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Nutritional Assessment of Children With Hematological Malignancies and Their Subsequent Tolerance to Chemotherapy

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ABSTRACT

Background: Our research goals were to assess the prevalence of malnutrition in children with cancer, observe malnutrition's effect on tolerance to chemotherapy, and establish malnutrition at onset as one of the prognostic factors in children with hematological malignancies.

Methods: This prospective study examined children ages 1-15 years with a confirmed diagnosis of acute lymphoblastic leukemia (ALL) and non-Hodgkin lymphoma. Each child was subjected to a detailed history, anthropometric examination, and laboratory investigations. Based on the anthropometric measurements that used weight-for-age Z scores, we divided the children into 4 groups: group 1, without malnutrition; group 2, mild malnutrition; group 3, moderate malnutrition; and group 4, severe malnutrition. We analyzed data for each group regarding the behavior of blood indices, the quantum of hematological support, bone marrow remission status on day 28, adherence to protocol schedules, and complications in the first 4 months of intensive chemotherapy.

Results: Of the 34 patients in the study (mean age, 7.1 years; male:female ratio, 1.6:1), 79% had deficient calorie intake and 74% had deficient protein intake. Packed cell requirements and complications were significantly higher in malnourished children, whereas the requirement for platelet transfusions was statistically insignificant. Also, 50%, 40%, 38%, and 44% of children in groups 1, 2, 3, and 4, respectively, completed chemotherapy within the specified time period. At the end of the induction phase, 92%, 60%, 87%, and 77% of the patients in groups 1, 2, 3, and 4, respectively, achieved bone marrow remission. No deaths occurred in group 1; 1 death each occurred in groups 3 and 4, and 2 in group 2. When these deaths were extrapolated to the weight/height ratio (acute malnutrition), we found that all occurred in children with malnutrition, a statistically significant result.

Conclusions: Malnutrition is widely prevalent in children with ALL in India and has a significant bearing on the occurrence of life-threatening complications and short-term outcomes in these children. Malnutrition is also a significant factor influencing treatment planning and therapeutic decisions.

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BACKGROUND

Protein energy malnutrition (PEM) has been identified as a major health problem in India.[1] The majority of PEM cases (nearly 80%) fall in the mild and moderate categories and frequently go unrecognized.[2] The incidence of cancer and its mortality have been steadily rising in both developing and developed countries. Malnutrition in children with cancer causes decreased tolerance to and increased complications of subsequent chemotherapy.[3] Few studies have examined malnutrition in cancer patients and its effect on tolerance to chemotherapy, especially in the first few months of intensive therapy. Thus, we undertook this study to assess the prevalence of malnutrition in children with cancer 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 at onset as a prognostic factor in children with hematological malignancies.

METHODS

This prospective study conducted between August 2004 and July 2006 in a medical college hospital in coastal Karnataka included children between the

Table 1. Comparison of the Weight-for-Age, Height-for-Age, and Weight-for-Height Parameters in Each Study Group

Group	Number of Patients (%)	Weight-for-Age Z Score	Height-for-Age <-2 (%)	Weight-for-Height <-2 (%)
1	12 (35%)	−2 to +2	0 (0%)	0 (0%)
2	5 (15%)	−2.01 to −2.50	0 (0%)	1 (20%)
3	8 (24%)	−2.51 to −3.0	1 (13%)	8 (100%)
4	9 (26%)	<-3.0	2 (22%)	9 (100%)

ages of 1 and 15 years with a confirmed diagnosis of acute lymphoblastic leukemia (ALL) and non-Hodgkin lymphoma (NHL). Exclusion criteria were previous therapy, clinical and laboratory evidence of chronic diseases (eg, human immunodeficiency virus and disseminated tuberculosis), and French-American-British L_3 morphology.

Parents provided a detailed history, including a 3-day recall diet history. We conducted an anthropometric evaluation of each child, obtaining weight-for-age, height-for-age, and weight-for-height measures. Using weight-for-age Z scores (World Health Organization), we divided the children into 4 groups: group 1, without malnutrition (–2Z to +2Z); group 2, mild malnutrition (–2.01Z to –2.5Z); group 3, moderate malnutrition (–2.51Z to –3Z); and group 4, severe malnutrition (<-3Z). There were 12, 5, 8, and 9 patients in groups 1, 2, 3, and 4, respectively.

Blood counts—hemoglobin, total count, differential count, platelet count, and peripheral smear study—were measured. Other blood tests estimated total protein, albumin, blood urea, S-creatinine, serum glutamic pyruvic transaminase (SGPT), serum glutamic oxaloacetic transaminase, uric acid, and serum electrolytes. Chest x-rays were taken to rule out mediastinal involvement. We conducted bone marrow aspiration, biopsy studies, and flow cytometry in all patients to confirm the diagnosis.

After the patients' general conditions were stabilized, they were subjected to the 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.

We closely supervised all children and analyzed data regarding the behavior of blood counts, hematological support, bone marrow remission status at the end of day 28, adherence to protocol schedules, and complications (including febrile neutropenia and bleeding) in the first 4 months of intensive therapy.

