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Implications of undernutrition in children with acute lymphoblastic leukaemia during induction therapy – experience from a developing country

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ABSTRACT

Introduction: Undernutrition is an important prognostic factor in children with acute lymphoblastic leukaemia (ALL) and higher incidences of mortality are reported during induction remission in severely undernourished children. This study was conducted to assess the prevalence and implications of malnutrition among ALL children during induction therapy. **Methods:** All children ≤18 years diagnosed and treated for ALL at our institution, between June 2010 to July 2016 were included in this retrospective cohort study. Nutrition was assessed by body mass index-for-age *z*-scores calculated using World Health Organization's Anthro (<5 years) and Anthro-Plus Software (≥5 years). Children with a *z*-score of <-2 standard deviation (*SD*) were classified as undernourished. All events and outcomes were compared between undernourished and adequately nourished children. **Results**: A total of 72 children were included in this study. Nineteen (26.4%) were undernourished at the time of diagnosis. Twenty-eight (38.8%) children had significant weight loss. Sixty-seven of them attained remissions by the end of induction chemotherapy. Five children who died had significant weight loss. Children with significant weight loss during induction phase had a higher risk of developing complications such as febrile neutropenia, pneumonia, mucositis, and drug interruptions. Those with a deteriorating nutritional status had a higher chance of poor treatment outcome (p=0.05, CI=95%). **Conclusion**: It is important to assess and monitor the nutrition status of children and timely nutritional intervention is essential. A simple, cost effective nutritional intervention that will decrease morbidity and mortality associated with the disease must be devised.

Keywords: acute lymphoblastic leukaemia, induction therapy, outcome, undernutrition

INTRODUCTION

The five years survival rate for acute lymphoblastic leukaemia (ALL) is more than 80% in many developed countries, but the cure rate is lower in developing countries. The causes of poorer outcomes in developing countries are multifactorial, and these include limited resources for diagnosis, limited access to treatment, diagnostic delays due to lack

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of awareness, infections, and underlying increased incidence of undernutrition. One of the major issues in improving survival rates of children with ALL in developing countries is the increased rate of mortality during the induction phase, which is again attributed to infections, undernutrition, and poor tolerance to treatment. When compared to developed countries, a higher proportion of children in developing countries have undernutrition at the time of diagnosis and also higher number of high risk patients presenting with advanced disease than low risk patients (Maldonado *et al.*, 2015).

Advanced disease status alters nutritional state, causing protein and micronutrient deficiencies. Poor nutritional status in turn influences the course of disease and survival prospects. Various studies have proven that undernourished children with ALL have poorer clinical outcomes when compared to normally nourished children, due to decreased tolerance to chemotherapy, altered metabolism of chemotherapy drugs, and increased infection rates (Gokcebay *et al.*, 2015).

MATERIALS AND METHODS

This retrospective cohort study was conducted in the Division of Paediatric Hemato Oncology, at Sri Ramachandra Institute of Higher Education and Research, Chennai, India as a part of the Indian Council of Medical Research's (ICMR) Short Term Studentship (STS) programme. Institutional Ethics Committee approval was obtained. Participant's parental consent was also obtained.

All patients, between 1-18 years of age, who were diagnosed with ALL and treated throughout the course of induction therapy at our medical centre were included in the study. Patients above 18 years, those presenting with a relapse, those who have started treatment at another medical facility, and those who have abandoned treatment were excluded.

The study was conducted over a period of two months. The patients' medical records were accessed, and the necessary data were retrieved. These included demographic data, hospital identity, date of diagnosis, risk stratification, and drugs used in induction therapy. The patient's height in centimetres (cm) and weight in kilograms (kg) were noted from the medical records, on day 1 (day of diagnosis), and during every admission. Laboratory records were accessed and the presence of anaemia, hypoalbuminemia, and hypokalaemia at diagnosis were noted. Any events during treatment such as febrile neutropenia, drug interruption and dose modification, mucositis, blood products requirement, and infections were noted.

