

**Original Article****Oral Nutritional Supplementation in Children Treated for Cancer in Low- and Middle-Income Countries Is Feasible and Effective: the Experience of the Children's Hospital Manuel De Jesus Rivera "La Mascota" in Nicaragua**

Nicolò Peccatori¹, Roberta Ortiz², Emanuela Rossi³, Patricia Calderon², Valentino Conter¹, Yesly García², Andrea Biondi¹, Darrel Espinoza², Francesco Ceppi⁴, Luvy Mendieta⁵ and Maria Luisa Melzi¹.

¹ Centro di Emato-Oncologia Pediatrica Maria Letizia Verga, S. Gerardo Hospital, University of Milano-Bicocca, Monza, Italy.

² Department of Hematology/Oncology, Children's Hospital Manuel de Jesus Rivera, Managua, Nicaragua.

³ Center of Biostatistics for Clinical Epidemiology, Department of Medicine and Surgery, University of Milano-Bicocca, Monza, Italy.

⁴ Pediatric Hematology-Oncology Unit & Pediatric Hematology-Oncology Research Laboratory, Division of Pediatrics, Department of Woman-Mother-Child, University Hospital of Lausanne, Lausanne, Switzerland.

⁵ Department of Nutrition, Children's Hospital Manuel de Jesus Rivera, Managua, Nicaragua.

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Abstract. Children with cancer are particularly vulnerable to malnutrition, which can affect their tolerance of chemotherapy and outcome. In Nicaragua approximately two-thirds of children diagnosed with cancer present with under-nutrition. A nutritional program for children with cancer has been developed at "La Mascota" Hospital. Results of this oral nutritional intervention including difficulties, benefits, and relevance for children treated for cancer in low- and middle-income countries are here reported and discussed.

Keywords: Childhood cancer, Nutrition, Low- and middle-income countries.

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Correspondence to: Valentino Conter, Centro di Emato-Oncologia Pediatrica Maria Letizia Verga, S. Gerardo Hospital, University of Milano-Bicocca. Via Pergolesi 33, 20900 Monza (MB), Italy. Fax: (011) 39-039-2301646. E-mail: valentino.conter@gmail.com

Introduction. The pediatric population diagnosed with cancer is at high risk of malnutrition for cancer and treatment related effects. Children with cancer tend to become malnourished during treatment because of multiple reasons. Pain, anorexia, hormonal and inflammatory components, low physical activity, taste aversions and chronic medications are all factors which lead to decreased oral calories intake and can contribute to malnutrition.^{1,2} Malnutrition can affect the tolerance of both chemotherapy and

radiotherapy, may increase the risk of comorbidities and influence overall survival.³

Approximately 80% of children and adolescents who are diagnosed with cancer live in low- and middle-income countries (LMICs), where access to quality care and chances of cure are limited. In LMICs, malnutrition represents one of the major obstacles to effective pediatric care, together with late diagnosis, abandonment of therapy, suboptimal supportive care, and inefficient health-care delivery systems.⁴

In LMICs it is estimated that the prevalence of malnutrition averages 50% in children with cancer.⁵ In Nicaragua, the prevalence of malnutrition in children under 5 years of age according to UNICEF is 30%, with 23% of children presenting severe malnutrition and 7% moderate malnutrition.⁶ A study performed in the hemato-oncology centers of the AHOPCA (Asociación de Hemato-Oncología Pediátrica Centro-Americana)⁷ countries, between 2004 and 2007, showed that nutritional status of children with cancer at diagnosis was normal in 37% of patients, moderately depleted in 18% and severely depleted in 45%.⁸ In Nicaragua at the Children's Hospital Manuel de Jesus Rivera "La Mascota" (HIMJR), 67% of patients were classified as malnourished at diagnosis, including 47.9% with severe malnutrition.⁹

On the basis of these evidences, a nutritional program for children diagnosed with cancer who were inadequately nourished was developed at HIMJR, in collaboration with the Pediatric Hemato-Oncology Center of Monza (Milano-Bicocca University), in the context of the Monza International School of Pediatric Hematology/Oncology (MISPHO) initiative.¹⁰

HIMJR is the only hospital of Nicaragua where children with cancer can be treated; approximately 250 children with cancer per year are referred from the whole country.

The nutritional program started in February 2016 with the objectives to reduce the adverse effect of malnutrition on treatment related morbidity and improve clinical outcome.

The aim of this study is to assess the role of oral/enteral supplementation in children treated for oncological diseases in the context of LMICs, where this intervention still needs to be properly investigated.

