Original Article

Effects of pre-existing undernutrition on treatment-related complications and treatment outcomes in children with acute lymphoblastic leukemia: A tertiary care center experience

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ABSTRACT

Background: Our study aimed to assess the influence of undernutrition on treatment tolerance, treatment-related complications, and treatment outcomes in acute lymphoblastic leucomia (ALL) patients during induction and maintenance phase of chemotherapy and subsequent follow-up visits. **Materials and Methods:** This retrospective, cohort study was conducted between January 2005 and September 2012 in the Departments of Pediatrics and Radiation Oncology in a tertiary care Medical College and Hospital of Eastern India. Using weight-for-age Z scores (WHO), we divided the 159 ALL patients into 4 groups: Group 1 without malnutrition, Group 2 with mild undernutrition, Group 3 with moderate undernutrition, and Group 4 with severe malnutrition. Data regarding blood counts, hematological support, bone marrow remission status and complications during treatment, and follow-up records were analyzed and compared to find out the impact of undernutrition on treatment tolerance and outcomes in different groups. **Results:** During the intensive phase of chemotherapy treatment, tolerance was assessed by the nadir of absolute neutrophil count and hemoglobin which fell significantly in moderate and severe malnutrition group. Significantly, more packed red blood cell support and platelet transfusions were required by those two groups $P < 0.002$ and $P < 0.001$, respectively. The incidence of febrile neutropenia was significantly more in severe malnutrition group ($P < 0.001$). Ninety-eight (61.63%) patients could not complete chemotherapy within the specified 145-day period of which 23 (76.67%) patients was of severe malnutrition group ($P < 0.002$). Remission after induction has shown declining trend with more undernutrition. A total of 24 patients relapsed in spite of bone marrow remission which was proportionately more from moderate and severe malnutrition group. During the 5-year follow-up, 20 patients died which was proportionately more in Group 3. **Conclusion:** Undernutrition adversely affect the final outcome, treatment tolerance, and treatment complications in children with ALL. So, baseline malnutrition should be considered as an important prognostic factor in therapeutic decision of ALL.

Key words: Acute lymphoblastic leucomia, complications, outcomes, undernutrition

INTRODUCTION

Acute lymphoblastic leukemia is the most common pediatric malignancy. It represents 25% of all childhood cancers and approximately 75% of all cases of childhood leukemia. A sharp peak of acute lymphoblastic leukemia (ALL) incidence is observed at 2-5 years of age.[1,2]

The results of the treatment of ALL in children depend not only on the biologic diversity of the leukemia cells and on the individual variability of drug metabolism, but also on the nutritional and socioeconomic status of the leukemic child.[3,4]

Protein energy malnutrition (PEM) has been identified as a major health problem in India.[3] The majority of PEM cases (nearly 80%) fall in the mild and moderate categories and frequently go unrecognized.[3,4] The effects of PEM on the therapeutic response of children with cancer are obviously relevant. The outcome of treatment in patients

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with ALL is clearly related to their nutritional status.[5,6] Studies conducted mainly in developing countries have shown malnutrition to be an important prognostic factor in such children. Malnutrition in children with leukemia causes decreased tolerance to and increased complications of subsequent chemotherapy and radiotherapy.[5,7] Few studies have examined malnutrition in ALL patients and its effect on tolerance to chemotherapy, especially in the first few months of intensive therapy.

The event-free survival of children with ALL in developed countries has increased substantially in the last 2 decades. Treatment with intensive protocols has brought the estimated probability of event -free survival at 6-7 years close to 75%. Although the prognosis of ALL has also improved in underdeveloped countries, the figures for event-free survival are lower, even when aggressive protocols are used.[8,9]

Unfavorable nutritional status could contribute to this observation. Mexican investigators demonstrated, for the first time, that malnutrition was an adverse prognostic factor in the outcome of children with standard risk ALL.[6]

Malnutrition is prevalent on large scale in hospitalized patients, who increases morbidity and mortality, reduces the effectiveness of medical treatment in our hospitals, and impairs the quality of life significantly. Early diagnosis and treatment of malnutrition is gaining the significance day by day.

Thus, we undertook this study to assess the influence of undernutrition in children with ALL and to observe its effect on tolerance to subsequent chemotherapy in terms of the incidence and severity of complications. We also aimed to establish malnutrition as a prognostic factor in children with ALL at the onset of chemotherapy in terms of survival and recurrence-free survival.

