AOSIS

Burkitt lymphoma – Nutritional support during induction treatment: Effect on anthropometric parameters and morbidity of treatment

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Authors:
Peter B. Hesseling[1]
Mona Tamannai[2]
Elena Ladas[3]
Glenn Afungchwi[4]
Edouard Katayi[5]
Francine Kouya[6]

Affiliations:
[1]Department of Paediatrics and Child Health, Stellenbosch University, South Africa

[2]Medecins Sans Frontieres, Berlin, Germany

[3]Division of Hematology, Oncology, and Stem Cell Transplantation, Department of Pediatrics, Columbia University Medical Center, United States

[4]Banso Baptist Hospital, Kumbo, Cameroon

[5]Mutengene Baptist Hospital, Mutengene, Cameroon

[6]Mbingo Baptist Hospital, Bamenda, Cameroon

Corresponding author:
Peter Hesseling,
pbh@sun.ac.za

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Background: Malnutrition is common in children diagnosed with cancer in Africa, and it adds to the morbidity and mortality of treatment. Nutritional support is known to reduce morbidity and mortality of treatment.

Aim: The aim of this study was to record changes in anthropometric parameters, morbidity and mortality in patients admitted with Burkitt lymphoma (BL) whose diet was supplemented with protein, vitamins and minerals during induction chemotherapy.

Methods: Seventy consecutive newly diagnosed BL patients were enrolled. The diet was supplemented with a daily egg, 200 mL F-75 formula and vitamins. Guardians received 3 cups of dry rice and $1 daily to buy and prepare meals for the patient and themselves whilst in the hospital. Height, weight, triceps skinfold (TSF) and mid-upper arm circumference (MUAC) were recorded on days 1 and 28. Co-morbidities at diagnosis were treated, and neutropenia and febrile episodes managed with a standard protocol. Two patients who died within 24 h after admission were excluded from the anthropometric analyses.

Results: The mean age was 8 (range 2–16) years and the male:female ratio was 42:28. The St Jude stage distribution was as follows: Stage I = 6%, II = 4%, III = 69%, IV = 21%. Weight for age was < 10th centile at diagnosis in 18% (but influenced by tumour mass). Weight was unchanged or increased by ≥ 5% in 66% of patients on Day 28. The TSF was < 3rd centile in 47% of patients and increased by ≥ 0.5 cm in 57%. The MUAC was < 3rd centile in 16% of patients at diagnosis and in 10% of patients on Day 28. Febrile episodes in 60% and neutropenia in 18% of patients were successfully treated. Two patients died from presumed renal failure. The overall death rate (including the two deaths within 24 h after admission before chemotherapy was started) was 5.5% ($n = 4$).

Conclusion: The TSF improved in the majority and the MUAC improved in some patients. Febrile neutropenia and febrile episodes could be successfully managed. The death rate during induction was lower than in our previously published results with the same chemotherapy protocol. Dietary supplementation should be a standard component of treatment in paediatric patients with cancer.

Introduction

Endemic Burkitt lymphoma (BL), a highly aggressive lymphoma, is the most common childhood cancer in sub-Saharan Africa. The age standardised rate is 3.3 in the sub-Saharan region and 2.6 in the north-west region of Cameroon.[1,2]

Limited resources, such as unaffordable or unavailable drugs and limited supportive care, have led to the development of treatment with high frequency cyclophosphamide (CPM) during induction therapy. A 61% one-year disease-free survival rate was recorded in Cameroon with this treatment protocol, compared to survival rates of ≥ 80% in developed countries.[3,4,5]

Families in north-west and south-west Cameroon are mainly poor subsistence farmers and often live far away from the treatment centre. Guardians have to stay in hospital with the patient, provide meals for their child and pay the hospital bills. In this study free treatment was provided.

Malnutrition (weight for age < 5th centile) was present in 50% of patients with BL in Malawi and in 30% of patients with BL in Cameroon on admission.[3,6] Tolerance for chemotherapy and survival

rates are influenced by the nutritional status.[7,8,9,10] Malnutrition is associated with a higher rate of neutropenia and serious infections, treatment delays, reduced chemotherapy tolerance and a poorer outcome.[8] The impact of nutritional status on outcomes in children with cancer is an important but neglected area of research.[11] Prevention of early deaths during the induction phase of treatment is important to improve the overall survival rate.