Material and Methods. Patients with cancer, aged one month to 17 years, diagnosed between February 2016 and March 2017 at the HIMJR were screened for nutritional status by a qualified nutritionist at diagnosis. The nutritional status assessment was based on weight, height or length and the anthropometric measures of mid upper arm circumference (MUAC) and triceps skin fold thickness (TSFT), as already reported.⁸

TSFT and MUAC percentiles were estimated for age and gender using the LMS procedure according to the CDC and WHO growth charts.¹¹

Patients were considered adequately nourished (AN) if both TSFT and MUAC were >10th percentile, severely depleted (SD) if TSFT or MUAC <5th percentile, and moderately depleted (MD) in all other cases.

Eligible for the study, after obtaining written informed consent from parents or legal guardians, were: 1) patients inadequately nourished at diagnosis, 2) patients with borderline nutritional status at diagnosis undergoing intensive chemotherapy, considered at high risk of developing under-nutrition by the nutritionist and treating physician, and 3) patients developing under-nutrition during the treatment. Children with advanced disease at diagnosis and eligible only for palliative care were excluded.

Patients entered in the study were given oral polymeric hyper-caloric formulas containing a balanced mixture of proteins, fats, and carbohydrates according to the indication by age for patients up to 10 years or older (up to 17 years). Parents were instructed to reconstitute formulas with water and to administer them to their children at home after discharge from the hospital. The adherence to the nutritional treatment was ascertained by the nutritionist from parents' interviews.

Only when oral feeding was not considered possible or safe, formulas were administered through enteral feeding. Nutritionists and treating physicians decided the schedule of nutritional reassessments on the basis of the clinical conditions and the treatment plan for each patient.

Gender, date of birth, date of diagnosis, dates of nutritional assessment and type of cancer were recorded. The data were collected in the Pediatric-Oncology-Network-Database (POND).¹²

This study has made a comparison with a historical cohort of patients with comparable characteristics diagnosed from 2004 to 2007 at HIMJR,⁸ to evaluate the impact on event-free-survival (EFS) of the addition of nutritional support. Their nutritional status has been here re-classified according to the schema adopted in the current study.

Statistical analysis. Patients' characteristics were described using frequency, percentages, medians and interquartile range (IQR). The 1-year EFS was estimated in the overall cohort of 104 patients, and a comparison between the cohort in the study and the historical one was made using Kaplan Meier

survival curves and tested using Andersen pseudo-values regression, adjusting for type of tumor and nutritional status at first evaluation. This test was adopted due to the extremely different follow-up duration of the two cohorts.

P-values were considered statistically significant if lower than 0.05. Statistical analyses and figure were done with SAS v9.4, STATA and R.

Results. A total of 259 children were diagnosed with cancer at HIMJR in the period of the study; of them, 104 entered the study and received nutritional supplementation. Nutritional formulas were given free of charge and were accepted by all families.

Patients' characteristics at the onset of disease are described in **table 1**. Forty-four were female (42.3%), and 60 were male (57.7%); 34 were affected by acute lymphoblastic leukemia (ALL), 5 by acute myeloid leukemia, 13 by lymphomas and 52 by solid tumors, including brain tumors

(n=20), retinoblastoma (n=3), bone and soft-tissue sarcoma (n=15), Wilms' tumor (n=7) and others (n=7). Diseases were clustered in two groups - leukemia/lymphomas and solid tumors- for further analyses.

At the start of the nutritional support, the median age was 7.0 years (IQR: 3.4-11.5). Almost all patients (n=99) were exclusively orally supplemented; in only three patients the nutritional formula was administered via nasogastric tube and in two via gastrostomy. The nutritional supplementation was started within one month from diagnosis in 63 cases (60.6%), between 1 and 2 months in 9 patients (8.6%) and later than 2 months in 32 cases (30.8%). At first work-up (before supplementation) according to their anthropometric measurements patients were overall classified as follows: 65.4% severely depleted, 13.5% moderately depleted and 21.1% borderline/adequately nourished (considered at risk of developing under-nutrition during treatment) (**Table 1**).

Table 1. Patients' characteristics and nutritional status pre- and post-supplementation, by type of tumor.

