Malnutrition, maintenance dose intensity and event-free survival in children with acute lymphoblastic leukemia

Javier Enrique Ibarra-Colado[a] and Leonardo Verduzco-Rodríguez[b]

[a]Department of Pediatrics. [b]Department of Oncology. Hospital Regional del Río Blanco. México. Secretaría de Salud. Congregación Vicente Guerrero. México.

The role of malnutrition in event-free survival (relapse or death) in children with acute lymphoblastic leukemia (ALL), admitted at the Rio Blanco Regional Hospital, is assessed. The files of children under 12 years of age with ALL, diagnosed and treated from 1990 to 1997 were analyzed. According to the score z (≤ 1.28) of the weight/age, height/age, and weight/height anthropometric indicators, children were classified into two groups: nourished and malnourished children. Event-free survival curves were made and the impact that other risk factors had on prognosis was analyzed. The association of age, white blood cells and nutritional status, in the presence of an unfavorable event was estimated, using a multiple regression model. Twenty-three patients were studied, of which 12 suffered malnutrition. The mortality rate among the malnourished children was of 50% versus 9.1%, among the nourished children in the survival curve, and in the log rank test the weight versus age was of significant influence ($p < 0.04$). The two most relevant risk factors for the presence of events were malnutrition and L2 type leukemia. In a multiple regression model, malnutrition was the only factor associated with the presence of events. Malnutrition was a risk factor for the presence of unfavorable events, being even more important than age and white blood cell count. Prospective studies that analyze the relationship of malnutrition and ALL, as well as the pharmacokynetics of antineoplastic agents in malnourished patients, are needed.

Key words: acute lymphoblastic leukemia, malnutrition.

Ibarra-Colado JE, Verduzco-Rodríguez L. Malnutrition maintenance dose intensity and event-free survival in children with acute lymphoblastic leukemia. Rev Oncol 2002;4(6):308-13.

Malnutrición, intensidad de dosis de mantenimiento y supervivencia libre de eventos en niños con leucemia linfoblástica aguda

Se evalúa el papel de la malnutrición en supervivencia libre de eventos (recaída o muerte) en niños con leucemia linfoblástica aguda (LLA) ingresados en el Hospital Río Blanco Regional.

Se analizaron las historias clínicas de niños de edades inferiores a los 12 años con LLA diagnosticados y tratados desde 1990 a 1997. Se clasificaron a los niños en dos grupos: niños nutridos y niños malnutridos de acuerdo con la puntuación z (≤ 1,28) de los indicadores antropométricos peso/edad, talla/edad y peso/talla. Se hicieron curvas de supervivencia libre de eventos y se analizó el impacto que otros factores de riesgo tuvieron en los pronósticos. Se estimó la asociación de la edad, leucocitos y estado nutricional en presencia de un evento desfavorable usando un modelo de regresión múltiple.

Se estudiaron 23 pacientes, 12 de los cuales sufrieron malnutrición. La tasa de mortalidad entre los niños malnutridos fue del 50% comparada con 9,1% en la curva de supervivencia entre los niños bien nutridos y en la prueba de log rango el peso frente a edad tuvo una influencia significativa ($p < 0,04$). Los dos factores de riesgos más relevantes para la presencia de eventos fueron la malnutrición y la leucemia tipo L2. En un modelo de regresión múltiple, la malnutrición fue el único factor asociado con la presencia de

Correspondence: J. E. Ibarra-Colado.
Hospital Regional de Río Blanco.
Secretaría de Salud.
Entronque Autopista Orizaba-Puebla, s/n.
94375 Río Blanco, Ver. México.
E-mail: xeic@prodigy.net.mx
E-mail: verducol@prodigy.net.mx

Received 28 August 2001; Revised 20 June 2002; Accepted 25 June

eventos.
La malnutrición fue un factor de riesgo para la presencia de eventos desfavorables, siendo incluso más importante que la edad y el recuento de leucocitos. Hacen falta estudios prospectivos que analicen la relación entre la malnutrición y la LLA, así como la farmacocinética de los agentes antineoplásticos en pacientes mal nutridos.

Palabras clave: leucemia linfoblástica aguda, malnutrición.