The Anthro Software of the World Health Organization (WHO) (version 3.0.1; Department of Nutrition, WHO) was used to calculate the body mass index (BMI) and BMI-for-age z-score of patients up to the age of five years (60 months). The WHO Anthro-plus software (version 1.0.2) was used to calculate the BMI and BMI-for-age z-score for children above five years of age (completed 60 months). Nutritional status was classified according to the WHO criteria (WHO, 2009; WHO, 2006). The study cohort was categorised into three groups:

- Undernourished – patients with a z-score >2 standard deviation (*SD*) below mean BMI-for-age (<-2SD)
- Adequately nourished – patients with a z-score between 2*SD* below (-2SD) and 1*SD* (+1*SD*) above the mean BMI-for-age
- Over-nourished – patients with a z-score above 1*SD* (+1*SD*) above mean BMI-for-age.

Weight loss >10% or a decrease in BMI *z*-score by ≥1*SD* below the previous *z*-score was considered significant.

Anaemia was diagnosed according to WHO criteria. Febrile neutropenia was defined as the occurrence of a single oral temperature of >38.3 ^{0}C (101.4F) or 38 ^{0}C(101F) for >1 hour along with an absolute neutrophil count (ANC) <500 or 1000 with predicted rapid decline during the next 48 hours.

Children with age >1 year and <10 years, white blood count (WBC)< 50,000/ mm^3, good response to prednisolone, no testicular involvement, no bulky disease, and no high risk cytogenetics were considered as standard risk.

Children with high risk cytogenetics like BCR ABL positivity, iAMP 21, MLL and T (1:19) positivity, hypodiploidy, poor response to prednisolone, and minimal residual diseases (MRD) positive at the end of induction, T-cell phenotype were considered to be of high risk.

Statistical analysis was done using SPSS version 17.0. Demographics and clinical variables were analysed using frequencies and percentages for categorical variables. We also determined the associations between various parameters including nutritional status at diagnosis and outcomes. Crude odds ratio (OR) and 95% confidence interval (CI) were calculated with those 'attaining remission' as the reference category. The statistical significance level was set at 5%.

RESULTS

Among 84 children who were diagnosed with ALL at our centre, between June 2010 and June 2016, one child abandoned treatment and 11 children continued further treatment at their native places. Thus, the final study population included 72 children.

Table 1 demonstrates the demographic and medical characteristics of the children. A total of 19 (26.3%) children were undernourished at diagnosis. Among these 19 who were undernourished, 15 (78.9%) also had anaemia. There was a strong association between the nutritional status of children and socioeconomic status (p<0.038, with 95% CI); malnutrition was found to be more common among children of lower socioeconomic status (Table 2). The mean *z*-score at diagnosis was -0.53 (*SD*: ±2.36). Thirty eight out of the 72 (52.7%) patients had weight loss; 28 (73.6%) of this 38 had significant weight loss. There was no statistical significance between socioeconomic status and significant weight loss (Table 3).

Table 4 gives the details of the events during induction phase. A total of 16 children had induction therapy free of events. Febrile neutropenia, mucositis, pneumonia, and drug interruptions were found to be more common in those who had significant weight loss than in those who were undernourished at diagnosis, but only febrile neutropenia was found to be statistically significant among the other variables (p=0.001).

DISCUSSION

Adequate nutrition in children with cancer is essential to maintain optimal growth and development, decrease toxicity, enhance survival outcome, and improve quality of life (Owens *et al.,* 2013). The heightened risk of infections in undernourished patients and the increased risk of toxicity from chemotherapy in these children are the main obstacles to improve the survival rates of ALL in developing countries. Undernutrition increases treatment-related mortalities and morbidities, leads to abandonment of therapy, and has a negative effect on the quality of life. In developed countries, undernutrition is reported to occur in less than 10% of children with ALL, whereas a higher

