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Nutritional status and cytokine concentration during chemotherapy in Mexican children: A longitudinal analysis

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ABSTRACT

Objective: The aim of this study was to assess whether the nutritional status of children with cancer is influenced by variations in cytokine concentrations observed during chemotherapy. We also evaluated whether this relationship could be modified by nutritional status at diagnosis and type of cancer.
Methods: Mexican children with lymphoma or solid tumors were evaluated at diagnosis and at 2- and 6-mo follow-up visits. Blood samples were obtained to determine serum prealbumin, tumor necrosis factor (TNF)-α, interleukin (IL)-6, leptin concentrations, and hemoglobin. Children were classified as undernourished (UN) or well nourished (WN), according to prealbumin concentration. The influence of each cytokine on prealbumin concentration was analyzed by time-series regression model.
Results: Fifty patients (ages 2–17 y) were enrolled. There were 17 children with lymphomas and 33 with solid tumors. At baseline, 56% were UN and 26% presented anemia; the frequencies of UN children were higher for those with lymphoma than for those with a solid tumor ($P = 0.003$). By nutritional status, UN children presented lower leptin ($P = 0.002$) but higher IL-6 concentrations ($P = 0.009$) than the WN group. Children with lymphoma presented lower prealbumin ($P = 0.003$), but higher TNF-α ($P = 0.001$) and IL-6 ($P = 0.011$) concentrations than those with solid tumors. At follow-up, the concentration of prealbumin increased and IL-6 decreased in children with lymphoma. Multivariate analysis demonstrated that decreases in prealbumin concentration at the end of follow-up were associated with increases in IL-6 and TNF-α concentration during chemotherapy.
Conclusions: These results suggest that the cytokine responses during chemotherapy are related to nutritional status at the end of 6 mo of treatment regardless of the initial nutritional status and the type of cancer.

Introduction

The literature suggests that as many as 46% of children and young adults with cancer become malnourished [1,2]. This prevalence varies considerably among studies, depending on tumor type, disease evolution, treatment, techniques to assess nutritional status, and the definition of undernourishment used [1–6]. The consequences of malnutrition include an increased risk for complications, a decreased response and tolerance to treatment, and high relapse and low survival rates. In fact, nutritional status is considered to be an important prognosis factor [2,3,7]. The cause of malnutrition in the pediatric cancer population is multifactorial, including complex interactions between energy and substrate metabolism, as well as the production and release of endogenous mediators such as the proinflammatory cytokines tumor necrosis factor (TNF)-α and interleukin (IL)-6, which alter metabolism and amplify the inflammatory response, leading to undernutrition by inducing anorexia and muscle wasting [8–10]. Previous studies have suggested that cytokines, mainly IL-6, are associated with disease status and poor prognosis in adult cancer patients [11]. In addition, the concentrations of other mediators, such as leptin, which are involved in the cancer-induced anorexia, have been

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found to be inversely related to those of inflammatory cytokines in adult patients with cancer [12,13].

To date, few studies have examined the variations in cytokine concentrations by nutritional status or by type of cancer (solid tumors and hematologic malignancies) at diagnoses or during therapy, and the majority of these studies had been performed with children with leukemia [14–19]. Additional research is required for a longitudinal evaluation of the relation of changes in cytokine concentration.

The main aim of this study was to assess whether nutritional status at the end of a 6-mo period of chemotherapy would be influenced by variations in cytokine concentration during therapy. We also evaluated whether this relationship could be modified by nutritional status at diagnosis or by the type of cancer.

Materials and methods

Study population

The study was conducted in the Medical Nutrition Research Unit in a Pediatric Hospital, Mexican Institute of Social Security (IMSS), in Mexico City, Mexico. The selected patients (N = 50, enrolled at diagnosis) were children 2 to 17 y of age who had been recently diagnosed with lymphoma or a solid tumor and for whom both written consent signed by their parents and informed assent by the children were obtained. Children who had previously been treated for cancer in another institution were excluded. The children were followed during the 6-mo period of chemotherapy. Anthropometry and blood samples were obtained at each appointment: at baseline (i.e., immediately before starting chemotherapy) and at 2- and 6-mo follow-ups. No child experienced acute fluid retention (edema) or dehydration or fever on days preceding measurements. The chemotherapeutic agents that had been prescribed by the attending oncologists, according to the type of cancer, were vincristine, cyclophosphamide, bleomycin, vinblastine, actinomycin D, and methotrexate.