INTRODUCTION

Given the advance achieved in the last 30 years in the treatment of acute lymphoblastic leukemia (ALL), this is no longer considered as an untreatable disease. At present, around 70%-80% of ALL children with standard risk factors are maintained in full remission for more than 5 years[1-4]. Although the initial white blood cell count and the age of the patient when the diagnosis is made are the two most reliable indicators, both for the remission duration and for survival[5,6], other clinical characteristics have been associated with the prognosis[7,8]. The type of population we treat in our country frequently has a rural background and low socio-economic conditions, resulting in frequent nutritional deficiencies that may modify the results seen in the anti-leukemic therapy[9]. Malnutrition is present in 20% to 50% of the Mexican children with leukemia, and malnutrition has been recognized as another factor that may modify the prognosis[10-14].
This work was conducted to assess the role that malnutrition and maintenance dose intensity play in the event-free survival in ALL children admitted at the Rio Blanco Regional Hospital (RBRH). This is a second level institution, where a population, characterized by a low socio-economic level, from a rural background and not entitled to social security, is treated.

METHODS

The files of patients under 12 years of age with ALL, diagnosed at the RBRH and treated with the same management protocol described before, were analyzed[15]. All of them came from a rural area of Mexico, located in the state of Veracruz, corresponding to Chandy's level I patients[16]. Given their low socio-economic level, it was not possible to transfer them to third level oncological centers and they received free treatment.

Patients

All the files were of patients under 12 years of age with ALL treated at the RBRH between 1990 and 1997. The ALL diagnosis was established based on the clinical history, peripheral blood smear, and bone marrow aspirate study. After admission, a lumbar puncture was made for the colony-stimulating factor (CSF) cytochemical study and chest X-rays were taken to all the patients. Neither cytogenetic nor immunophenotypic studies were performed because these resources are unavailable as in most of the second level Mexican hospitals.

Nutritional status

The WHO-NCHS anthropometric indicators assessed in the population of reference were: weight/age, height/age, and weight/height, assigning to each the corresponding score z value (score z = [actual value - ideal value [p50]/std. desviation]). In case that the score z values for any of the above variables were ≤ 1.28 (percentile 10), the child was classified as a malnourished child. Thus, all the children who have a high level of malnutrition, in accordance with the standards in force in our country, were included[17].

Treatment

For treatment purposes, the definition of standard risk patients were those patients that met the following criteria: patients over 2 years of age and under 9 years of age, less than 50,000 white blood cells in peripheral blood and L1 morphology, according to the FAB criteria. The rest of the patients were considered high risk patients.
The remission induction treatment was carried out for 5 weeks, with three drugs: vincristine weekly and daily prednisone in all patients, using doxorubicine or epirubicine as the third drug weekly. Only the high risk patients were given cyclophosphamide as the fourth drug when the white blood count at admission was over 100,000.
The consolidation was made with cyclophosphamide and citarabin in almost half of the cases, and with asparaginase in the rest. The post remission or maintenance treatment was made with oral mercaptopurine daily and oral methotrexate every week for 3 years, with monthly pulses of vincristine and prednisone for standard risk patients. High risk patients were also given doxorubicin and cyclophosphamide in monthly pulses.
Prophylaxis to the nervous system in standard risk patients was made through triple intrathecal chemotherapy every 8 weeks for 2 years, with the following drugs: methotrexate, citarabin, and hydrocortisone. Only one standard risk patient was managed with radiotherapy. High risk patients were given 1,800 cGy of radiotherapy in case they had over 100,000 white blood cells in peripheral blood and intrathecal methotrexate as a single drug. The rest was given the same triple intrathecal chemotherapy regimen as the standard risk patients.
Since 1993, two late intensification blocks were added at 6 and 12 months, with vincristine weekly in four dosages,

asparaginase daily in 10 dosages and prednisone daily for 4 weeks. Details on the dosage employed in this protocol are described in apreviously published paper15. There was no difference between the treatment given to well-nourished and malnourished children.

Statistical analysis

In order to analyze the event-free survival, patients were distributed in two groups: nourished and malnourished. Event-free survival was defined as the total remission of the disease without relapse in any site, without development of a second neoplasia and without death of the patient. No patients have been excluded.

The survival curves were calculated according with the Kaplan and Meier method. The survival differences were estimated through the log rank method. The comparison between the two groups was estimated using Fisher's exact test and Student's «t» test. The impact of other prognostic factors on the event-free survival, such as age, sex, white blood cell count at the moment the diagnosis was made, morphology of the blasts according to the FAB classification, and the presence of adenomegalies, hepato or splenomegaly, were analyzed. Finally, a multiple regression model was applied to estimate the association between the presence of unfavorable event (relapse or death) and the following risk factors: age, white blood cell count, and malnutrition according to the weight/age parameter. The information was captured and analyzed with the Epi-Info 6.04 (CDC, Atlanta, Ga.) and Graph-pad Prism Version 3.0 programs. A value of $p < 0.05$ was considered as significant.