The majority (85%) of BL patients have advanced disease and a large abdominal facial tumour burden, and they may eat and drink poorly during the first 3 days of treatment.[3,6]

Weight for age (W/A) is an inaccurate parameter of nutrition in the acute setting. Weight for height (W/H) is a better parameter of nutrition but may be influenced by factors such as tumour mass, oedema and ascites on admission in children with large tumours. The triceps skinfold (TSF), an indicator of body fat, and the mid-upper arm circumference (MUAC), an indicator of lean body mass, correlate with the golden standard of body composition, the DEXA scan, and are more appropriate objective measurements of nutrition.[11,12,13] The 5th centile for TSF in patients aged 4 to 14 years ranges from 5 mm to 6 mm in boys and from 6 mm to 8 mm in girls. The 5th centile for MUAC ranges from 126 mm to 172 mm in boys and 115 mm to 174 mm in girls.[14]

The objective of this descriptive prospective study was to document the anthropometric parameters and co-morbidities in newly diagnosed BL patients, to record morbidity of treatment and to measure the changes in anthropometric parameters during the 28-day induction treatment period in patients who received a standardised treatment protocol and a daily dietary supplement of protein, minerals and vitamins.

Methods

The study was supervised by a resident paediatrician (MT). Seventy-two consecutive patients were admitted with BL between April 2010 and March 2011 to the Banso, Mbingo and Mutengene Baptist Hospitals in the north-west and south-west regions of Cameroon. Two patients who died of advanced disease within 24 h of admission were excluded from anthropometric analysis. Standard diagnostic procedures on admission included fine needle aspiration (FNA), an abdominal ultrasound (US) with measurement of the largest intra-abdominal mass, bone marrow aspiration (BM), cerebrospinal fluid (CSF) cytology, a full blood count (FBC), malaria smear, sickle cell test, human immunodeficiency virus (HIV) screening test, urinalysis and microscopy of faeces. The FBC was repeated before every chemotherapy pulse on days 8 and 14 and when fever occurred. The St Jude staging system was used.[15]

All patients were treated with the 2008 Cameroon BL protocol. Induction therapy commenced with 48 h of parenteral hydration at $3L/M^2$ and oral allopurinol to prevent tumour lysis. A metoclopramide tablet was given 2 h before

and 4 h after chemotherapy to prevent vomiting. Furosemide was used when needed to achieve a target urinary output of ≥ 3 mL/kg/h during the first 48 h. Chemotherapy was started 24 h after the onset of hydration and consisted of 40 mg/kg CPM (oral or intravenous), 12.5 mg intrathecal methotrexate and 12.5 mg intrathecal hydrocortisone on days 1, 8 and 15. The response to treatment was assessed on Day 28 by clinical assessment and abdominal US prior to starting maintenance chemotherapy. The response to and outcome of treatment will not be discussed in this article.

Every patient received a boiled egg, 200 mL of World Health Organization (WHO) F-75 formula and a multivitamin tablet as inpatients every day during the first 14 days, and guardians were provided with eggs and multivitamin tablets on discharge to be given daily at home until the follow-up visit on Day 28. Guardians, who have to stay with the patient in the ward, received a daily ration of three cups of dry rice and $1 in cash to buy and prepare local food for their child and themselves. Parenteral nutrition was not available. Parents in general strongly object to nasogastric tube feeding, and this was rarely used.

Anthropometric observations included measurement of weight (W) in kg and height (H), MUAC and TSF in cm, with a standardised scale, Harpenden calliper and a United Nations Children's Fund (UNICEF) measuring tape on days 1 and 28. Nurses were trained to perform these measurements. Two successive measurements were performed and the average value was recorded. Percentiles of W/A, H/A and body mass index (BMI) were determined with WHO Anthroplus software. Weight-for-age percentiles were only determined in children ≤ 10 years because WHO standards above age 10 years are not available.[14,15]

Coexisting diseases such as malaria and urinary or intestinal parasites were treated. A blood transfusion was considered when the haemoglobin dropped ≤ 7 g/dl. Neutropenia was defined as a total white blood cell count of ≤ 1.0×10^9/L. Fever was defined as a single episode of a temperature of ≥ 38.5°C or two episodes ≥ 38°C within a 24-hour period. A malaria smear was performed immediately, and treatment was given if found positive. If negative, first-line antibiotic treatment with intravenous gentamicin and ampicillin was started immediately irrespective of the white cell count. Blood cultures were not available. A cephalosporin was added if fever persisted > 48 h. Mucositis was treated with oral nystatin and acyclovir. The full cost of treatment, including hospitalisation, investigations, all medicines and transport for follow-up visits, was provided at no cost to the guardians.

The treatment protocol was approved by the Institutional Review Board of the Cameroon Baptist Convention and parents gave informed signed consent.