Anthropometry

To determine body mass index (BMI), body weight was measured with an electronic scale (Tanita BWB-700, Tanita Corporation, Tokyo, Japan) while the children were wearing lightweight clothing. Height was measured to the nearest 0.1 cm with a wall-mounted stadiometer (Seca 222, Seca Corp., Oakland Center, Columbia, MD, USA). BMI was calculated as weight (kg) divided by the square of the height (m); BMI *z*-scores were obtained, in accordance with the US Centers of Disease Control and Prevention (CDC) normative curves, by using the computer software Epi-Info (EPI-INFO 2000, release 3.2.2, CDC, Atlanta, GA, USA) [20]. Trained technicians carried out the measurements of body weight and height.

Blood analyses

Venous blood samples (~5–6 mL) were collected between 0800 and 0900 after an overnight fast and were used to determine serum concentrations of prealbumin, hemoglobin, IL-6, TNF-α, and leptin. Clotted blood samples were centrifuged (4°C; 3000*g*; 15 min), and aliquots of each serum were immediately frozen (−80°C) until used for biochemical determinations. Concentrations of IL-6 and TNF-α were determined by using high-sensitivity enzyme-linked immunosorbent assay kits (R&D Systems, Inc. Minneapolis, MN, USA). Leptin concentrations were determined by radioimmunoassay with a commercial kit (Millipore Corporation, Billerica, MA, USA). Prealbumin concentration is considered a reliable and sensitive marker of protein status in pediatric cancer patients [21] and, therefore, a proxy for nutritional status. Prealbumin concentrations were evaluated with a quantitative turbidimetric test by nephelometry (Behring Nephelometer ProSpec, Dade Behring, Germany). Children were classified as undernourished (UN) or well nourished (WN), according to prealbumin concentration (cutoff 0.20 g/L). All assays were carried out in duplicate; coefficients of variation were <10%.

Ethics

All participants and their parents provided informed consent. The study was conducted in accordance with the Helsinki Declaration and approved by the Research and Ethics Committee of the Pediatric Hospital, Mexican Institute of Social Security (IMSS), in Mexico City, Mexico.

Statistical analysis

Data were expressed as median and range. Comparisons between continuous variables were performed by using the Mann–Whitney U test and Wilcoxon test after data had been tested for normal distribution, based on skewness, kurtosis, and the Shapiro–Wilk test. The comparison of cytokine concentration changes and family of chemotherapeutic agent (classified as family) were assessed by Friedman rank test. The effect of each cytokine on prealbumin concentration was analyzed by using a time-series regression model (panel data, by using a generalized least-squares estimator with random-effects model for between-regression estimations) employing the random-effects option of the xtreg command from Stata SE 11.0 (College Station, TX, USA). Data were clustered by diagnosis (lymphoma or solid tumor) and adjusted by age and sex. Statistical significance was defined at $P < 0.05$.

Results

Baseline characteristics

From 100 pediatric patients identified as being eligible, 57 met the selection criteria; however, 7 declined to participate. Of the 50 participating patients, 42% were male; 17 were diagnosed with lymphoma and 33 with solids tumors; 56% were UN (13

Table 1
Characteristics of study population

Characteristic	All children at baseline (N = 50)	Completed follow-up (n = 26)	Attrition (n = 24)
Female (n)/male (n)	29/21	14/12	15/9
Age (y)*	11.2 (2, 17)	10.9 (3, 16)	12 (2,17)
z-BMI	−0.030 (−3.6, 2.4)	−0.55 (−3.6, 2.0)	0.61 (−2.4, 2.4)
Nutritional status			
Undernourished (n)	28 (56%)	18 (69%)	10 (42%)†
Well nourished (n)	22 (44%)	8 (31%)	14 (58%)
Hematologic status			
Normal (n)	37 (74%)	7 (27%)	6 (25%)
Anemia (n)	13 (26%)	19 (73%)	18 (75%)
Diagnosis			
Lymphomas‡ (n)	17 (34%)	9 (35%)	8 (33%)
Solid tumors§ (n)	33 (66%)	17 (65%)	16 (67%)
Therapy			
Chemotherapy (n)	44 (88%)	23 (88%)	21 (88%)
Chemotherapy plus radiotherapy (n)	6 (12%)	3 (12%)	3 (12%)

