Paediatrica Indonesiana

p-ISSN 0030-9311; e-ISSN 2338-476X; Vol.63, No.3(2023). p.146-51; DOI: https://doi.org/10.14238/pi63.3.2023.146-51

Original Article

Differences in induction phase outcomes of acute lymphoblastic leukemia between well-nourished and malnourished pediatric patients

Meilani Puspasari Simarmata, Nelly Rosdiana, Arlinda Sari Wahyuni

Abstract

Background Leukemia is the most common malignancy in childhood. Malnutrition is the main nutritional disorder occurring in children with cancer. Nutritional supportive care is a medical modality that has been associated with improved tolerance to chemotherapy, survival, and quality of life, as well as decreased risk of infection in children undergoing cancer therapy.

Objective To examine differences in induction phase outcomes in well-nourished and malnourished pediatric acute lymphoblastic leukemia (ALL) patients.

Methods This prospective study was conducted in newly-diagnosed ALL patients aged 1 to 18 years who underwent induction phase chemotherapy at Haji Adam Malik General Hospital, Medan, North Sumatera. Mid-upper arm circumference (MUAC) was used to determine nutritional status. Patient characteristics such as complete blood count (CBC) at the time of diagnosis, occurrence of febrile neutropenia, duration of induction, length of hospital stay, and remission status were collected. We analyzed differences in CBC, frequency of febrile neutropenia, as well as duration of induction and hospital stay between well-nourished and malnourished patients. We also assessed the difference in remission attainment between the two groups.

Results There were 21 subjects in each group. Compared to well-nourished subjects, malnourished ones had a higher median incidence of febrile neutropenia [1 (range 0 to 30) *vs.* 3 (range 0-4); P=0.04], longer mean induction duration [64.2 (SD 11.5) vs. 71.2 (SD 10.6) days; P=0.046], and longer median hospital stay [30 (range 19 to 56) *vs.* 36 (range 22-49) days; P=0.001] compared to well-nourished subjects. There was no significant difference in CBC parameters and remission status after induction between the two groups.

Conclusion Malnourished pediatric ALL patients had a significantly higher incidence of febrile neutropenia, duration of induction phase, and duration of hospital stay compared to well-nourished ALL patients. **[Paediatr Indones. 2023;63:146-51; DOI: https://doi.org/10.14238/pi63.3.2023.146-51**].

Keywords: *acute lymphoblastic leukemia; malnutrition; induction phase outcomes*

Leukemia is the most common malignancy in childhood, involving uncontrollable proliferation of abnormal leukocytes. The prevalence of acute leukemia is 30-40% of all childhood cancers; 82% are acute lymphoblastic leukemia (ALL) and 17% are acute myeloblastic leukemia (AML).[1] The proliferation of lymphoid precursor cells originate from B lymphocytes in 80% of cases, and from T lymphocytes in the remainder.[2] Out of 486 cancer cases in children in 2000-2004 in Dr. Sardjito Hospital, Yogyakarta, 35% were ALL cases.[3] In 2018, there were 72 newly-diagnosed ALL patients in Haji Adam Malik General Hospital, accounting for 48% of childhood cancer cases.

Malnutrition a deficiency of energy, protein, and other nutrients, is the main nutritional disorder occurring in children with cancer. Malnutrition in cancer can be caused by the disease, inherent patient condition, and therapeutic factors. These factors may affect metabolism, leading to decrease in appetite, which further promotes weight loss.[4] The prevalence of malnutrition in childhood cancer was 50-60%.

From the Department of Child Health, Universitas Sumatera Utara Medical School, Medan, North Sumatera, Indonesia.

Corresponding author: Meilani Puspasari Simarmata. Jalan Bunga Lau No 17, Medan 20136, North Sumatera, Indonesia. Email: meilanisimarmata90@gmail.com

Submitted January 5, 2022. Accepted June 27, 2023.

Malnutrition is one of several prognostic factors in ALL. Children with malnutrition are more prone to infection and less able to tolerate the given treatment. During the continuation phase of chemotherapy, an undernourished child is at higher risk for relapse and death. One study found that the chance of dying during the initial phase of ALL treatment was 2.6 times lower in well-nourished children than in undernourished children.[5] In industrialized countries, malnutrition occurred in <10% of standard-risk ALL children, but studies from developing countries are lacking.[6]

Nutritional supportive care is a medical modality associated with improved tolerance to chemotherapy, increased survival rate and quality of life, as well as decreased risk of infection in children undergoing anticancer therapy.[7] Induction is an important chemotherapy phase, in which maximum destruction of leukemic cells occurs.[8] Therefore, nutritional status evaluation at the initial diagnosis and its possible association with induction phase outcome is needed. This study aims to examine differences in induction phase outcomes between well-nourished and malnourished pediatric ALL patients.