Results

The 70 study patients included 42 boys and 28 girls with a mean age of 8 (range 2 to 16) years. Burkitt lymphoma was

confirmed on FNA in 76% and in the remainder on BM, CSF, abdominal US and clinical presentation. A marked reduction in tumour volume within 48 h was accepted as confirmation of the diagnosis in patients with a clinical diagnosis. The St Jude stage distribution was as follows: Stage I = 4 (6%), Stage II = 3 (4%), Stage III = 48 (69%) and Stage IV = 15 (21%). The US volume of the largest single abdominal mass (there usually are multiple masses) was > 400 mL in 32% of patients and < 400 mL in 49% of patients. The volume of the largest abdominal mass recorded exceeded 3000 mL. Abdominal US indicated ascites in two patients and a small pleural effusion in one patient.

On admission H/A was less than the 10th centile in 28 (42%), W/A less than the 10th centile in 12 (18%), and BMI less than the 10th centile in 50% of patients aged > 10 years. The TSF was less than the 3rd WHO centile in 46%, and the MUAC less than the 3rd WHO centile in 16% of patients.[16] On Day 28 the TSF had increased by 0.5 cm in 69%, and the MUAC was now less than or equal to the 3rd centile in 10% of patients (Table 1). Weight loss of ≥ 5% of body weight was recorded in 42% of patients, and weight gain in 24% of patients. Fifty per cent of patients, with a largest recorded single abdominal tumour of < 400 mL in volume, gained weight during induction therapy. Five of seven patients without abdominal masses (St Jude Stages I and II) gained > 1 kg in weight, and six of these patients had an increase in TSF of > 5 mm. Anthropometric data are summarised in Table 1, and individual patients' changes in TSF and MUAC are illustrated in Figure 1. Weight and height were not recorded in two and four patients, respectively, on admission, and height on Day 28 was not recorded in 11 patients.

Two patients (3%) died from presumed tumour lysis and renal failure shortly after the first course of chemotherapy. Co-morbidities at diagnosis included malaria, sickle cell trait, intestinal parasites, schistosomiasis and HIV sero-positivity and are listed in Table 2. Three patients developed renal failure after the first dose of chemotherapy, of whom two died within the first week. Neutropenia occurred in 12 (18%), febrile episodes in 42 (60%) and prolonged fever in 17 (24%) of patients. Fourteen patients (20%) received a blood transfusion. Other complications observed were diarrhoea and vomiting, mucositis, cough, dental problems, wound infection, chickenpox, skin infection and anal prolapse
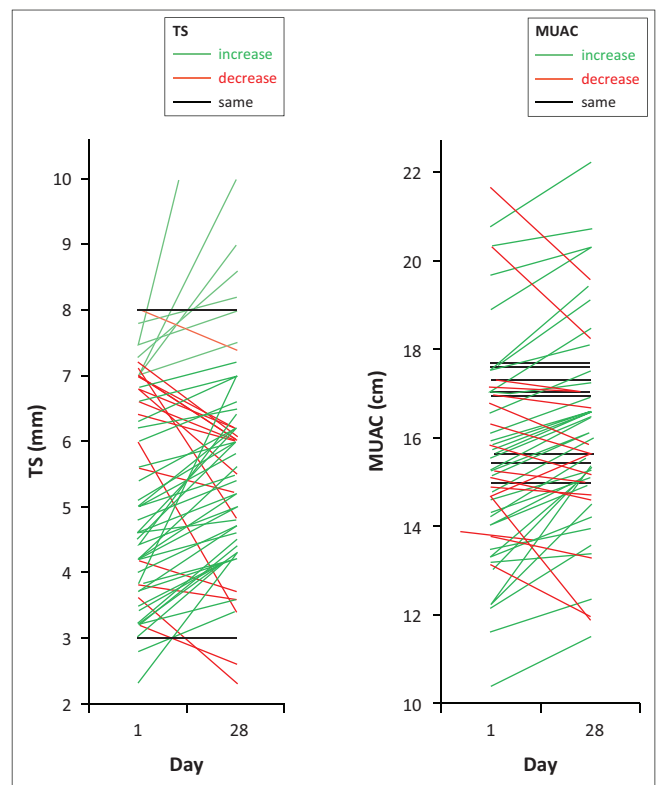
(which corrected spontaneously) (see Table 3). No other deaths occurred during the 28-day induction treatment period.

The limitations of this study, such as the unavailability of microbiological cultures, an intensive care unit, renal dialysis and parenteral feeding, were a result of the limited resources that were available in this setting at the time. We did not record the type and quantity of food that the parents gave to their children in addition to the daily dietary supplements.

MUAC, mid-upper arm circumference; TSF, triceps skinfold.