Patients characteristics	Type of tumor		Total N=104
	Leuk./Lymph. N=52	Solid tumor N=52	
	N (%)	N (%)	N (%)
Gender			
Female	19 (36.5)	25 (48.1)	44 (42.3)
Male	33 (63.5)	27 (51.9)	60 (57.7)
Age			
<1	1 (1.9)	0 (0.0)	1 (1.0)
1-5	25 (48.1)	19 (36.5)	44 (42.3)
6-9	10 (19.2)	11 (21.2)	21 (20.2)
10-17	16 (30.8)	22 (42.3)	38 (36.5)
Type of supplementation			
Oral	52 (100.0)	47 (90.4)	99 (95.2)
Via nasogastric tube	0 (0.0)	3 (5.8)	3 (2.9)
Via gastrostomy	0 (0.0)	2 (3.8)	2 (1.9)
Time from diagnosis to suppl. beginning			
< 1 month	36 (69.2)	27 (51.9)	63 (60.6)
1-2 months	5 (9.6)	4 (7.7)	9 (8.6)
> 2 months	11 (21.2)	21 (40.4)	32 (30.8)
Nutritional status before supplementation			
SD	31 (59.6)	37 (71.1)	68 (65.4)
MD	7 (13.5)	7 (13.5)	14 (13.5)
AN	14 (26.9)	8 (15.4)	22 (21.1)
Nutritional status after supplementation*			
SD	14 (36.8)	15 (57.7)	29 (45.3)
MD	6 (15.8)	6 (23.1)	12 (18.8)
AN	18 (47.4)	5 (19.22)	23 (35.9)

*Data available in 64 patients. SD=severely depleted, MD=moderately depleted, AN=adequately nourished.

Table 2. Distribution of patients by nutritional status pre- and post-nutritional intervention, by type of tumor.

Nutritional status before supplementation	Nutritional status after supplementation			
	SD	MD	AN	Total
	N (%)	N (%)	N (%)	N (%)
Leuk./Lymph.				
SD	12 (50.0)	3 (12.5)	9 (37.5)	24 (63.2)
MD	1 (33.3)	0 (0.0)	2 (67.7)	3 (7.9)
AN	1 (9.1)	3 (27.3)	7 (63.6)	11 (28.9)
Total	14 (36.8)	6 (15.8)	18 (47.4)	38
Solid tumor				
SD	11 (57.8)	4 (21.1)	4 (21.1)	19 (73.1)
MD	2 (66.7)	1 (33.3)	0 (0.0)	3 (11.5)
AN	2 (50.0)	1 (25.0)	1 (25.0)	4 (15.4)
Total	15 (57.7)	6 (23.1)	5 (19.2)	26

SD=severely depleted, MD=moderately depleted, AN=adequately nourished.

Seventeen patients died of progressive disease, and 23 did not have a nutritional follow-up. Thus, nutritional reassessment after supplementation was performed in 64 patients at a median time from the first assessment of 2.7 months (IQR 2.0-5.4); 29 of them were severely depleted (45.3%), 12 moderately depleted (18.8%) and 23 adequately nourished (35.9%) (**Table 1**). Compared with the first evaluation there was a decrease in the percentage of severely depleted patients in both leukemia/lymphoma groups (from 63.2 to 36.8%) and the solid tumor group (from 73.1 to 57.7%). Furthermore, in leukemia/lymphoma group, we observed an increase in the percentage of adequately nourished patients from 28.9% to 47.4% (**Table 2**)

Overall, 55% of patients in leukemia/lymphoma group and 35% in the solid tumor group improved their condition or remained in an adequately nourished status. There was not a significant statistical difference between the proportions of patients improved by type of tumor (p -value=0.104).

The 1-year EFS of the overall cohort of patients recruited in this study was 70.1%, which compares favorably with that of a historical cohort of patients treated at HIMJR and not supplemented, who had a 1-year EFS of 60% (SE=2.8), p -value=0.022 (**Figure 1**).

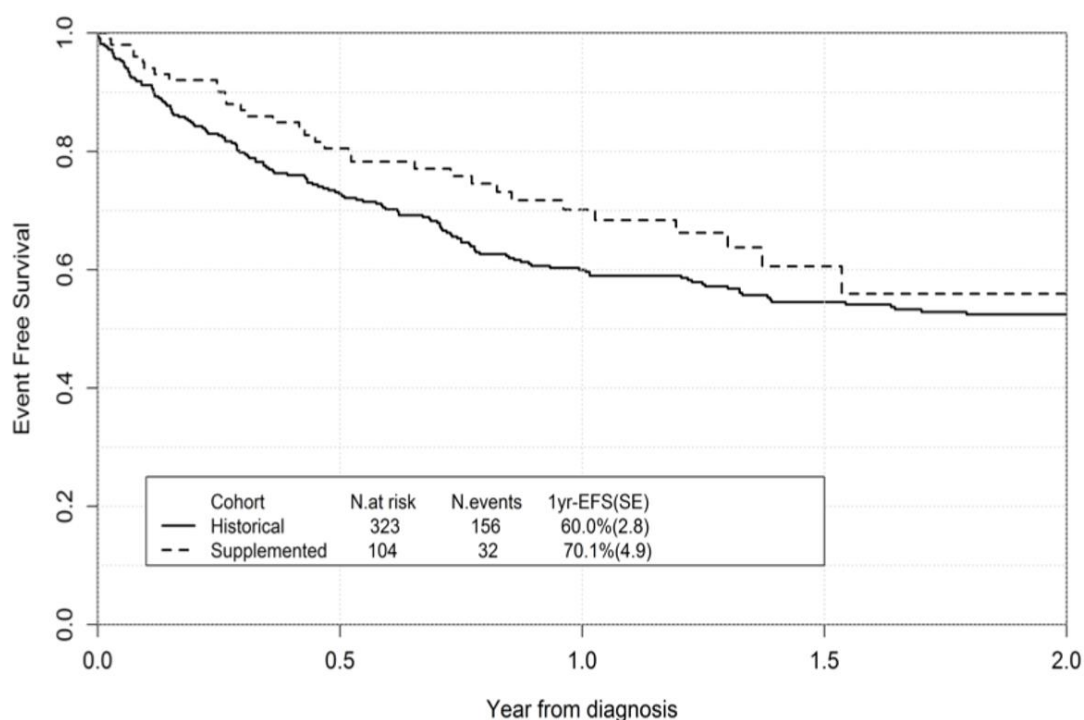
Adjusting for the type of tumor and nutritional status at diagnosis the supplemented cohort seemed to have statistically significant 1-year EFS higher than the historical cohort (p -value=0.013, gain in EFS of about 13%, 95% CI=[2.9%-24.0%]).