Table 1. Patients' demographic and medical characteristics at diagnosis

Characteristics	*n*	*%*
Age at diagnosis	72	
< 5 years	31	43.1
6 -10 years	19	26.4
>11 years	22	30.5
Gender		
Male	52	72.2
Female	20	27.8
Socioeconomic class (modified Kuppuswamy scale)		
Class 1	15	20.8
Class 2	21	29.2
Class 3	13	18.0
Class 4	12	16.7
Class 5	11	15.3
Risk stratification		
Standard risk	33	45.8
High risk	39	54.2
Anaemia at diagnosis	47	
Undernourished	19	40.4
Adequately nourished	22	46.8
Overnourished	6	12.8
Hypoalbuminemia at diagnosis	12	
Undernourished	5	41.7
Adequately nourished	6	50.0
Overnourished	1	8.3
Hypokalemia at diagnosis	6	
Undernourished	3	50.1
Adequately nourished	2	33.3
Overnourished	1	16.6

Socioeconomic class: class 1 – upper; class 2 – upper middle; class 3 – lower middle; class 4 – upper lower; class 5 – lower

Table 2. Correlation between socioeconomic status and nutritional status

Socioeconomic class	*Nutritional status at diagnosis*			*Total n (%)*	*p value*
	Undernourished	*Adequately nourished*	*Over nourished*		
Class 1	3	6	6	15 (20.8)	0.038
Class 2	5	16	0	21 (29.2)	
Class 3	3	8	2	13 (18.1)	
Class 4	2	7	3	12 (16.7)	
Class 5	6	4	1	11 (15.2)	
Total	19	41	12	72 (100.0)	

Table 3. Correlation between nutritional status at diagnosis and significant weight loss during induction phase

Nutritional status at diagnosis	*At diagnosis n (%)*	*No. of patients with significant weight loss during induction n (%)*	*p value*
Undernourished	19 (26.4)	5 (17.9)	0.205
Adequately nourished	41 (56.9)	16 (57.1)	
Over nourished	12 (16.7)	7 (25.0)	
Total	72 (100.0)	28 (100.0)	

Table 4. Correlation between nutritional status at diagnosis and events during treatment

Events	*Nutritional status*				*Total*
	Undernourished, n=19		*Significant weight loss, n=28*		
	n (%)	*p*	*n (%)*	*p*	
Febrile neutropenia	7 (36.8)	0.203	10 (35.7)	<0.001	17
Dosage interruptions	5 (26.3)	0.273	7 (25.0)	0.496	12
Pneumonia	3 (15.8)	1.000	6 (21.4)	0.011	9
Mucositis	5 (26.3)	0.868	9 (32.1)	0.023	14

Table 5. Outcome of induction therapy

Outcome	*n (%)*
Attained remission	67 (93.1)
Died	5 (6.9)
Total	72 (100.0%)

rate of 21-52% has been reported in developing countries (Sala *et al.,* 2012). The prevalence of undernutrition among children and adolescents with cancer ranges from 8%-60%, depending upon the type of cancer, treatment modalities and methods used to measure nutritional status (Agarwal *et al.,* 2012).

There are no standard clinical practice guidelines for monitoring nutritional status in children with cancer. Weight as an accurate parameter of nutritional status may be unreliable in cases with significant tumour volume, organomegaly, or altered hydration status. Cancer therapy alters muscle and fat composition. An evaluation effective to identify the type of nutritional impairment – adipose and/or muscle, is therefore essential. Unfortunately, BMI (body mass index) cannot distinguish between fat mass and lean mass, thus making it a poor measure of body composition. Instead, mid upper arm circumference (MUAC) can be used for assessing fat-free mass and triceps skin folds (TSF) for measuring fat mass. These are widely recommended as they are feasible in low- and middle-income countries. They have also been found to be better parameters of nutritional assessment and correlate with outcomes (Jaime-Perez *et al.,* 2008).

The causes of undernutrition at diagnosis and during treatment are diverse. The dynamic interactions between primary disease, effect of multimodal therapies, other co-morbid features, and socioeconomic status of the patient makes it more complicated. The combined status of increased need, decreased intake, inadequate supply, and increased inflammation leads to

protein energy deficit and pathological sequelae of those deficits (Brinksma *et al.,* 2012). So, patients with high risk for undernutrition, such as advanced stage disease or needing intensive chemotherapy regimens, should be identified and monitored closely.