MethodsThis study was conducted in newly-diagnosed ALL patients at Haji Adam Malik General Hospital from December 2019 to December 2020. Inclusion criteria were children aged 1 to 18 years with ALL confirmed by bone marrow aspiration who underwent induction phase chemotherapy. Children with overweight/obesity or those who refused to participate were excluded. Based on their leukocyte count at the the time of initial diagnosis, patients were classified into standard risk (leukocytes <50,000/μL) and high risk (leukocytes >50,000/μL).[1] Mid-upper arm circumference (MUAC) was used to determine nutritional status. Patients were considered well-nourished if their MUAC was between the 5th to 95th percentile in the Frisancho table and malnourished if it was ≤5th percentile.[9]

Data collection was done for complete blood count [CBC (hemoglobin concentration, leukocytes, and platelets)] at the time of diagnosis, occurrence of febrile neutropenia, duration of induction, length of hospital stay, and remission status. Febrile neutropenia was defined as an axillary temperature of ≥38.0°C with a neutrophil count of <1,000/mm^3. Duration of induction was defined as the time in days required for the completion of induction. Length of hospital stay was defined as the time in days required from initial presentation to discharge. Remission status was obtained from the results of bone marrow aspirate microscopy after the induction phase.

Statistical analysis was done using *SPSS version 23.0* for *Windows* (*IBM*, Armonk, New York). Descriptive statistics are expressed in the form of mean (standard deviation/SD) for normally distributed data and median (range) for abnormally distributed data; categorical data are presented in the form of frequency. We analyzed differences in CBC parameters, frequency of febrile neutropenia, duration of induction, and length of hospital stay between the malnourished and well-nourished groups using the independent t-test and the Mann-Whitney test. The difference in the proportion of remission between the two groups was analyzed by using the chi-square test. This study was approved by the Ethics Committee of the Faculty of Medicine, Universitas Sumatera Utara/Haji Adam Malik General Hospital Medan.

Results

Subjects were divided into well-nourished and malnourished groups. There were 21 subjects in each group, which consisted of 14 male subjects (66.7%) and 7 female subjects (33.3%). The mean age of subjects was 7.5 years in the well-nourished group and 6.9 years in the malnourished group. The malnourished group had more high-risk patients than the well-nourished group (28.6% vs. 23.8%, respectively). One subject in each group underwent a 25%-to -50% reduction in chemotherapy dose due to granulocytopenia and/or thrombocytopenia. The baseline characteristics of subjects are described in **Table 1**.

Differences in hematologic outcomes, occurrence of febrile neutropenia, length of hospital stay, and duration of induction can be seen in **Table 2**. There was no significant difference in CBC parameters between the two groups. Median leukocyte counts in the well-nourished and malnourished groups were 12.5 (range 1.0-551.17) x103/μL *vs.* 6.94 (range 0.85 to 287.94) x103/μL, respectively, but this difference was not statistically significant (P=0.66).

The median frequency of febrile neutropenia

in the malnourished group [2 (range 0 to 4)] was twice that in the well-nourished group [1 (range 0-3)] (P=0.04). We also found significant differences between the well-nourished and malnourished groups in median length of hospital stay [30 (range 19-56) days *vs.* 36 (range 22-49), P=0.001] and mean duration of induction phase [64.2 (SD 11.5) days *vs.* 71.2 (SD 10.6) days, P=0.046] (**Table 2**).There was no significant difference in remission status in the malnourished and well-nourished groups (85.7% *vs.* 71.4%, respectively; RR 0.833; 95%CI 0.604 to 1.15; P=0.454) (**Table 3**).

