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RESEARCH PAPER

Time of Attainment of Clinical Remission and Peripheral Blood Count Recovery during Induction Chemotherapy for Childhood Acute Lymphoblastic Leukemia

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Abstract

Background: Acute lymphoblastic leukemia(ALL) is the most common pediatric malignancy. Infection and bleeding are the leading cause of death during induction chemotherapy in childhood ALL. So, proper knowledge about anticipated infection and bleeding are very important during this period. But the duration of clinical remission and recovery of peripheral blood count during induction chemotherapy is not well reported in literature.

Objective: The aim of the study was to determine the time of attainment of clinical remission and recovery of peripheral blood count after initiation of induction chemotherapy and to determine if the duration of clinical remission and peripheral blood count recovery differs between therapeutic risk groups.

Methods: This prospective observational study was conducted from January 2021 to December 2021 in the Department of Paediatric Haematology and Oncology, BSMMU. Newly diagnosed admitted Eighty-Six ALL of both sexes aged 1 to 17.9 years were included. After commencing chemotherapy, physical examination was recorded every day until clinical remission and complete blood count (CBC) was recorded one to two days interval until peripheral blood count recovery. The number of packed red blood cell (PRBC) and platelet transfusions and the number of days of intravenous antibiotics were recorded.

Results: Mean duration of clinical remission, complete Hemoglobin (Hb), Absolute neutrophil count(ANC) and platelet recovery was 8.4 ± 4.5 days, 25±7.9 days, 23.3±5.6 days and 21.8±6.4 days respectively (p<0.01). Time to attain partial recovery of platelet was 14.0±4.9 days in high risk and 19.2±5.3 days in standard risk group. PRBC transfusion requirement was 2.2±1.2 units in high risk group and 1.7±0.8 units in standard risk group (p<0.05). Time to attain partial recovery of ANC, number of days with I/V antibiotics and duration of treatment interruption were higher in high risk group.

Conclusion: Time of clinical remission was similar between risk group. Platelet recovery occurred earlier than Hemoglobin (Hb) and absolute neutrophil count (ANC) recovery. Transfusion and supportive care requirement were more in high risk group during induction chemotherapy. So, more supportive care should be arranged up to three weeks of induction period to increase survival of high risk childhood ALL.

Keywords: Peripheral blood count recovery, Childhood, Acute lymphoblastic leukemia(ALL)

Introduction

Acute lymphoblastic leukemia (ALL) is the most common pediatric malignancy. It represents 28% of all childhood cancers.[1] Currently 5 years overall survival is more than 90% in childhood ALL.[1,2] Though survival rate of childhood ALL exceed 90% in the western world, it is still very low in developing countries. Infection and bleeding are the predominant causes of mortality. Typically ALL is treated by chemotherapy in different phases-induction, consolidation and maintenance therapy. The aim of initial treatment is to achieve induction of complete remission. Complete remission is achieved when no evidence of leukemia is found by clinical examination, absence of peripheral blood blasts, bone marrow blast <5% and recovery of peripheral blood cell count.[3] Regeneration of bone marrow occurs after a few weeks of induction chemotherapy with or without stem cell rescue. Bone marrow restoration after chemotherapy is generally monitored by repeated complete blood

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count and peripheral blood film examinations. Usually reached its nadir in the first or second weeks. This period is very crucial for patients. Intensive clinical follow up and accurate laboratory analysis is very important for caring during this period. As a result, there is decrease in morbidity and mortality of patients, caused by anemia, bleeding and infections.[4] During induction period, chemotherapy associated toxicity like life threatening infection, bleeding and anemia are more prevalent.[5] The sooner the peripheral blood counts recover these complications become less.[6] To predict and prevent complications during induction chemotherapy, a good understanding about the period of peripheral blood count recovery is very important. On the other hand, rapidity of response is also a prognostic factor for ALL.[7,8] Along with other prognostic factors, a prompt decrease in leukemic blast and recovery of peripheral blood count are recognized as the predominant factor, as there is a remarkable association of relapse with low peripheral blood count after completion of induction chemotherapy.[9] So, the purpose of this study was to determine the time of clinical remission and the recovery of peripheral blood count after initiation of induction chemotherapy and to determine if this recovery differs between therapeutic risk groups.