z-BMI, body mass index *z*-score
*Values expressed as median (minimum, maximum).
† χ^2 analysis, $P = 0.050$.;
‡Hodgkin. lymphoma (n = 8) and non-Hodgkin lymphoma (n = 9).
§Ovarian carcinoma (n = 1), neuroectodermal tumor (n = 1), teratosarcoma (n = 1), medulloblastoma (n = 2), Ewing's sarcoma (n = 2), astrocytoma (n = 3), Wilm's tumor (n = 4), rhabdiomyosarcoma (n = 6), and osteosarcoma (n = 13).

lymphomas; 15 solid tumors); and 26% presented anemia. Osteosarcoma (n = 13) was the most frequently diagnosed of the solid tumors, with only one more case of non-Hodgkin lymphoma than of Hodgkin lymphoma (Table 1). By nutritional status, UN children presented higher IL-6 ($P < 0.001$) and lower leptin ($P = 0.009$) and hemoglobin concentrations ($P = 0.002$) than WN children; these differences were all statistically significant (Table 2). Stratification by cancer type demonstrated that children with lymphoma presented significantly lower prealbumin and hemoglobin concentrations, but higher concentrations of TNF-α and IL-6 than those with solid tumors. Leptin concentration was not statistically significant (Table 2). The frequency of UN was higher in children with lymphoma than in children with a solid tumor (76% versus 45%, respectively).

Follow-up

During follow-up, 5 children died because of to complications such as infection, myelosuppression, or metastasis; 10 patients dropped out because their parents did not want to continue the study; and 9 patients presented blood samples that were insufficient to measure biochemical variables. Therefore, 26 children (9 with lymphomas; 17 with solid tumors) completed the study. At baseline, the clinical data and characteristics of the 24 children no longer in the study were comparable to those who completed follow-up, with the exception that the proportion of undernourishment was significantly higher in those who remained in the study (Table 1).

At the end of follow-up, a decrease in the frequency of UN was observed. Of the 18 children (8 lymphomas; 10 solid tumors) who were undernourished at baseline, only 11 remained undernourished at the end of follow-up (3 lymphomas; 8 solid tumors). TNF-α and IL-6 concentrations at follow-up decreased in both UN and WN children, although the decrease of IL-6 was statistically significant only in UN children (Table 3). We evaluated the BMI changes at 6 mo of follow-up minus BMI at 2 mo because in children the weight implies growth, and it does not change by the individual. We conducted Spearman correlations between the BMI and cytokines concentration. Only a correlation between TNF concentration and BMI changes were observed ($r = -0.44$; $P = 0.020$). The analysis of biochemical variables stratified by type of cancer showed that the concentration of prealbumin increased and those of IL-6 and TNF-α decreased in the group with lymphomas, whereas no changes were observed in children with solid tumors. Leptin concentration did not differ (Fig. 1). The analysis of the concentration of cytokines with the type of chemotherapeutic agent that children received during the study showed that the concentration of IL-6 and TNF-α decreased in all families at 6 mo, with the exception of alkylating agents and TNF-α concentration in plant product families; whereas leptin concentration remained

Table 2
Concentrations of cytokines and serum markers for Mexican children (N = 50) in the study, stratified by nutritional status and type of cancer