TABLE 1. **Characteristics of patients with lymphoblastic leukemia when admitted, in terms of their nutritional status**

Characteristic	Nourished (n = 11)	Malnourished (n = 12)	Value of p
Average age	4.27	6.16	0.11
Male	6 (55%)	6 (50%)	0.82
Under 2 years of age	1 (9%)	1 (8%)	0.74
Over 9 years of age	2 (18%)	1 (8%)	0.59
Hemorrhagic syndrome	1 (9%)	4 (33%)	0.18
Adenomegalies	8 (73%)	5 (42%)	0.14
Splenomegaly	8 (73%)	5 (42%)	0.14
Hepatomegaly	7 (64%)	6 (50%)	0.40
Mediastinal mass	2 (18%)	1 (8%)	0.46
Fever	7 (64%)	9 (75%)	0.44
High risk	7 (63%)	7 (58%)	0.56
L2 ALL	2 (18%)	6 (50%)	0.12
White blood cells > 50,000	3 (27%)	5 (42%)	0.39
Platelets < 50,000	8 (73%)	7 (58%)	0.61
Hb-average	6.27	4.36 g%	0.06
White blood cells-avg.	58×10^9/l	62.7×10^9/l	0.88
Platelets-average	90.2×10^9/l	50.7×10^9/l	0.26
Dosage 6-MP*	50.9	57.8	0.17
Dosage MTX**	13.9	15.5	0.51

* Average maintenance dosage in mg/m^2/day. ** Average maintenance dosage in mg/m^2/week. ALL: acute lymphoblastic leukemia.

TABLE 2. **Risk factors and their relationship with the occurrence of unfavorable event in the evolution of children with acute lymphoblastic leukemia**

Risk factor	Unfavorable event	Frequency	OR	p*
Male (n = 12)	8	66.6%	2.4	0.27
Malnourished (n = 12)	9	75.0%	5.25	0.06
Under 2 years of age (n = 2)	1	50.0%	0.76	0.69
Over 9 years of age (n = 3)	2	66.6%	1.6	0.60
L2 type (n = 8)	7	87.5%	10.2	0.04
< 50,000 white blood cells (n = 8)	4	50.0%	0.68	0.69

* Fisher's exact test.

RESULTS

Characteristics of the population

Twenty-three patients diagnosed with ALL were studied with an age average of 5.2 years and a range between 1 and 12 years. Only two children were under 2 years of age and three patients were 9 or more years of age. They were distributed into two groups, according to their nutritional status. Twelve of these patients were malnourished patients, seven of them had weight/age score z values between −1.28 and −2, and four presented a more severe malnutrition with a score z of ≤ 2. Another patient was considered as a malnourished patient because he had a low weight with regards to his height. The eleven remaining children had a proper nutritional status. The characteristics of both groups during admission are shown in table 1. The average hemoglobin was lower in the malnourished children. The rest of the variables under study did not show significant differences, both groups are comparable.

Within the group of undernourished children 7 (63%) and 7 (58%) among the well-nourished group were considered high risk. The presence of ALL type L2 was more frequent among the undernourished than in the group of the well nourished children (50% versus 18%), without this difference being of statistical relevance (table 1).

TABLE 3. **Evolution of children with acute lymphoblastic leukemia**

	Well-nourished (n = 11)	Malnourished (n = 12)	OR	p*
Relapse	3 (27.3%)	6 (59%)	2.55	0.25
Bone marrow relapse	2 (18.2%)	3 (25%)	1.47	0.54
CNS relapse	2 (18.2%)	4 (33.3%)	2.17	0.37
Death	1 (9.1%)	6 (50%)	9.02	0.04
With relapse	1 (9.1%)	3 (25%)	3.27	0.26
Event	4 (36.4%)	9 (75%)	4.84	0.07

* Fisher's exact test.