Discussion

Malnutrition has been proposed as a prognostic factor in childhood ALL.[10] One study reported that malnutrition was found in 66% children who were newly diagnosed with ALL.[11] Induction phase is a chemotherapy stage aiming to achieve remission (normal peripheral blood, normocellular bone marrow, and <5% lymphoblasts).[12] In this phase, patients are at risk of experiencing severe infections or other complications.[13]

Most patients in our study were male. Several other ALL studies also reported higher prevalences in males than females.[7,13,14] The mean age was 7.5 years in the well-nourished group and 6.9 years in the malnourished group. A study in Semarang reported a

Table 1. Characteristics of subjects

Characteristics	Well-nourished (n=21)	Malnourished (n=21)
Gender, n		
Male	14	14
Female	7	7
Mean age (SD), years	7.5 (4.4)	6.9 (4.0)
Risk group, n		
Standard risk	16	15
High risk	5	6
Decreased chemotherapy dose, n (%)		
Yes	1	1
No	20	20

Table 2. Differences in outcomes between well-nourished and malnourished subjects

Variables	Group		P value
	Well-nourished	Malnourished	
Mean hemoglobin level (SD), g/dL	6.2 (3.3)	5.9 (2.7)	0.799*
Median leukocyte count (range), x103/µL	12.5 (1.0-551.17)	6.94 (0.85-287.94)	0.66**
Median platelet count (range), x103/µL	26.0 (3.0-145.0)	26.0 (4.0-447.0)	0.763**
Median frequency of febrile neutropenia (range), times	1 (0-3)	2 (0-4)	0.04**
Median length of hospital stay (range), days	30 (19 to 56)	36 (22 to 49)	0.001**
Mean duration of induction phase (SD), days	64.2 (11.5)	71.2 (10.6)	0.046*

*Independent-Ttest, **Mann-Whitney test

Table 3. Analysis of remission status between the well-nourished and malnourished groups

Variables	Remission status			RR (95%CI)	P value
	Remission	No remission	Total		
Well-nourished, n	15	6	21	0.833 (0.604 to 1.150)	0.454*
Malnourished, n	18	3	21		

*Chi-square test

median age of 6.58 years in childhood ALL.[15] ALL can be stratified into high- or standard-risk categories.[12] In our study, more children in the malnourished group belonged to the high-risk category than to the well-nourished group. Overall, high-risk patients had twice the mortality rate of standard- risk ones.[16] Malnutrition was associated with a lower survival rate due to bone marrow relapses. Relapses can occur if patients receive a sub-optimal chemotherapy dose during the maintenance phase, such as due to poor tolerance of treatment.[17] In our study, one subject in each group had to receive a reduced chemotherapy dose due to granulocytopenia and/or thrombocytopenia.

In our study, there were no significant differences in CBC parameters between groups. A previous study found that only hemoglobin concentration was significantly lower in malnourished compared to well-nourished children.[8] However, the incidence of febrile neutropenia was significantly higher in the malnourished group than in the well-nourished group. Febrile neutropenia in cancer is an emergency complication, requiring rapid identification and intervention.[18] Malnutrition in children with cancer was associated with an increased risk of infections.[19] Infections are still the major causes of morbidity and mortality in acute leukemia,[20] with a higher incidence of sepsis in malnourished children with ALL.[21]

Our malnourished patients had significantly longer length of hospital stay than well-nourished patients. This result was in agreement with previous findings.[8,21] Prolonged hospital stay could be due to organ dysfunction, infectious or metabolic complications.[22]

The duration of induction was significantly longer in the malnourished compared to the well-nourished group. Another study also found that the majority of ALL children who did not complete chemotherapy on time were severely malnourished.[23] Disturbances in drug metabolism in malnourished children may lead to delayed chemotherapy and increased toxicity.[24] A study reported a higher rate of rapid early response to chemotherapy in well-nourished than malnourished patients.[21]

In our study there was no significant difference in remission status between the two groups. This finding is in contrast to those a previous study in which cases with undernutrition showed a downward tendency in remission following induction. Moreover, relapse cases often came from the moderate and severe malnutrition categories.[23]

Previously, Tandon et al. demonstrated the importance of identifying nutritional status in pediatric ALL patients. They found that hypoalbuminemia, folate deficiency, and B12 deficiency were associated with increased toxicity, which resulted in increased mortality during the induction phase.[11] During the induction phase, ALL patients were also at risk of weight loss. Twenty-six percent of ALL children lost weight during the induction phase and most had complications, such as infections and bleeding, during this period.[25] Nutritional interventions in children with ALL may improve nutritional status and chemotherapy tolerance.[24,26]

We found that ALL children with malnutrition experienced more episodes of febrile neutropenia, longer hospitalizations, and longer induction phase than well-nourished ones. Nutritional assessment and therapy are required for children with ALL to improve their quality of life, reduce infection and drug toxicity, as well as improve survival.[27,28] However, we noted no difference in remission status between the two groups. These results could have been due to other factors that influence prognosis, such as initial leukocyte count, age, immunological phenotype, sex, and the presence of chromosome abnormalities.