RESULTS

Of the 34 patients in this study (mean age, 7.1 years), the male:female ratio was 1.6:1 (n=21:13). Among the boys, 2 were <2 years old, 12 were 2-10 years, and 7 were >10 years of age. Eight girls were 2-10 years old, and 5 were >10 years.

The clinical features of disease included fever (97%), pallor (76%), bleeding manifestations (50%), bone and joint pains (14%), splenomegaly (79%), hepatomegaly (85%), lymphadenopathy (68%), mediastinal mass (12%), and testicular enlargement (3%).

Anemia was one of the most common manifestations; 20 children (59%) had hemoglobin levels <8 g/dL, and 11 (32%) had levels between 8 and 10 g/dL. The remainder had values above 10 g/dL. The total leukocyte count at diagnosis ranged widely, from <10,000 mm^3 to >1,000,000 mm^3. More than 75% of the patients had thrombocytopenia. Eighteen patients had a blast count >30% in the peripheral smear, and 4 did not have any blasts in the peripheral smear. Seven of the 34 children had total serum protein <5.7 g%, whereas 11 had serum albumin <32 g%. SGPT was more than twice the normal level in 2 of the 34 patients. Blood urea was increased beyond the reference value for age in 3 patients and serum creatinine in 4. Serum uric acid was >5.5 mg/dL in 6 patients.

Twenty-seven patients (79%) had deficient calorie intake (6, 5, 8, and 8 in groups 1, 2, 3, and 4, respectively), and 25 (74%) had deficient protein intake (5, 5, 7, and 8 in groups 1, 2, 3, and 4, respectively).

Table 1 shows the prevalence of acute and chronic malnutrition in each group. The various demographic parameters were distributed equally among the 4 groups; hence, we could compare them statistically (Table 2).

We assessed disease outcome in the various groups based on the amount of hematological support required (packed cells and platelets), episodes of febrile neutropenia, number of deaths, remission rate, and adherence to the chemotherapy schedule, ie, number of days required to complete the standard chemotherapy protocol (Tables 3 and 4).

Nearly 50%, 40%, 38%, and 44% of children completed chemotherapy in groups 1, 2, 3, and 4, respectively, within the specified 145-day period, which was statistically insignificant (P=.93). At the end of induction, 92%, 60%, 87%, and 77% of the patients in groups 1, 2, 3, and 4, respectively,

Table 2. Distribution of Various Clinical and Laboratory Parameters in Each Study Group

1. Age					
Group	**n**	**<2 years (%)**	**2-10 years (%)**	**>10 years (%)**	
1	12	0 (0%)	11 (92%)	1 (8%)	
2	5	0 (0%)	2 (40%)	3 (60%)	
3	8	1 (13%)	6 (74%)	1 (13%)	
4	9	1 (11%)	3 (33%)	5 (56%)	
2. Gender					
Group	**n**	**Male (%)**	**Female (%)**		
1	12	7 (58%)	5 (42%)		
2	5	2 (40%)	3 (60%)		
3	8	6 (75%)	2 (25%)		
4	9	6 (67%)	3 (33%)		
3. Total Leukocyte Count					
Group	**n**	**<4,000 (%)**	**4,000-10,000 (%)**	**10,000-1,000,000 (%)**	**>1,000,000 (%)**
1	12	3 (25%)	3 (25%)	5 (42%)	1 (8%)
2	5	3 (60%)	0 (0%)	2 (40%)	0 (0%)
3	8	3 (37%)	3 (37%)	1 (13%)	1 (13%)
4	9	0 (0%)	3 (33%)	3 (33%)	3 (33%)
4. Blast Morphology					
Group	**n**	**L_1 morphology**	**L_2 morphology**		
1	12	6 (50%)	6 (50%)		
2	4	2 (50%)	2 (50%)		
3	8	4 (50%)	4 (50%)		
4	8	3 (38%)	5 (63%)		

achieved bone marrow remission status; this finding was not statistically significant (χ^2=2.71, P>.05). No patients died in group 1, while 1 death each occurred in groups 3 and 4, and 2 in group 2. This result was statistically insignificant (χ^2=5.44, P>.142). Extrapolating each of the deaths to weight/height (acute malnutrition) revealed that all deaths occurred in children with malnutrition and none occurred in the well-nourished group, a statistically significant result (χ^2=4.03, P=.045).

DISCUSSION

Over the past 5 decades, the treatment of ALL has been based on prognostic factors. A few earlier studies[4] 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.

Viana et al[5] compared malnutrition with the risk of relapse in ALL, while Lobato-Mendizabal et al[4] compared malnutrition to the 5-year disease-free survival rate. Two Indian studies—Kumar et al[6] and Jain et al[7]—included 25 and 44 children, respectively, on therapy for ALL and studied factors of prognostic significance with respect to tolerance to chemotherapy. Both studies were prospective in nature and excellently designed.