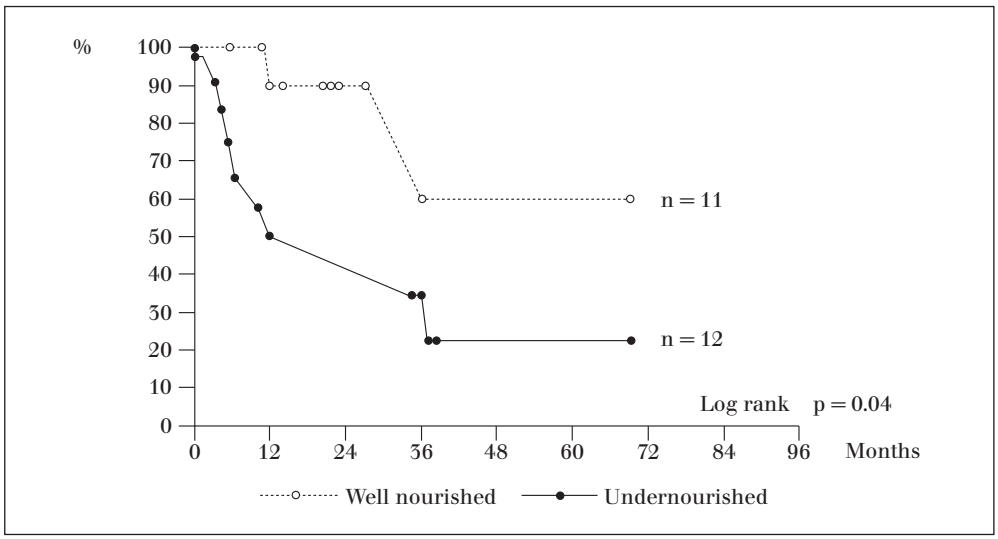

Fig. 1. Event-free survival curve (Kaplan-Meier) in two groups of children with acute lymphoblastic leukemia: nourished and malnourished children. Differences are significant according to the log rank test.

It is worth mentioning that the intensity of the average dosage of the chemotherapy employed was similar in both groups. The maintenance average dosage of 6 mer-captopurine (mg/m^2/day) and of methotrexate (mg/m^2/ week) were analyzed, and for both drugs the dosage employed in malnourished patients was higher. Ho-wever, this was not a significant difference (table 1).

Prognostic factors and adverse events

The risk factors associated with the presence of an adverse event, either relapse or death, were researched during its evolution. In the univariate analysis, we found that the two major factors were the presence of malnutrition and the L2 type ALL with odds ratio of 5.25 and 10.20, respectively. In the case of the L2 type, a statistical significance was achieved (table 2).

Unfavorable events were more frequent in malnourished patients because they were present in up to 75% of them, as compared to a frequency of 36.4% in nourished children. Relapses, both to bone marrow and to central nervous system, were more frequent in children with a nutritional deficit, without showing a statistical significance. Deaths were significantly more frequent among malnourished patients ($p < 0.05$), who had a mortality rate of 50% versus 9.1% in children with a proper nutritional status. The patients without tumor activity died from chemotherapy related complications, either bleeding or infection, and four patients died from leukemic infiltration (table 3).

TABLE 4. **Correlation of the occurrence of unfavorable events with risk factors in children with acute lymphoblastic leukemia. Multiple regression**

Variable	t ratio	p value
Cell count	1.240	0.23
Age (months)	1.086	0.29
Weight/age*	2.571	0.01

* Score z values.

Survival curve

Through the log rank test, weight for age has a significant influence on the event-free survival in children with ALL ($p = 0.04$). In figure 1, the estimated survival, according to the Kaplan Meier curve, is shown. The event-free survival in two and three years was better in nourished children, being of 90% and 60%, respectively. However, in malnourished children, the event-free survival was of 40% and 20% ($p = 0.04$). After 5 years, in the group of patients with a good nutritional status, this survival rate accounts to 60%, while that rate in malnourished children has fallen up to 20% (fig. 1).

Correlation of the presence of an unfavorable event with prognostic factors

It has been considered that the major poor prognostic factors are age and white blood cell count. To estimate the association between the presence of unfavorable event, either relapse or death, risk factors and malnutrition, we applied a multiple regression model, where there was no linear relationship between the variables and they are independent. Results show only malnutrition, measured by the weight/age ratio, contributes significantly to the development of unfavorable events in patients with ALL treated at the Rio Blanco Regional Hospital (table 4).

DISCUSSION

At the moment the ALL diagnosis is made, it is common that children of developing countries show some malnutrition degree. In Brazil, Viana[18] reported that 15% of the children with ALL were malnourished, while in Mexico, Lobato-Mendizábal[14] and Gómez-Almaguer[10] found frequencies that range between 20 and 50%. In this work, and using the weight versus age criterion, ALL was associated with malnutrition in 52% of cases. This is a higher figure than that expected in the pediatric population in our hospital, as 35 out of every 100 children released show some degree of malnutrition.