MATERIALS AND METHODS

This retrospective, single institutional cohort study was conducted between January 2005 and September 2012 in the Departments of Pediatric Medicine and Radiation Oncology of a Tertiary Care Medical College And Hospital of Eastern India. Patients with ALL who were registered in these two departments between January 2005 and January 2008 were enrolled in this study and followed-up till September, 2012.

The inclusion criteria were all children between the ages of 1 and 15 years with a confirmed diagnosis of ALL. Exclusion criteria were history of previous chemotherapy, clinical and laboratory evidence of chronic diseases (e.g., human immunodeficiency virus and disseminated tuberculosis), history of previous chromosomal disease and French-American- British (FAB) L3 morphology.

A detailed history of each and every patients and their heights and weights at baseline were obtained. Anthropometric measurements were obtained for each child and weight-for-age, height-for-age, and weight-for-height measures were calculated. Using weight-for-age Z scores (World Health Organization), we divided the children into four groups: Group 1, without malnutrition (−2 Z to +2 Z); Group 2, mild malnutrition (−2.01 Z to− 2.5 Z); Group 3, moderate malnutrition (−2.51 Z to − 3 Z); and Group 4, severe malnutrition (<−3 Z). Thus, 57, 41, 31, and 30 patients were categorized into Groups 1, 2, 3, and 4, respectively (total = 159).

Laboratory investigations which included complete blood count including hemoglobin, total leukocyte count, differential leukocyte count, and platelet counts were measured and recorded at baseline, twice a week during intensive phase of chemotherapy and weekly during maintenance phase of chemotherapy for all ALL patients. Baseline liver function tests, blood urea, serum creatinine, uric acid, and serum electrolytes were also monitored. Chest X-rays were taken to rule out mediastinal involvement. Bone marrow aspiration and biopsy studies, and flow cytometry were done in all patients for confirmation of the diagnosis.

After initial resuscitation and stabilization, definitive treatment was given as per MCP-841 modified National Cancer Institute protocol. This protocol consists of an initial 4-month period of intensive chemotherapy, including central nervous system prophylaxis therapy and a subsequent 24 months of maintenance chemotherapy.

All patients were monitored closely during the intensive phase when they were admitted in the pediatric medicine indoor. Thereafter, they were asked to follow-up at outpatient departments and were observed for the next 5 years after completion of maintenance chemotherapy, following the institutional protocol. Data regarding blood counts, hematological support, and bone marrow remission status at the end of day 28 (induction 1 phase), delay in between chemotherapeutic drugs and complications (including febrile neutropenia) were recorded, while the patients were subjected to the treatment protocol. All those data were compared between different groups as categorized based on nutritional status and the impact of malnutrition on treatment tolerance and treatment outcomes was analyzed. The follow-up records analyzed the survival (both overall and recurrence free) and pattern of relapse in different groups.

RESULTS AND ANALYSIS

A total of 159 patients (mean age 5.2 years) were included for the study. The baseline age and sex distribution of the patients in the four groups are shown in Table 1. Most of the patients (55.97%) belonged to the 1-10 years group. There was no significant baseline difference among the four groups. The male:female ratio was 1.41:1. Among the boys, 8 were <1 years old, 56 were 1-10 years, and 29 were >10 years of age. Five girls were <1 year age, 33 were 1-10 years old, and 28 were >10 years.

The clinical features of the patients recorded at presentation included fever in 145 (91.8%) patients, pallor in 138 (86.8%) children, bleeding manifestations in 84 (52.8%) patients, bone and joint pains in 22 (13.8%) children, splenomegaly in 130 (81.8%), hepatomegaly in 141 (88.7%) patients, lymphadenopathy in 114 (71.7%) of the study subjects, mediastinal mass in 14 (8.8%) patients, and testicular enlargement in 7 (4.4%) children.

Laboratory investigations revealed that hemoglobin levels <8 g/dL was present in 129 children (81.1%) at presentation. The total leukocyte count at diagnosis ranged widely, from <10,000/mm (13.5%)^3 to >1,000,000/mm^3 (18.2%). Thrombocytopenia was in 130 (81.13%) patients at the time of presentation. Eighty-two (51.57%) patients had a blast count >30% in the peripheral smear, and 18 (11.32%) did not have any blasts in the peripheral smear. In 29 (18.2%) patients, total serum protein <5.7 gm% of which 67% belonged to Group 4. Thirty-seven (23.3%) patients had serum albumin <3.5 gm% of which 54% belonged to Group 4.