Undernutrition present at the time of diagnosis in children with cancer, increases their vulnerability to alterations in the pharmacokinetics of anti-neoplastic agents. Pharmacokinetics of many drugs like methotrexate and anthracyclines are found to be influenced by the body composition of lean body mass and adipose tissue. At extremes of malnutrition, the pharmacodynamics of drugs are affected; and hence, their potential effectiveness is reduced (Murry, Riva & Poplack, 1998). There are only limited studies, which have evaluated the prevalence of undernutrition during the induction phase of treatment. Undernutrition at diagnosis is a poor prognostic factor resulting in lower event-free survival and greater treatment-related mortality. Tan *et al.* (2013) has reported that 15.1% of children were undernourished during the induction phase of ALL. Kumar *et al.* (2000) has reported 52% malnutrition among children with ALL and 36% weight loss during induction. Among our study population of 72 children, 19 (26.3%) were undernourished and 28 of them (38.8%) had significant weight loss during the induction period. Orgel *et al.* (2016) evaluated 2008 high risk ALL children and correlated the outcomes to duration of weight extremes during treatment. Underweight status was found to be associated with increased risk of fungal infections and haematological toxicity. Inferior event-free survival was reported in those who were found to be underweight for 50% of the time, between the end of induction and the start of maintenance.

Roy *et al.* (2013) has reported a higher incidence of febrile neutropenia in undernourished children with ALL. Altered nutritional and inflammatory status increase the risk of severe haematological toxicity following anti-cancer therapy (Alexandre *et al.,* 2003). There are significant treatment interruptions/modifications due to mucositis, co-morbid infections, and neutropenic status. Maldonado *et al.* (2015) and Sala *et al.* (2012) have correlated poor survival outcomes and treatment-related toxicity to undernourishment at diagnosis. Although a statistically significant association could not be found between malnutrition and mortality during induction to remission, Mejía-Aranguré *et al.* (1999) observed a strong relationship between the degree of malnutrition and the risk of death. He has quoted that undernourishment may influence early mortality during the induction to remission phase of the treatment. Severely undernourished children were found to have 3.5 times higher risk of death during induction than remission.

A study from St. Jude Children's Research Hospital had reported that infections contributed to 80% of deaths observed during the induction phase in children with ALL (Rubnitz *et al.* 2004). Marwaha *et al.* (2010) has reported an induction mortality of 10% and Rajeswari *et al.* (*2018*) has quoted it as 5.3% among children with ALL. Malnutrition compromises the integrity of the mucosal barrier and thereby predisposes these children to increased rate of infections. The induction mortality rate among our study population was 6.9% and all of them died due to infections. In our study, though there was no statistical significance to suggest that nutritional status at diagnosis was associated with outcomes, there was a strong association between a depletion in nutritional

status and treatment outcomes. In our study, all five children who died during induction phase had significant weight loss. The incidence of events, such as mucositis, pneumonia, and febrile illness, were more prevalent in patients who underwent significant weight loss through the course of treatment.

As undernutrition is a modifiable risk factor for the outcomes in ALL, longitudinal nutritional assessments should be incorporated and appropriate nutritional interventions should be implemented. Assessment should be a dynamic process and should be able to recognise at-risk patients to enable proactive care to those who are at the highest need of nutritional interventions. A study in Guatemala has demonstrated that correction of undernutrition in children with ALL within six months of diagnosis resulted in improvement of their survival rates as compared to the normally nourished children (Antillon *et al.,* 2013). Larger interventional studies with dietary modifications are lacking as there are methodological challenges to have randomised and double blinded studies for an accurate assessment. It has to be recognised that malnutrition is also a part of socioeconomic disadvantage and hence, simple and cost effective nutritional interventions can diminish the morbidity burden of undernourishment in low-income countries.

CONCLUSION

The incorporation of nutritional assessments into ALL treatment protocols, as well as adequate and appropriate nutritional interventions should become routine practices in clinical setting in order to improve the outcomes of remission during induction phase among childhood ALL patients.

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Authors' contributions

LMS, prepared the draft of the manuscript and reviewed the manuscript; LS, assisted in data collection and statistical analysis; AK, assisted in data entry and initial proof correction; JS, conceptualised and designed the study; DJ, assisted in reviewing the manuscript and data analysis.

Conflict of interest

Authors declare no conflict of interest.

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