Variable	Concentration*		*P*-value†
Nutritional status	Well nourished (n = 22)	Undernourished‡ (n = 28)	
Prealbumin (g/L)	0.25 (0.20, 0.38)	0.10 (0.05, 0.18)	<0.001
Hemoglobin (g/dL) TNF-α (pg/mL)	14 (9.6, 16.6)	12.5 (7.6, 16.4)	0.002
	1.5 (0.5, 6.3)	2.1 (0.19, 7.6)	0.421
IL-6 (pg/mL)	3.7 (0.57, 15.7)	10.8 (0.97, 65.9)	<0.001
Leptin (pg/mL)	7.9 (1.6, 55.6)	3.3 (0.9, 28.9)	0.009
Type of cancer	Solids tumor (n = 33)	Lymphoma (n = 17)	
Prealbumin (g/L)	0.21 (0.06, 0.38)	0.10 (0.05, 0.23)	0.003
Hemoglobin (g/dL)	14.0 (9.6, 16.6)	12.6 (7.6, 15)	0.031
TNF-α (pg/mL)	1.3 (0.19, 5.1)	3.2 (0.93, 7.6)	0.001
IL-6 (pg/mL)	5.2 (0.57, 30.7)	10.8 (2.7, 65.9)	0.008
Leptin (pg/mL)	6 (0.9, 55.6)	3.8 (1, 22.7)	0.287

IL-6, interleukin; TNF, tumor necrosis factor
*Data expressed as median (minimum, maximum).
†Data compared by using the Mann–Whitney U test.
‡Undernourished defined as prealbumin concentration <0.20 g/L.

Table 3
Concentrations of cytokines and serum markers for Mexican children (N = 26) who completed the study, stratified by nutritional status, at baseline and at 6 mo of therapy

Variable	Concentration*,†			
	Baseline		6 mo	
	WN n = 8	UN‡ n = 18	WN n = 15	UN n = 11
Prealbumin (g/L)	0.27 (0.22, 0.38)	0.10 (0.05, 0.18)§	0.22 (0.20, 0.34)‖	0.14 (0.08,0.19)§,‖
Hemoglobin (g/dL)	14.0 (12.3, 14.9)	12.7 (7.6, 16.4)	12.4 (8.8, 14.8)‖	11.7 (10.1, 12.6)
TNF-α (pg/mL)	1.3 (0.55, 2.3)	1.5 (0.50, 7.6)	0.88 (0.34, 4.4)	1.2 (0.45, 3.6)¶
IL-6 (pg/mL)	4.0 (0.57, 9.4)	10.8 (2.7, 47.2)§	2.7 (0.06, 11.9)	5.6 (0.97 10.8)‖,#
Leptin (pg/mL)	6.2 (1.6, 8.1)	3.8 (0.9, 12.3)	6.9 (1.4, 17.9)	5.8 (2.9, 23.6)

IL, interleukin; TNF, tumor necrosis factor; UN, undernourished; WN, well-nourished
*Data expressed as median (minimum, maximum).
†Data compared with Mann–Whitney U test and Wilcoxon test;
‡Undernourished defined as prealbumin concentration <0.20 g/L;
§P <0.05, WN vs UN at baseline and WN vs UN at 6 mo.
‖P <0.05, basal vs 6 mo.
¶P = 0.062, WN cs UN at 6 mo.
#P = 0.096, WN vs UN at 6 mo.