According to Macharia, the clinical characteristics of ALL are very different in developing countries: the ratio of children under 2 years of age and over 9 years of age with L2 type and immunophenotype T are more frequent than in developed countries[19]. The ratio of children with white blood cell counts over 50,000 per mm^3 is also higher in developing countries. As malnutrition is more frequent in these countries, the deficient nutritional status could explain these differences. In the population studied, we found some differences in the malnourished group as compared to the nourished group. In fact, the L2 type was more frequent (50% versus 18%), as well as the presence of adenomegalies and splenomegaly (73% versus 42%). The difference in their hemoglobin level was statistically significant, being lower in malnourished children, which can be attributed to deficit problems.

The survival rate in malnourished leukemic children is lower than in nourished children. This fact has been shown by various studies, such as the study conducted by Viana in Brazil, where 5-year mortality in his group of malnourished children amounted to 100%[18]. Mexican studies have reported a 5-year survival rate from 26% to 45%, while in nourished children, it ranges from 57% and 83%. In an analysis made of various studies published, Gómez-Almaguer et al concluded that the mortality risk is five times higher in malnourished children with ALL than in nourished children[10]. In fact, the mortality rate among the pediatric population with ALL of the Rio Blanco Regional Hospital was five times higher when they had any degree of malnutrition (50% versus 9.1%).

Not only is the mortality rate higher in malnourished children with ALL, but the presence of other unfavorable events, such as relapse either to bone marrow or to the central nervous system, is also more frequent. This issue was already suggested by Lobato-Mendizábal[14], who observed that a population with children with ALL with standard risk showed a lower survival rate, as a result of bone marrow relapse. The belief is that malnutrition leads to a reduction in the bone marrow reserve, which makes it necessary to use suboptimal dosages of maintenance chemotherapy, which has an unfavorable effect on prognosis. However, in the population studied in this work, the maintenance average dosages/m^2 of 6 mercaptopurine and methotrexate were higher in malnourished children than in the rest of them, although this difference was not significant. There are few studies regarding the pharmacokynetics of antineoplastic chemotherapy agents in malnourished children, but some reports on methotrexate have shown that this drug has a different behavior in malnutrition cases, with a slower clearance rate and higher toxic effects[20]. On the other hand, calculations of chemotherapy based on the body surface may not be optimal, as there is evidence that the lean body mass can better predict the dosage than when considering weight and body surface[21,22]. As there are differences between the lean body mass of the malnourished child and the nourished child, the possibility exists that we are not properly estimating the dosages of drugs. Other factors associated with the pharmacokynetics of the anti-cancer drugs must be studied, because the malnourished child presents various metabolic disorders, such as a lower concentration of serum proteins, a higher contents of body water, changes in the hepatic and renal functions, that may affect the drug distribution[23,24].

In short, malnutrition is an adverse prognostic factor in children with ALL. However, in this study, the event-free survival cannot be attributed to chemotherapy suboptimal dosages. It is necessary to conduct studies about the compliance with the treatment, even though it is given free of charge.

This study has some limitations. The fact that it has been found that factors, such as age and white blood cell count, are not associated with adverse effects can be due to the small size of the population studied. Likewise, some other variables, such as the immunological subtypes or the cell receptors, could not be included because in most of the Mexican hospitals, such as ours, these resources are unavailable. However, this work supports the existing reports in the literature on the importance that the nutritional condition has on the acute lymphoblastic leukemia prognosis in children.