In conclusion, malnourished children with ALL have a higher incidence of febrile neutropenia, a longer duration of the induction phase, and a longer length of hospital stay than well-nourished ones. Hematologic parameters in CBC and remission status were not significantly different between the two groups.

Conflict of interest

None declared.

Funding acknowledgement

The authors received no specific grants from any funding agency in the public, commercial, or not-for-profit sectors.

References

1. Permono B, Ugrasena IDG, Supriyadi E. Leukemia akut. In: Windiastuti E, Nency YM, Mulatsih S, Sudarmanto B, Ugrasena IDG, editors. Buku Ajar Hematologi-Onkologi Anak, 2018. Jakarta: BP IDAI;2018. p. 276-8, 282.
2. Howard MR, Hamilton PJ. Haematology: an illustrated colour text. 3rd ed. London: Churcill Livingstone Elsevier; 2008. p.42.
3. Herintya F, Mulatsih S, Prawirohartono EP. Association between nutritional status and outcome of childhood acute lymphoblastic leukemia treated with Wijaya Kusuma Protocol. Paediatr Indones. 2008;48:28-31. DOI: https://doi.org/10.14238/pi48.1.2008.28-32.
4. Maldonado-Alcazar A, Carlos J, Alberto C, Fajardo-Gutierrez A, Manuel J. Alterations of nutritional status in childhood acute leukemia. Clinical epidemiology of acute lymphoblastic leukemia - from the molecules to the clinic. InTech; 2013. DOI: https://doi.org/10.5772/52715.
5. Athifah A, Hidayati SN, Sulistiawati. Correlative study between nutritional status and remission outcome in childhood acute lymphoblastic leukemia in Dr. Soetomo General Hospital Surabaya. Biomol Health Sci J. 2019;2:27-30. DOI: https://doi.org/10.20473/bhsj.v2i1.12723.
6. Yazbeck N, Samia L, Saab R, Abboud MR, Solh H, Muwakkit S. Effect of malnutrition at diagnosis on clinical outcomes of children with acute lymphoblastic leukemia. J Pediatr Hematol Oncol. 2016;38:107-10. DOI: https://doi.org/10.1097/MPH.0000000000000428.
7. Kadir RAA, Hassan JG, Aldorky MK. Nutritional assessment of children with acute lymphoblastic leukemia. Arch Can Res. 2017;5:1-9. DOI: https://doi.org/10.21767/2254-6081.1000128
8. Hafiz MG, Mannan MA. Nutritional status at initial presentation in childhood acute lymphoblastic leukemia and its effect on induction of remission. Mymensingh Med J. 2008;17(2 Suppl):S46-51. PMID: 18946451.
9. Frisancho AR, Tracer DP. Standards of arm muscle by stature for the assessment of nutritional status of children. Am J Phys Anthropol. 1987;73:459-65.
10. Mejia-Arangure JM, Fajardo-Gutierrez A, Reyes-Ruiz NI, Bernaldez-Rios R, Mejia-Dominguez AM, Navarette-Navarro S, *et al.* Malnutrition in childhood lymphoblastic leukemia: a predictor of early mortality during the induction-to-remission phase of the treatment. Arch Med Res. 1999;30:150-3. DOI: https://doi.org/10.1016/s0188-0128(98)00026-8.
11. Tandon S, Moulik NR, Kumar A, Mahdi AA, Kumar A. Effect of pre-treatment nutritional status, folate and vitamin B12 levels on induction chemotherapy in children with acute lymphoblastic leukemia. Indian Pediatr. 2015;52:385-9. DOI: https://doi.org/10.1007/s13312-015-0642-x.
12. Nency YM. Perbedaan kebutuhan transfusi darah selama fase induksi pada leukemia limfoblastik akut. Sari Pediatri. 2011;13:271-4. DOI: https://doi.org//10.14238/sp13.4.2011.271-4.
13. Agnes M, Widjajanto PH, Damayanti W. Impact of malnutrition on febrile neutropenia in children with acute lymphoblastic leukemia during induction phase chemotherapy. Paediatr Indones. 2018;58:298-304. DOI: https://doi.org/10.14238/pi58.6.2018.298-304.
14. Mihalea C, Despina B, Adrienne H, Diana M. Nutritional parameters in children with acute leukemia. Acta Med Marisiensis. 2011;57:12-15.
15. Perdani RRW, Sudarmanto B. Hematological parameters and remission induction of childhood acute lymphoblastic leukemia. Paediatr Indones. 2018;58:71-4. DOI: https://doi.org/10.14238/pi58.2.2018.71-4.
16. Widiaskara IM, Bambang P, Ugrasena IDG, Ratwita M. Luaran pengobatan fase induksi pasien leukemia limfoblastik akut pada anak di Rumah Sakit Umum Dr. Soetomo Surabaya. Sari Pediatri. 2010;12:128-134. DOI: https://doi.org/10.14238/sp12.2.2010.128-34
17. Lobato-Menzibal E, Ruiz-Arguelles GJ, Marin-Lopez A. Leukaemia and nutrition. I: Malnutrition is an adverse prognostic factor in the outcome of treatment of patients with standard risk acute lymphoblastic leukemia. Leuk Res. 1989;13:899-906. DOI: https://doi.org/10.1016/0145-2126(89)90043-x.
18. Linga VG, Shreedhara AK, Rau ATK, Rau A. Nutritional Assessment of children with hematological malignancies and their subsequent tolerance to chemotherapy. Ochsner J. 2012;12:197-201.
19. Co-Reyes E, Li R, Huh W, Chandra J. Malnutrition and obesity in pediatric oncology patients: causes, consequences, and interventions. Pediatr Blood Cancer. 2012;59:1160-7. DOI: https://doi.org/10.1002/pbc.24272.
20. Bakhsi S, Padmanjali KS, Arya LS. Infections in childhood acute lymphoblastic leukemia: an analysis of 222 febrile neutropenic episodes. Pediatr Hematol Oncol. 2008;25:385-92. DOI: https://doi.org/10.1080/08880010802106564.
21. Khalid A. Evaluation of the nutritional status in children with acute lymphoblastic leukemia and its effect on the outcome of induction in a developing country. J Clin Oncol. 2017;35:e22004. DOI: https://doi.org/10.1200/JCO.2017.35.15_suppl.e22004.
22. Warrick K, Althouse SK, Rahrig A, Rupenthal J, Batra