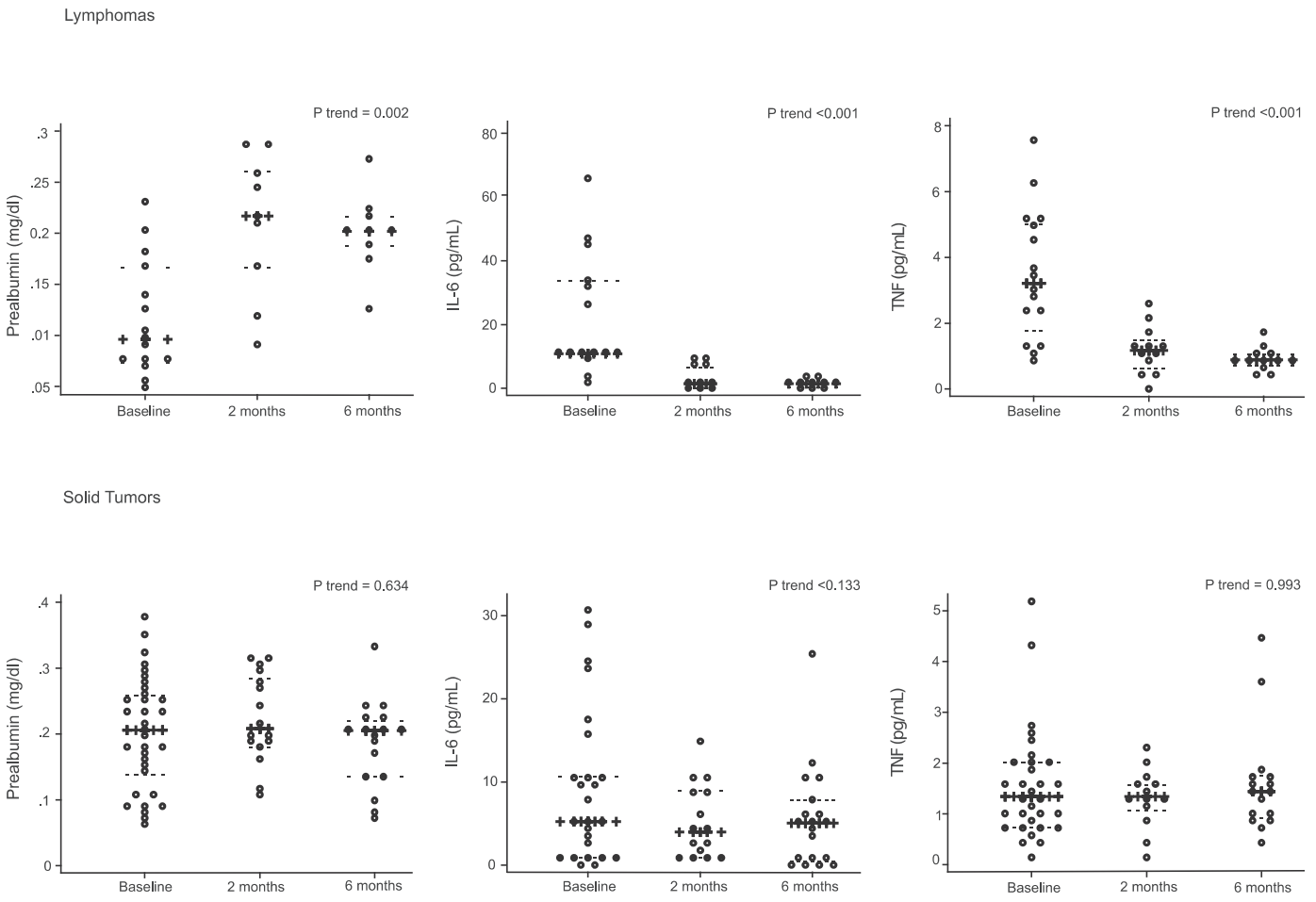

Fig. 1. Comparison of prealbumin, IL-6, and TNF-α serum concentrations for Mexican children with either lymphomas or solid tumors during the first 6 mo of therapy. IL, interleukin; TNF, tumor necrosis factor.

Table 4
Cytokines concentration changes and family of chemotherapeutic agent[*,†] values are median (interquartile range)