Rationale: For prevention of infection and bleeding it is essential to study about the risk period. So that additional care could be taken during this period to reduce mortality and morbidity of patients. But limited information is found in literature regarding clinical remission as well as peripheral blood count recovery time during induction chemotherapy. So that planning for supportive care could facilitates in reducing mortality and morbidity. In addition, prospective estimation about duration of clinical remission and peripheral blood count recovery may be helpful to assess required supportive care between different risk groups. So the new knowledge obtained from this study will be utilized for planning of additional supportive care delivery in resource limited settings of Bangladesh as well as other developing countries.

Materials and Methods

This prospective observational study was conducted on Eighty-Six newly diagnosed ALL of both sexes aged 1 year to less than 18 years who were admitted into the Department of Pediatric Hematology and Oncology(PHO), Bangabandhu Sheikh Mujib Medical University(BSMMU). Partially treated patients and patients who received steroids in the past were excluded from the study. Informed written consent from the guardian was obtained during enrollment. Data were collected using a preformed data collection sheet. Baseline demographic characteristics, detailed history and thorough physical examination and baseline complete blood count were recorded. Chemotherapy was given to all patients with ALL according to United Kingdom Acute Lymphoblastic Leukemia(UKALL) 2003 protocol after stratifying risk according to NCI risk stratification criteria(Standard risk: age 1 to <10 years, total count of WBC <50,000/cumm, High risk: age ≥10 years, total count of WBC ≥50000/cumm). Regimen-A was given to the standard risk and regimen-B was specified for the high risk group. Induction phase is the first phase of the protocol, which comprises 35 days. In case of regimen A, the chemotherapeutic agent used in induction phase includes oral dexamethasone, L-asparaginase, 6-mercaptopurine. However, in regimen-B another drug daunorubicin was given additionally. PRBC transfusion was given when Hb <5 mmol/L. In case of hyperleukocytosis whole blood was given instead of PRBC and counted under PRBC number to ease the calculation. Platelet transfusion was given when platelet count < 20,000 cells/uL, any bleeding manifestation and before first IT/TIT if count was <50,000 cells/uL. In case of febrile neutopenia, IV antibiotics were given and treatment was interrupted as per institutional guideline.

After commencing chemotherapy, physical findings were recorded 1-2 days interval to observe resolution of presenting clinical features. The number of packed red blood cell and platelet transfusion, duration of IV antibiotic usages and treatment interruption(steroid and other chemo stopped for more than 2 days) were recorded. The complete blood count with peripheral blood film was recorded 1-2 days apart until recovery; performed as a routine practice. After discharge data were collected from Outpatient department follow up. Bone marrow morphology was checked in the Department of PHO, BSMMU to see bone marrow remission status. CBC was done by Automated Haematology analyzer (SYSMEX XS-800i) and it was manually checked. Clinical remission was considered when absence of presenting sign symptoms. Total enrolled patients were eighty-six. Among them four patients were in irregular follow up and ten patients died. So, remission and recovery was evaluated in seventy-two patients. ANC recovery day was defined as the first day of three consecutive values of ANC >500 cells/uL obtained on different days following nadir. Platelet recovery day was defined as the day of Platelet value >50,000 cells/uL at least 7 days after transfusion. The day when Hb level was more than 5 mmol/L without red cell transfusion in

2 weeks was defined as Hb recovery day. Partial recovery day was defined when ANC>500 cells/uL, platelet > 50,000 cells/uL, Hb>5 mmol/L. Complete recovery day was defined when ANC>1000 cells/uL, platelet>100000 cells/uL and Hb>6 mmol/L.

Statistical analysis was performed by using SPSS (Statistical Package for the Social Sciences) for windows version 22. To compare quantitative data between two risk groups, an unpaired Student's t- test was done. To compare the means of three groups ANOVA test was done and for intergroup comparison Boneferroni post Hoc test was done. *p*-value <0.05 was considered as significant.

Results

Among 82 studied patients, 66 (80.5%) patients were <10 years and 16(19.5%) patients were ≥10 years of age. Mean age was 6.1±4.2 years. Male patients were 51(62.2%), female patients were 31(37.8%). 75(91.5%) immunophenotyping was B cell and 7(8.5%) were T cell type. 73% (60) presented with total count of WBC <50000 cells/uL and 27% (22) presented with ≥50000 cells/uL. 59%(48) patients belonged to standard risk (SR) group and 41% (34) patients was in high risk group (HR). Most common presenting features were fever (96%), pallor (89%), history of blood transfusion (85%), Hepatomegaly (81%) and Splenomegaly (68%). Other less common presenting features were bone/joint pain, lymphadenopathy, bleeding, bony tenderness, headache and respiratory distress.