Almost all studies, including those from the Children's Cancer Study Group (CCSG)[8] and St Jude's Children's Research Hospital (SJCRH),[9] have established that the age group most commonly affected by ALL is children 2-10 years old. The CCSG reported the incidence of ALL in the 2-10 age group to be approximately 77%, and SJCRH studies reported the incidence as 73%. Our rate was similar (65%). A slight male preponderance in our study was also similar to that in the SJCRH and CCSG studies. Fever, anemia, bleeding manifestations, and organomegaly were the most frequent clinical features noted in our study, as well as in the others.[8,9]

In the present study, 59% of patients had a hemoglobin level <8 g/dL that was comparable to the SJCRH[9] (52%) and Medical Research Council (MRC)[10] (54%) studies. The total leukocyte count determines the tumor burden of a patient with ALL and forms an important prognostic factor. In most studies,[9-11] including ours, hyperleukocytosis was observed in 13%-15% of children with ALL. Thrombocytopenia is a common and important feature at diagnosis. Of our 34 patients, 20% had platelet count >1,500,000/mm^3, whereas in the SJCRH[9] and MRC[10] studies, the rates were 32% and 15%, respectively.

Table 3. Outcomes in Each Study Group

1. Number of Transfusions (Packed Cells)				
Group	**n**	**Consumed by the entire group**	**Mean (SD)**	**Significance**
1	12	21	1.75 (0.57)	Kruskal-Wallis test
2	5	15	3.2 (0.84)	$P < .001$
3	8	22	2.75 (0.7)	highly significant
4	9	32	3.56 (0.88)	
2. Platelet Transfusion				
Group	**n**	**Consumed by the entire group**	**Mean (SD)**	**Significance**
1	12	35	2.93 (1.98)	Kruskal-Wallis test
2	5	22	4.4 (2.97)	$P = .15$
3	8	32	4.13 (2.75)	insignificant
4	9	50	6.78 (5.78)	
3. Febrile Neutropenia				
Group	**n**	**Episodes for the entire group**	**Mean (SD)**	**Significance**
1	12	20	1.67 (0.65)	$\chi^2 = 28.226$
2	5	11	2.2 (1.04)	$P = .001$
3	8	22	2.75 (0.71)	highly significant
4	9	28	3.11 (1.05)	

SD, standard deviation.

The prevalence of malnutrition in our study is similar to that of the Jain et al[7] and Kumar et al[6] studies in India. However, the prevalence is much higher compared to global rates of malnutrition in the general population worldwide[12] and also higher than in Brazil (Viana et al).[5]

Tolerance to chemotherapy was assessed in terms of febrile neutropenic episodes, remissions, death, or treatment delay (Table 4). The number of episodes of febrile neutropenia was significantly higher in the present study compared to the studies of Kumar et al[6] and Jain et al,[7] probably because the entire study group was comprised of children with ALL being treated with the same protocol, all of whom received high-dose marrow-toxic chemotherapy. The rate may also have been higher because of the close follow-up and better compliance of the patients in our study, which resulted in the earlier recording of febrile episodes. Also, Jain et al[7] comprised all cancers and different treatment regimens, including those not specifically targeted at the bone marrow.

In our study, deaths and delays in treatment were more common in malnourished children, and well-nourished children had better remission rates. These results are consistent with previous studies on the subject.

In developing countries such as India, malnutrition can be an important prognosticating factor in the final outcome in children with malignancies in general and those with ALL in particular. Not only does malnutrition have an overwhelming influence on complication rates, but it is also a major factor in determining a treatment schedule and making therapeutic decisions. Although the effect of malnutrition on long-term survival is outside the purview of this study, there can be no doubt that the influence of malnutrition during the first few months of therapy affects long-term survival: The high prevalence of malnutrition in

Table 4. Tolerance to Chemotherapy: A Comparison Among Various Studies

	Present Study		**Kumar et al Study[6]**		**Jain et al Study[7]**	
Weight/age	<-2 SD	>-2 SD	<80%	>80%	<-2 SD	>-2 SD
Number	22 (65%)	12 (35%)	13 (52%)	12 (48%)	25 (57%)	19 (43%)
Episodes of febrile neutropenia	61	20	4	3	7	6
Remission	17 (77%)	11 (92%)	5 (38%)	7 (58%)	13 (52%)	11 (58%)
Deaths	4 (18%)	0 (0%)	2 (15%)	0 (0%)	12 (48%)	8 (42%)
Treatment delay	13 (59%)	6 (50%)	-	-	7 (28%)	3 (16%)

SD, standard deviation.

children with ALL indicates that it should be considered in all therapeutic and protocol-making decisions in patients living in developing countries who have childhood malignancies. A follow-up study of these cases over 5 years will be helpful in determining the long-term effect of malnutrition on survival in children with ALL and is strongly recommended.

CONCLUSIONS

Malnutrition is widely prevalent in children with ALL in India and has a significant bearing on the occurrence of life-threatening complications and short-term outcomes in these children. It is also a significant factor influencing treatment planning and therapeutic decisions. To prevent unwanted complications, the nutritional build-up and subsequent support of children with ALL must be carried out prior to starting chemotherapy.

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