Hundred and twenty-five (78.6%) patients had deficient calorie intake (29, 25, 36, and 35 in Groups 1, 2, 3, and 4, respectively) as was obtained from the 3-day recall questionnaire collected at the time of presentation and recorded in the files. Hundred and seventeen (73.6%) patients had deficient protein intake (22, 24, 36, and 35 in Groups 1, 2, 3, and 4, respectively) as obtained from the case files.

Mean (range) weight-for-age Z score was −1.56 (−3.68 to +3.92). Mean (range) height-for-age Z score was − 0.575 (−3.87 to +2.86). Mean (range) weight-for-height Z score was −0.42 (−3.12 to 3.76). FAB morphology L1:L2 was 97:62. Table 2 shows the weight-for-age, height-for-age, and weight-for-height for each group.

During the intensive phase of chemotherapy, treatment tolerance was assessed by the nadir of absolute neutrophil count (ANC) and fall in hemoglobin (%) as compared to baseline. This is depicted in Tables 3 and 4 respectively. The incidence of nadir of ANC <500 mm^3 was most common in Group 3. However, nadir of ANC between 500 and 1500/mm^3 was most common in Group 2 [Table 3]. There was >6 gm% fall in hemoglobin (%) as compared to baseline values most commonly in Group 4 (23.33%), which was statistically significant as compared with Group 1 normally nourished children ($P < 0.03$) [Table 4].

Treatment tolerance and related complications were also assessed during the intensive phase of chemotherapy based on the hematological support required (number of packed cells and platelets transfused), episodes of febrile

Table 1: Baseline age and sex distributions of the patients (*n*=159)

Group	No. of patients	Male (%)	Female (%)	Age <1 year	1-10 years	>10 years
1	57	35 (61.40)	22 (38.60)	4 (7.01)	36 (63.16)	17 (29.82)
2	41	26 (63.41)	15 (36.58)	4 (9.76)	20 (48.78)	17 (41.46)
3	31	17 (54.84)	14 (45.16)	3 (9.68)	18 (58.06)	10 (32.26)
4	30	15 (50)	15 (50)	2 (6.67)	15 (50)	13 (43.33)

Table 2: Comparison of the weight-for-age, height-for-age, and weight-for-height parameters in the study groups (*n*=159)

Group	Weight-for-age	Number of patients (%)	Height-for-age <−2 SD (%)	Weight-for-height <−2 SD (%)
1	−2 SD to +2 SD	57 (35.8)	1 (1.7)	1 (1.7)
2	−2.01 SD to -2.5SD	41 (25.8)	2 (4.9)	3 (7.3)
3	−2.5 SD to 3 SD	31 (19.5)	2 (6.5)	16 (51.6)
4	<−3 SD	30 (18.9)	4 (13.3)	24 (80)

SD: Standard deviation

Table 3: Nadir of absolute neutrophil count reached by each group during intensive phase of chemotherapy

Nadir of absolute neutrophil count during intensive phase (Group)		<100/m^3%	100-500/mm^3%	500-1500/mm^3%	>1500/mm^3%
1	57	8 (14.03)	30 (52.63)	16 (28.07)	3 (5.26)
2	41	7 (17.07)	15 (36.59)	17 (41.46)	2 (4.88)
3	31	8 (25.8)	17 (54.84)	5 (16.13)	1 (3.23)
4	30	7 (23.33)	12 (4.00)	11 (36.67)	0

neutropenia, number of deaths occurring during intensive phase of treatment, remission rate after completion of intensive phase, delay in treatment, that is, more days required to complete the intensive phase chemotherapy protocol compared to the standard 145-day regimen. These treatment tolerance parameters are shown in Tables 5 and 6. Table 5 shows that significantly more packed red blood cell (PRBC) support was required by patients with moderate malnutrition ($P < 0.002$) and patients with severe malnutrition ($P < 0.001$) as compared to Group 1 with no malnutrition. Platelets transfusion required by Group 4 patients was also statistically significant compared to Group 1 ($P < 0.003$). The incidence of febrile neutropenia was significantly more in Group 4 compared with Group 1 ($P < 0.001$).