Complete recovery of Hb, ANC and platelet occurred in 41(56%), 57(79%) and 57(79%) of patients respectively. Time to attain complete recovery of Hb, ANC and Platelet were 25±7.9 days, 23.3±5.6 days and 21.8±6.4 days respectively.

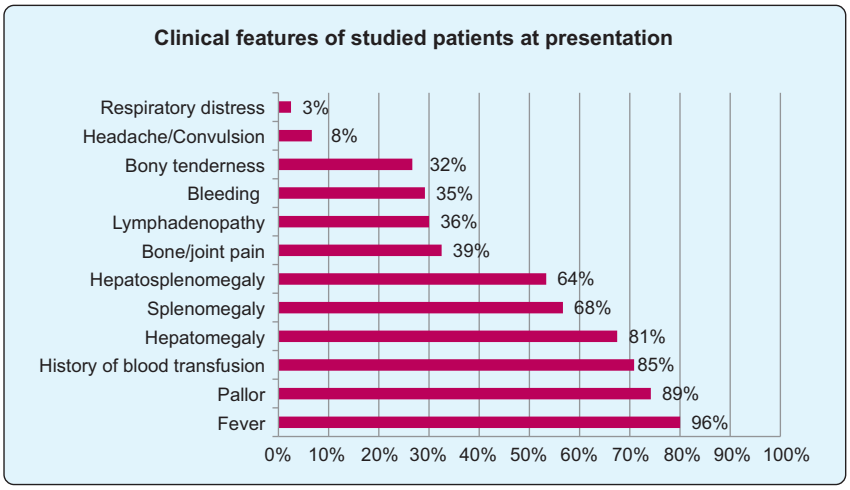

Figure1: Horizontal simple Bar diagram showing frequency of clinical features of study population (n=82) in percentage

Table I: Comparison of time to complete hemoglobin(Hb), absolute neutrophil count (ANC) and platelet recovery (n=72)

	Complete recovery			
	Hb (n=41)	ANC (n=57)	Platelet (n=57)	*p*-value
Mean±SD (Days)	25.0±7.9	23.3±5.6	21.8±6.4	0.008**
Range (Days)	4-35	12-34	6-34	
Group comparison				
Hb vs ANC				0.584
Hb vs Platelet				0.007**
ANC vs Platelet				0.154

Data were expressed as mean ± SD, *P* value <0.05 =Significant
n=number of recovered patient

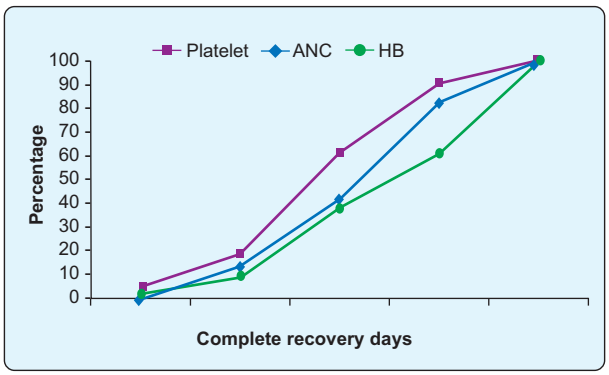

Figure 2: Line chart shows the percentage of patient with complete recovery day

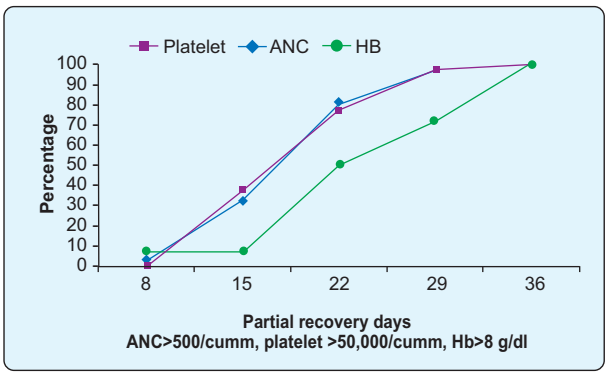

Figure 3: Line chart shows the percentage of patient with partial recovery day.