S. Factors associated with a prolonged hospital stay during induction chemotherapy in newly diagnosed high risk pediatric acute lymphoblastic leukemia. Leuk Res. 2018;71:36-42. DOI: https://doi.org/10.1016/j.leukres.2018.06.013.

23. Roy A, Saha A, Chakraborty S, Chattopadhyay S, Sur P. Effects of pre-existing undernutrition on treatment-related complications and treatment outcomes in children with acute lymphoblastic leukemia: a tertiary care center experience. Clin Cancer Investig J. 2013;2:143-8. DOI: https://doi.org/10.4103/2278-0513.113637.
24. Barr RD, Gomez-Almaguer D, Jaime-Perez JC, Ruiz-Arguelles GJ. Importance of nutrition in the treatment of leukemia in children and adolescents. Arch Med Res. 2016;47:585-92. DOI: https://doi.org/10.1016/j.arcmed.2016.11.013.
25. Al Ani M. Nutritional status of acute childhood lymphoblast leukemia (ALL) pre & post induction chemotherapy. Iraqi J Comm Med. 2008;3:198-203.
26. Antillon F, Rossi E, Molina AL, Sala A, Pencharz P, Valsecchi MG, *et al.* Nutritional status of children during treatment for acute lymphoblastic leukemia in Guatemala. Pediatr Blood Cancer. 2013;60:911-5. DOI: https://doi.org/10.1002/pbc.24377.
27. Owens JL, Hanson SJ, McArthur JA, Mikhailoy TA. The need for evidence based nutritional guidelines for pediatric acute lymphoblastic leukemia patients: acute and long-term following treatment. Nutrients. 2013;5:4333-46. DOI: https://doi.org/10.3390/nu5114333.
28. Pramanik R, Sheng X, Ichihara B, Heisterkamp N, Mittelman SD. Adipose tissue attracts and protects acute lymphoblastic leukemia cells from chemotherapy. Leuk Res. 2013;37:503-9. DOI: https://doi.org/10.1016/j.leukres.2012.12.013.