References

1. Veerman AJ, Hahlen K, Kamps WA, et al. High cure rate with a moderately intnsive treatment regime in non-high-risk childhood acute lymphoblastic leukemia, results of protocol ALL VI from the Dutch Childhood Leukemia Study Group. J Clin Oncol 1996;14(3):911-8.
2. Reiter A, Schrappe M, Ludwig WD, et al. Chemotherapy in 998 unselected childhood acute lymphoblastic leukemia patients. Results and conclusions of the multicenter trial ALL-BFM 86. Blood 1994;84(9):3122-33.
3. Rivera GK, Pui CH, Hancock ML, et al. Update of St. Jude XI for childhood acute lymphoblastic leukemia. Leukemia 1992;6(Suppl 2):153-6.
4. Rivera GK, Pinkel D, Simone JV, Hancock ML, Crist WM. Treatment of acute lymphoblastic leukemia: 30 years´ experience at St. Jude Children's Research Hospital. N Engl J Med 1993;329:1289-95.
5. Simone JV. Verzosa MS, Rudy JA. Initial features and prognosis in 363 children with acute lymphocytic leukemia. Cancer 1975;36:2009-108.
6. Smith M, Arthur D, Camitta B, et al. Uniform approach to risk classification and treatment assignament for children with acute lymphoblastic leukemia. J Clin Oncol 1996;14(1):18-24.
7. Miller DR, Leiken S, Albo D. Prognostic importance of morphology (FAB Classification) in childhood acute lymphoblastic leukemia. Br J Haematol 1981;48:199-206.
8. Ribeiro RC, Pui CH. Prognostic factors in childhood acute lymphoblastic leukemia. Hematol Pathol 1993;7(3): 121-42.
9. Ávila CA, Chávez VA, Shamah LT, Madrigal FH. La desnutrición infantil en el medio rural mexicano. Análisis de las encuestas nacionales de alimentación. Salud Pública Mex 19;1993:35:658-66.
10. Gómez-Almaguer D, Ruiz Argüelles G, Ponce de León S. Nutritional status and socio-economic conditions as prognostic factors in the outcome of therapy in chidlhood acute lymphoblastic leukemia. Int J Cancer 1998;11 (Suppl): 52-55.
11. Reilly JJ, Odame I, McColl JH, McAllister PJ, Gibson BES, Wharton BA. Does Weight for Height have Prognostic significance in children with acute lymphoblas-tic leukemia? Am J Pediatr Hematol Oncol 1994;16(3): 225-30.
12. Marín-López A, Lobato-Mendizabal E, Ruiz-Argüelles G. La desnutrición es un factor pronóstico adverso en la respuesta al tratamiento y supervivencia de pacientes con leucemia aguda linfoblástica de riesgo habitual. Gac Med Mex 1991;127(2):125-165.
13. Lobato-Mendizábal ME, Ruiz-Argüelles GJ. Efecto del tratamiento quimioterápico sobre el estado nutricional y su repercusión en la respuesta terapéutica de pacientes con LLA de riesgo estándar. Sangre 1990;35(3):189-95.
14. Lobato-Mendizábal E, Ruiz-Argüelles GJ, Marín-López A. Leukaemia and nutrition, I. Malnutrition is an adverse prognostic factor in the outcome of treatment of patients with standard-risk acute lymphoblastic leukaemia. Leuk Res 1989;13:899-906.
15. Verduzco-Rodríguez L, Ibarra-Colado J. Tratamiento de leucemia aguda linfoblástica en niños de escasos recursos en un hospital comunitario del estado de Veracruz. Rev Invest Clin 1998; 50:477-81.
16. Chandy M. Childhood acuty lymphoblastic leukemia in India: an approach to management in a three-tier society. Med Pediat Oncol 1995;25:197-203.
17. Norma Oficial Mexicana NOM-008-SSA2-1993. Control de la nutrición, crecimiento y desarrollo del niño y del adolescente.
18. Viana MB, Murao M, Ramos G, et al. Malnutrition as a prognostic factor in lymphoblastic leukaemia: a multivariate analysis. Arch Dis Child 1994;71:304-10.
19. Macharia WM. Comparison of prognostic determinants in childhood acute lymphoblastic leukaemia in negroid and caucasian populations. East African Med J 1996;73: 638-42.
20. Mihraniana MH, Wang YM, Daly JM. Effects of nutritional depletion and repletion on plasma metotrexate pharmacokinetics. Cancer 1984;54(10):2268-71.
21. Morgan DJ, Bray KM. Lean body mass as a predictor of drug dosage. Implications for drug therapy. Clin Pharmacokinetic 1994;26(4):292-307.

22. Rajeswari R, Shetty PA, Gothoskar BP, Akolkar PN, Gokjihale SV. Pharmacokinetics of metotrexate in adult Indian patients and its relationship to nutritional status. Cancer Treat Rep 1984;68(5):727-32.
23. Bidlack WR, Brown RC, Mohan C. Nutritional parameters that alter hepatic drug metabolism, conjugation and toxicity. Fed Proc 1986;45(2):142-8.
24. Walter-Sack I, Klotz U. Influence of diet and nutritional status on drug metabolism. Clin Pharmacokinet 1996; 31(1):47-64.