Treatment outcome was assessed by the number of patients completing intensive phase chemotherapy within the specified 145 days period, bone marrow remission at the end of induction 1 phase of MCP-841 protocol and death during intensive phase of chemotherapy as shown in Tables 6, 7 and 8 respectively. Ninety-eight (61.63%) patients could not complete chemotherapy within the specified 145-day period of intensive phase chemotherapy as shown in Table 6. Of them, 31 (54.39%) patients belonged to Group 1, 23 (56.10%) patients belonged to Group 2. Table 6 also tells that 21 (67.74%) patients of Group 3 and 23 (76.67%) patients of Group 4 could not complete chemotherapy within the specified period. The difference between Group 1 and Group 4 was statistically significant ($P < 0.002$).

At the end of induction 1 phase of MCP-841, that is, after 28 days of intensive chemotherapy, 52 (91.2%), 34 (82.9%), 24 (77.4%), and 23 (76.7%) of the patients in Groups 1, 2, 3, and 4, respectively, achieved bone marrow remission status; this finding was clinically significant, showing declining trend with more undernutrition; but not statistically significant ($P > 0.05$). Table 7 shows 19 (11.95%) of the patients did not achieve remission after 28 days of induction. However, the difference between the groups was not statistically significant ($P > 0.05$).

During intensive phase of chemotherapy, eight patients died of which two patients (3.5%) belonged to Group 1, one (2.4%) from Group 2, two (6.5%) from Group 3, and three (10%) from Group 4. This result was statistically insignificant. Comparing weight-for-height (acute malnutrition) for each of the patients having death as outcome, all deaths occurred in children with malnutrition and none occurred in the well-nourished group, a statistically significant result ($P < 0.005$) [Table 8].

Of the 151 patients asked to follow-up at the outpatient departments of Medical College and Hospitals, Kolkata, 29 (19.21%) were lost to follow-up. Out of the 122 patients who were on regular follow-up, 24 patients relapsed in spite of bone marrow remission achieved after intensive phase chemotherapy as shown in Table 9. Of them, seven (15.2%) belonged to Group 1, six (19.3%) belonged to Group 2, five (21.7%) were from Group 3, and six (23.3%) were from Group 4. Though this result is not statistically

Table 4: Fall of hemoglobin during intensive phase as compared with baseline hemoglobin of each patient during the intensive phase

Fall of hemoglobin during intensive phase as compared with baseline (*n*=159) (Group)		Fall by>6 gm%	Fall by 4-6 gm%	Fall by 2-4 gm%
1	57	8 (14.03)	22 (38.60)	21 (36.84)
2	41	6 (14.63)	18 (43.90)	12 (29.27)
3	31	7 (22.58)	12 (38.71)	9 (29.03)
4	30	7 (23.33)	14 (46.67)	7 (23.33)

Table 5: Treatment complications during intensive phase of chemotherapy based on the hematological support required and incidence of febrile neutropenia

Number of PRBC transfusion (Group)	Number of patients	Required by group	Mean (±SD)	Test of significance Kruskal-Wallis test
1	57	113	1.98 (±0.61)	
2	41	87	2.12 (±0.87)	*P*=0.46 (NS)
3	31	102	3.29 (±0.91)	*P*<0.002(SS)
4	30	117	3.90 (±0.98)	*P*<0.001(SS)
Number of platelet transfusion				Kruskal-Wallis Test
1	57	198	3.47 (±2.12)	
2	41	142	3.46 (±3.46)	*P*=NS
3	31	189	6.10 (±4.52)	*P*=NS
4	30	218	7.3 (±5.69)	*P*<0.003
Febrile neutropenia		Number of episodes		Chi-square test
1	57	81	1.42 (±0.67)	
2	41	72	1.76 (±0.81)	*P*=NS
3	31	93	3.00 (±1.12)	*P*=NS
4	30	114	3.80 (±0.97)	*P*<0.001(SS)

Table 6: Patients not completing intensive phase chemotherapy within the specified 145 day period (*n*=98)

Groups	No. of patients not completing treatment within the specified 145-day period %	*P* value
1	31 (54.39)	NA
2	23 (56.10)	NS
3	21 (67.74)	NS
4	23 (76.67)	<0.002

NA: Not applicable, NS: Not significant

Table 7: Patients not achieving remission after the induction 1 phase of MCP-841, that is, after 28 days of intensive chemotherapy (*n*=19)

Remission not achieved (Groups)	Number of patients not achieved remission after induction, i.e., 28 days of chemotherapy (%)	*P* value
1	7 (12.7)	NA
2	5 (12.5)	0.49(NS)
3	4 (13.8)	0.46(NS)
4	3 (11.1)	0.37(NS)