Table III: Comparison of time required duration of recovery between standard risk and high risk patient of ALL during induction chemotherapy

	Standard Risk(days)	High Risk(days)	*p* value
Partial recovery of platelet (n=35)	19.19±5.31	14±4.93	0.019^{s}
Complete recovery of platelet (n=57)	20.64±6.7	21.22±5.94	0.754^{ns}
Partial recovery of ANC (n=35)	17.93±5.79	18.5±5.01	0.825^{ns}
Complete recovery of ANC (n=57)	23.13±5.23	23.53±6.63	0.806^{ns}
Partial recovery of Hb (n=14)	23.1±10.05	22.5±5.8	0.914^{ns}
Complete recovery of Hb (n=41)	24±8.07	27.73±7.04	0.184^{ns}

s= significant, ns= not significant, n=number of patient.

Complete ANC and platelet recovery occurred mostly during 22 to 29 days and complete Hb recovery occurred during 29-35 days.

Average time to attain clinical remission was 8.4 ± 4.5 days. This study found average duration to achieve clinical remission was longer (9.5±5.2) days in HR group. It is 7.9±4.1 days in SR group. Among high risk patients sixty percent (15) required intravenous (IV) antibiotics whereas 42% (20) of SR patients required IV antibiotics. Treatment interruption found in 48% (12) patients of HR group and 31% (15) patients of SR group.

Time to attain partial recovery of platelet was 14.0±4.9 days in high risk and 19.2±5.3 days in standard risk group.

Discussion

This study found maximum childhood Acute lymphoblastic leukemia (ALL) fall in the age group <10 years which is consistent with other studies.[9,10] Male predominance was found in other studies as well.[11] Fever and pallor were more prevalent (Figure 1) than other studies.[12] This may be due to delayed diagnosis and referral causing advanced presentation. This study found platelet recovered earlier than ANC and Hb (Table I). Which is consistent with another study; where same protocol were used. [4,13] In a Bangladeshi study Yesmin et al. found the median time for platelet recovery was 22 days, which was one day later than ANC recovery.[14] In HR group partial platelet recovery was significantly earlier (p<0.05) than SR group (Table II). This finding consistent with a Danish study, where partial recovery of platelet occurred average 4 days earlier in HR group.[4] This study recorded less number of patients partial recovery day than complete recovery day. This can be explained by the fact that daily CBC was not done and some patients experienced treatment interruption due to febrile neutropenia and restarting of treatment occurs following recovery of count. In our study two patient's ANC never went into the nadir; even after getting chemotherapy their ANC were always more than 1000 cells/uL. There were 28 patients who achieved complete ANC recovery without documenting the day of partial recovery. Among those, one patient's ANC

was always above 500 cells/uL, eight patients had treatment interruption more than 7 days and interestingly rest of the patients achieved complete recovery from low count within 1 to 4 days interval period. 27 patients achieved complete platelet recovery without documenting the day of partial recovery. Causes of this event included treatment interruption (6 patients), platelet transfusion (14 patients), platelet count was always above >50,000 cells/uL (in 2 patients). Partial platelet and ANC recovery occurred mostly between day 15 to day 22. On the other hand, partial Hb recovery was delayed (Figure 3).

But Grunnan and Rosthoj found Hb and PLT recover earlier than ANC.[4] In this study Hb recovery is considered 15 days after transfusion and PLT recovery is considered 7 days after transfusion. Complete ANC and platelet recovery occurred mostly during 22 to 29 days and complete Hb recovery occurred during 29-35 days (Figure 2). Grunnan and Rosthoj found complete PLT recovery occurred in 3rd week but Hb and ANC recovery delayed to even 5th week and One-quarter of patients were still neutropenic at the end of induction.[4] Rauf et al also found 20% of patients not recovered at the end of induction.[15] This study found average duration to achieve clinical remission was longer in HR group. This may be due to high tumor load causing massive organomegaly taken more time to resolve. This study found transfusion requirement was more in HR group; this finding consistent with others study.[16]

This study found no significant difference between two risk group in days of antibiotic usages (Table II). Grunnan and Rosthos also found similar finding.[4] Mean duration of treatment interruption was not significantly different between risk groups. This can also be explained by the study of Rajeswari et al. where risk group did not affect the rate of infections.[17] The present study has some limitations that need to be mentioned. Complete blood count was not possible to record daily and it was a single center study.

Conclusion

In conclusion this study found three cell lines recovered at different time period. Platelet recovery occurred earlier than hemoglobin and absolute neutrophil count recovery. No significant difference was found in duration of clinical remission between standard and high risk group. Time to attain partial recovery of platelet was shorter in high risk group and transfusion requirement was higher in high risk group. However, time to attain partial recovery of ANC, I/V antibiotics and duration of treatment interruption were higher in high risk group. Multi-center studies are required to potentiate these findings.

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