high risk group at tertiary care hospital of Rawalpindi.

Schultz *et al*.,[16] conducted a study in 2007 and concluded response to medications was different in all the risk groups of patients suffering from ALL. We made two groups standard risk and high risk and concluded that despite intensive chemotherapy regimen high risk group had lower remission rate as compared to standard risk group.

Hasegawa *et al*.[17] published an interesting study in 2020 regarding if risk-adjusted therapy for pediatric non-T cell ALL improves outcomes for standard risk patients. They did a long term follow up and found out that it was effective for long term event free survival. Our study was slightly different from Hasegawa *et al*. as we did not follow the patients for long and assessed the outcome at 29th day but our results were similar to that of them that risk-adjusted therapy may be better for these patients as outcome was significantly different in the two groups

Marshall *et al*.,[18] published a study in 2013 regarding high-risk childhood acute lymphoblastic leukemia in first remission treated with novel intensive chemotherapy. They concluded that novel chemotherapeutic agents were efficacious in these patients but were toxic as well. They suggested risk-directed management and trials of novel therapies. We also found out that response rate is different for high risk and standard risk groups and they should be dealt with different management approach.

## LIMITATIONS OF STUDY

Limitations of our study were that patients were followed up for 29 days only, therefore long-term impact of treatment could not be established. These results reflect outcome of standard treatment offered in our setting and could not be generalized to other settings of our country.

## CONCLUSION

Patients in standard risk group have high remission rate after induction chemotherapy as compared to high-risk group. Patients in high-risk group have more complications and higher treatment related mortality as compared to standard risk group.

**Conflict of Interest:** None.

**Funding Source:** None.

**Authors' Contribution**

Following authors have made substantial contributions to the manuscript as under:

SN & MT: Data acquisition, data analysis, critical review, approval of the final version to be published.

AA & TG: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

SJ & NUN: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity

of any part of the work are appropriately investigated and resolved.

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