NA: Not applicable, NS: Not significant

Table 8: Patients who expired during the intensive phase of chemotherapy (*n*=8)

Death during treatment Group	Number of patients (%)	*P* value
1	2 (3.5)	NS
2	1 (2.4)	NS
3	2 (6.5)	NS
4	3 (10)	NS

NA: Not applicable, NS: Not significant

Table 9: Patients who relapsed on follow-up in spite of bone marrow remission achieved after intensive phase chemotherapy (*n*=24 out of 122 patients)

Relapse after remission (during 5 years follow-up)	Number of patients on follow-up	Number of patients having relapse %	*P* value
1	46	7 (15.2)	NA
2	31	6 (19.3)	NS
3	23	5 (21.7)	NS
4	22	6 (23.3)	NS

NA: Not applicable; NS: Not significant

significant, it is clinically significant. During the 5-year follow-up, seven (12.2%) of Group 1, four (9.8%) of Group 2, five (16.1%) of Group 3, and four (13.3%) of Group 4 died in the 5th year. The most common cause of death in the follow-up group was relapse and related complications as confirmed by bone marrow aspiration and biopsy.

DISCUSSION

Over the past 5 decades, the treatment of ALL has been based on prognostic factors. A few earlier studies correlated malnutrition in childhood ALL and 5-year disease-free survival, but little research has examined malnutrition and its effect on tolerance to chemotherapy, especially in the first few months of intensive therapy.[6]

Viana *et al.*,[10] compared malnutrition with the risk of relapse in ALL, while Lobato-Mendizabal *et al.*,[6] compared malnutrition to the 5-year disease-free survival rate and established a positive correlation. Two Indian studies—Kumar *et al.*,[7] and Jain *et al.*,[11] included 25 and 44 children, respectively, on therapy for ALL and studied factors of prognostic significance with respect to tolerance to chemotherapy. They established definite poor treatment tolerances and increased complications in undernourished patients.

In our study, we categorized the children in four groups according to nutritional status and mainly took weight for age as the main yardstick. Treatment tolerance was assessed by nadir values of an absolute neutrophil count during intensive phase of chemotherapy and nadir values of hemoglobin during intensive phase. A total of 23.33% of the patients in Group 4 (group with severe malnourished children) showed nadir values of absolute neutrophil count below 100, whereas that was 14.03% in Group 1, normally nourished children. Overall, nadir values of absolute neutrophil counts and hemoglobin percentages were lower in the moderately and severely malnourished children as compared to the normal nutrition group as evidenced by Tables 2 and 3. So, treatment-related anemia and fall in absolute neutrophil counts are proportional to the poor nutritional status. Our study also proved that treatment tolerance became poor with the poorer nutritional status as significantly more PRBC support was required by patients with moderate malnutrition ($P < 0.002$) and patients with severe malnutrition ($P < 0.001$) as compared to Group 1 with no malnutrition. Similar results were also obtained with respect to platelets transfusion. The incidence of febrile neutropenia was significantly more in Group 4 when compared with Group 1 ($P < 0.001$) during intensive phase of treatment and nonachievement of remission after induction 1 phase was higher in severe and moderate malnutrition group as compared to no nutrition or mild malnutrition group. During the 5-year follow-up, seven (12.2%) of Group 1, four (9.8%) of Group 2, five (16.1%) of Group 3, and four (13.3%) of Group 4 died in the 5th year. The most common cause of death in the follow-up group was relapse and related complications as confirmed by bone marrow aspiration and biopsy.

In developing countries like India, undernutrition is an important prognostic factor in the final outcome, treatment tolerance and treatment related complications in children with malignancies like ALL. PEM not only has an overwhelming influence on complication rates but should be considered as a major factor in determining a treatment schedule and making therapeutic decisions.

CONCLUSION

Undernutrition adversely affects the final outcome

of chemotherapy in children with ALL. Treatment tolerance assessed by the nadir of absolute neutrophil count and hemoglobin fell significantly in the group with moderate and severe undernutrition. PRBC and paletelets support was required in significantly higher numbers in Groups 3 ($P < 0.002$) and 4 ($P < 0.001$). There was significantly more episodes of febrile neutropenia ($P < 0.001$), more number of days to complete treatment and relapse in children with ALL belonging to Groups 3 and 4. So baseline PEM status of the patients should be considered as an important prognostic factor in therapeutic decision of ALL.

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