	Basal	2 mo	6 mo
	Alkylating agents		
TNF-α (pg/mL)	1.6 (1, 2.4)	1.1 (0.8, 1.4)	1.2 (0.9, 1.6)
IL-6 (pg/mL)	9.4 (2.7, 29.2)	1.8 (0.64, 7.8)	5.2 (1.4,8.1)
Leptin (pg/mL)	6.3 (2.9, 14.6)	6.4 (2.8, 9.7)	8.6 (3.9, 13.4)
	Antimetabolites		
TNF-α (pg/mL)	2.9 (1.3, 3.6)	1.5 (0.81, 2.1)	1.1 (0.69, 1.5)[‡]
IL-6 (pg/mL)	10.8 (8.6, 34.3)	10.0 (1.6, 10.1)	2.1 (1.5, 4.3)[‡]
Leptin (pg/mL)	3.8 (1.5, 7)	9.2 (4.6, 10.7)	9.4 (4.3, 15.4)
	Antitumor antibiotics		
TNF-α (pg/mL)	1.4 (0.84, 2.2)	1.1 (0.51, 1.3)	0.87 (0.69, 1.2)[‡]
IL-6 (pg/mL)	10.8(5.2, 10.8)	2.6 (0.57, 8)	4.1 (1.2, 5.3)[‡]
Leptin (pg/mL)	6.2 (2.5, 15.1)	8.0 (2.9, 10.7)	8.9 (5.8, 13.6)
	Plant products		
TNF-α (pg/mL)	1.6 (1.1, 2.7)	1.6 (1.3, 1.7)	1.3 (0.93, 1.7)
IL-6 (pg/mL)	10.7 (2.7, 10.8)	2.4 (1.3, 5.3)	2.7 (0.24, 8.1)[‡]
Leptin (pg/mL)	3.8 (2.3, 7.5)	4.9, (2.9, 7.8)	4.6 (2.9, 12.6)
	Miscellaneous		
TNF-α (pg/mL)	2.9 (1.8, 4.1)	1.4 (0.5, 2.1)	1.1 (0.86, 1.3)[‡]
IL-6 (pg/mL)	18.3 (6.4, 40)	1.3 (0.64, 10)	2.7 (1.5, 2.8)[‡]
Leptin (pg/mL)	3.6 (2, 5.4)	7.8 (2.9, 10.5)	5.7 (2.9, 13.6)

IL, interleukin; TNF, tumor necrosis factor
*Alkylating agents (cyclophosphamide, ifosfamide; cisplatin, carboplatin, nitrosoureas, dacarbazine); antimetabolites (methotrexate, Ara-C); antitumor antibiotics (doxorubicin, bleomycin, epirubicin, dactinomycin, fluorouracil, daunorubicin); plant products (vincristine, vinblastine, etoposide); and miscellaneous (hydrocortisone, prednisone, dexamethasone, asparaginase).
†Values are median (interquartile range).
‡Comparison intragroups with Friedman Rank; $P < 0.05$.

Table 5
Statistical analysis of the association of concentrations of TNF-α, IL-6, and leptin and changes in prealbumin concentrations in sera at 6 mo

Variable	Time-series regression		
	Coefficient	SE	*P*-value
TNF-α	−0.0158	0.0041	<0.0001
Sex	−0.0260	0.0189	0.168
Age	0.0023	0.0039	0.551
IL-6	−0.0017	0.0004	<0.0001
Sex	−0.0172	0.0330	0.601
Age	0.0059	0.0045	0.186
Leptin	0.0018	0.0011	0.124
Sex	−0.0251	0.0212	0.238
Age	0.0036	0.0032	0.256

IL, interlukin; SE, standard error; TNF, tumor necrosis factor

unchanged (Table 4). Multivariate analysis demonstrated that the decreases in prealbumin concentration from baseline to the end of follow-up were associated with increases in IL-6 and TNF-α concentration during chemotherapy. Such associations remained after adjusting for age, sex, basal nutritional status, and the type of cancer (Table 5).

Discussion

We present evidence that variations in cytokine concentration during chemotherapy for children with cancer influenced their nutritional status, regardless of whether the child was undernourished at the start of treatment. We found that initial UN was more frequent in children with lymphoma than in those with a solid tumor, which was likely associated with the high concentration of cytokines detected in this group. Our results are comparable not only to those of Saarinen et al. [14] and Siimes et al. [17], who reported that malnutrition at diagnoses was more frequent in hematologic cancer than in other types of cancer, but also to the results of Kuvibidila et al. [19], who found high rates of UN in children with leukemia. To assess nutritional status, we used the same method as had Kuvibidila et al. Our findings contrast with those reported in a recent analytical review, which concluded that the prevalence of UN is higher in children with solid tumors than in children with hematologic cancer [7]. It is probable that this difference was due to either variations in the diagnostic techniques used to assess nutritional status, or to the definition of malnutrition. The studies reviewed used BMI, mid-upper arm circumference, or triceps skinfold to identify UN, whereas we evaluated nutritional status by determining the concentration of prealbumin. This is a more robust method because it is more precise than anthropometric measurements and because the mass of the tumor does not influence the result [16,19,21,22].