Discussion. Malnutrition remains a critical health issue for pediatric oncology in LMICs, where the nutritional status of children with cancer has an important effect on the outcome, being associated with the risk of abandonment and low tolerance of therapy.^{8,9,13} Thus, children with oncological diseases should be regularly assessed for nutritional status and supported, as recommended by the SIOP PODC (Nutrition Working Group of the Society of Pediatric Oncology), that presented a framework for establishing and monitoring nutritional care, based on the infrastructure of institutions in LMICs.¹⁴

A recent study performed in Guatemala in childhood ALL showed that establishing an appropriate nutritional program may overcome the adverse prognostic impact of malnutrition.¹⁵ Data on effects of oral/enteral nutritional support programs in pediatric cancer patients are, however, quite limited.¹⁶ Thus, there is still a need for further investigations to assess feasibility, costs and efficacy of nutritional interventions in children with cancer treated in LIMICs.

Our experience demonstrates that oral supplementation with polymeric formulas has a favorable impact on the nutritional status in a relevant number of cases. Overall, in this study after the supplementation, 55% of patients in leukemia/lymphoma group and 35% in the solid tumor group improved their condition or remained in an adequately nourished status despite the toxicity of treatment. This intervention also appears to have contributed to improving the 1-year EFS as also reported in the Guatemala experience.¹⁵

Figure 1. Event free survival by cohort: supplemented vs. historical one



The 1-year EFS comparison p-value between the supplemented and the historical cohort performed by the Andersen pseudo-values regression was 0.022.

However, since a significant fraction of patients with severe malnutrition (23/43) did not improve their nutritional status, it may be inferred that a more intensive nutritional support with enteral feeding could have been more beneficial for these patients. In this study enteral-tube-feeding (ETF) was administered only in very few cases (5/104), due to fear of complications, particularly in patients with neutropenia, thrombocytopenia, and mucositis. These reasons may have played a role in inducing reluctance in both physicians and families to use ETF. The use of ETF may however be feasible also in these circumstances as suggested by a study published in 2001, which showed that tube feeding was safe and cost-effective in children treated with intensive chemotherapy.¹⁷ Data in this field remain however extremely limited.¹⁸ The risk-benefit of the use of ETF should thus be carefully investigated, in order to define the most appropriate strategies of nutritional support in these patients, particularly in LMICs where the need of enteral nutrition but also the risk of complications may be higher compared to high-income countries.

Another aspect of interest regards the use of commercial formulas. In our experience, these formulas, which are expensive and not easily available in LMICs, were often not well accepted by the patients and their parents, who would have

instead favored homemade preparations. It should thus be considered the appropriateness of homemade oral supplements as a viable alternative, as described by a study conducted in Brazil.¹⁹

Although the weaknesses related to the small number of patients, the shortage of personnel, the lack of standardization between first and second nutritional evaluation and the heterogeneity of disease population, this study in our opinion provides important information. Our experience indicates that oral nutritional support in children treated for cancer in LMICs may be helpful to improve outcome and that homemade formulas should be considered according to the local contexts. Large prospective studies should be conducted to establish the best cost-effective methodologies in LMICs and the role of enteral nutrition in the patients not responding to oral supplementation.

Malnutrition in children with cancer should not be tolerated as an inevitable process,³ also and above all in LMICs, where nutritional interventions with the aim to prevent or reverse malnutrition should be part of routine supportive care in the treatment plan for childhood cancer.

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