FIGURE 1: Changes in triceps skinfold and mid-upper arm circumference.

TABLE 2: Co-morbidities on admission in 70 patients.

Co-morbidity	Number	Percentage
Malaria	6	9
Sickle cell trait	5	7
Intestinal parasites	7	10
Schistosomiasis	1	1
HIV seropositive	2	2

HIV, human immunodeficiency virus.

TABLE 3: Morbidity during treatment.

Event	Number	Percentage
Febrile episode	42	60
Fever > 48 h	17	24
Neutropenia	12	18
Diarrhoea, vomiting, gastroenteritis	9	13
Blood transfusion	14	20
Mucositis	4	6
Cough	2	3
Dental problems	2	3
Varicella	1	1
Skin infection	1	1
Wound infection	2	3
Anal prolapse	1	1

TABLE 1: Anthropometric parameters on days 1 and 28.

Parameters	Day 1 (%)	Day 28 (%)
Weight for age < 10th centile	18	-
Weight gain ≥ 5%	-	21
Weight loss ≥ 5%	-	34
Weight unchanged	-	45
Height for age < 10th centile	42	-
Body mass index < 10th centile	50	-
MUAC < 3rd centile	16	10
TSF increase > 0.5 cm	-	57
TSF < 3rd centile	47	-

MUAC, mid-upper arm circumference; TSF, triceps skinfold.

Discussion

The H/A was less than the 10th centile in 42% and the W/A less than the 10th centile in 18% of patients. This confirms the high prevalence of poor nutrition in patients with BL at diagnosis. However weight reflects the short-term nutritional status at diagnosis and is overestimated in patients who have a large total tumour mass at diagnosis. Weight gain by Day 28 was recorded in 21% of all the patients but in 71% (5/7) of patients who had no abdominal masses (Stage I and II disease) and in 50% of children who presented with smaller abdominal tumours. Co-morbidities such as malaria and intestinal parasites, which may adversely affect the nutritional state, were identified and fully treated on admission.

The egg, 200 mL of F75 and multivitamin tablet, which provided a minimum daily intake of 8 g of good quality protein and additional vitamins, minerals and trace elements, was supplemented by the food (mainly rice, maize, vegetables and fruit) that the parents prepared.

An increase of the TSF in 57% of patients, and a reduction in the number of children with a MUAC less than the third centile from 16% to 10%, indicates that the nutritional support had a positive effect. Fever, febrile episodes and co-morbidities were managed without serious consequences. Laboratory facilities were too limited to accurately quantify renal function.

There were two deaths during induction treatment, constituting a 2.8% death rate during treatment. If the two patients who died before chemotherapy was commenced are added, the overall death rate was 5.5% (4/72). No patients abandoned treatment. This death rate is significantly lower ($P = 0.009$, $p < 0.5$) than the 8.5% (24/129) rate recorded in a cohort of patients who had previously been treated with the same chemotherapy protocol at the same hospitals, but for whom the nutritional support provided was limited.[3] The French–African Paediatric Oncology Group reported a 5.1% death rate with CPM induction treatment in 178 patients, but their exclusion of 79 patients from the analysis for unspecified reasons does not allow for a fair comparison.[17] In a recent Malawian study, doxorubicin was added to CPM during induction, and a 12% death rate was reported during the first 28 days. Ten of the seventy-eight Malawian patients, however, died before treatment was instituted and were not included as early deaths.[18] All episodes of neutropenia and fever were successfully treated. The two deaths from renal failure may have been prevented if renal dialysis had been available.

We could find no publications on the changes in nutritional status and the effect of dietary support during the first month of treatment in children with endemic BL with which to compare our findings.

Although supplements of protein, vitamins and trace elements were provided, we did not record the type and quantity of food that the parents prepared and gave to their children. We intend to provide an optimal diet to our patients in the future and to educate parents how best to prepare available and affordable local food with the help of trained dieticians.

Conclusion

We have demonstrated that good enteral nutritional support during induction chemotherapy in a malnourished population of patients with BL resulted in an improvement in nutritional parameters in the majority of patients and was associated with a low morbidity and death rate during induction treatment. Nutritional support should be a standard component of treatment in all children with cancer.

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Competing interests

The authors declare that they have no financial or personal relationships that may have inappropriately influenced them in writing this article.

Authors' contributions

P.B.H. was the principal investigator. M.T. was the physician conducting study at the Banso Baptist Hospital. E.L. was responsible for expert advice on nutrition. G.A. was responsible for the data collection and management. F.K. was the physician conducting study at the Mbingo Baptist Hospital. E.K. was the physician conducting study at the Mutengene Baptist Hospital.

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