In the present study, we observed that changes in the concentration of prealbumin after chemotherapy were related to differences in cytokine concentration but were not associated with baseline nutritional status. A probable explanation of this finding is that the catabolic activity of the cytokines had a shorter duration in those whose cytokine concentration had decreased earlier. Interestingly, the concentration of cytokines decreased in both WN and UN children, but such decrease was milder in children who were UN at baseline. This observation is in line with evidence suggesting that undernourished children have a worse prognosis than children who start chemotherapy while in a state of adequate nutrition [7,23–25].

Thus, it seems evident that undernutrition was associated with high concentrations of cytokines. However, how changes in cytokine concentration during chemotherapy influence nutritional status is not well understood. For example, both Saarinen et al. [14] and Siimes et al. [17] showed that serum TNF-α gradually decreases during treatment, but such decrease does not correlate with the final nutritional status. In contrast, Kuvibidila et al. [19] found that undernourished children present elevated TNF-α concentrations that do not vary during chemotherapy. In the present study, the variations in the concentrations of both cytokines and prealbumin were higher at baseline and during chemotherapy in the group of undernourished children. Thus, the net result was that children who had decreased cytokine concentration showed improvement in nutritional status, regardless of whether they had been undernourished at baseline.

We recognize the following limitations in our study: 1) the number of children who did not finish the study, which consequently affected the final sample size and 2) the lack of information regarding energy intake because energy intake may affect nutritional status.

However, the baseline characteristics of the group of children who did not finish the study were comparable to those of the analyzed group, with the exception of the proportion of UN. In this regard, the group of children who did not finish the study was comparable to our analyzed group in most of the baseline characteristics, except for the proportion of UN. In the group that completed the study, the frequency of UN was significantly greater than that in the attrition group; thus, there were a sufficient number of undernourished patients to conduct the analysis. Although the power to detect differences was not achieved for the between-group comparisons (75–92%) for the different biochemical variables, the general linear-model approach permitted us to analyze simultaneously the relationships among variation in cytokine concentration, basal nutritional status, and type of cancer. This analysis demonstrated a consistent and significant association between variations in cytokine concentration and final nutritional status. We did not measure energy intake: However, it seems that this is a less

important variable in cancer patients, as Brinksma et al. [26] found that variations in energy intake does not influence the final nutritional status of children who undergo chemotherapy. Finally, we recognize that differences in the medications used, according to the type of cancer, may have influenced the results; for instance, the treatment for lymphoma included the use of steroids, whereas that for solid tumors did not. This is important because the effect of steroids on cytokine concentration is widely accepted. In this study, the analysis of cytokine concentration with the type of chemotherapeutic agent that children received during the study showed that the concentration of IL-6 and TNF-α decreased at 6 mo, with the exception of alkylating agents and TNF-α concentration in the plant product families; whereas leptin concentration remained unchanged. We still think that variations in cytokine concentration influenced nutritional status of children at the end of chemotherapy; whether such variation is associated with specifics chemotherapeutic agents treatment is not the focus of this investigation. To close, another limitation was the very limited number of cytokine assessed.

The present study had the following two strengths: 1) the longitudinal design, which allowed us to evaluate variations in cytokine concentration and changes in nutritional status during the follow-up, and 2) the use of prealbumin concentration to assess nutritional status as this more robust assessment of nutritional status has been proposed as the best proxy for nutritional status analysis because it reflects protein status in this population and is not influenced by tumor mass [16,20].

Conclusions

These results suggest that cytokine responses during chemotherapy are related to nutritional status at the end of 6 mo of treatment regardless of the initial nutritional status and the type of cancer. Given the importance of nutritional status and its relation with the prognosis of disease, it is imperative to implement nutritional support in this population from the time of diagnosis and during therapy. This is especially important in developing countries, where undernourishment in pediatric cancer patients at the time of diagnosis is more prevalent.

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