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RESEARCH

Relationship between nutritional status and treatment-related neutropenia in children with nephroblastoma

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Background: Assessment of nutritional status of paediatric oncology patients is crucial, as it may influence treatment and clinical outcomes. Concurrent malnutrition and cancer in children may lead to reduced chemotherapy delivery due to impaired tolerance and increased toxicity.
Aim: This study aimed to determine the relationship between nutritional status and the prevalence, frequency and duration of treatment-related neutropenia in a cohort of South African children with nephroblastoma.
Methods: Seventy-seven children between the ages of 1 and 12 years diagnosed with nephroblastoma at Inkosi Albert Luthuli Central Hospital (IALCH), Durban, between 2004 and 2012, were studied prospectively. Nutritional status was assessed using weight, height, mid-upper arm circumference (MUAC), triceps skinfold thickness (TSFT) and serum albumin. The administration of filgastrim (Neupogen®) was used as a surrogate for neutropenia and the frequency and duration of its use was recorded.
Results: There was a significant relationship between the prevalence of treatment-induced neutropenia and malnutrition defined by MUAC. The mean frequency and duration of neutropenia was significantly higher in those classified as malnourished using MUAC. There was a positive correlation between frequency and duration of neutropenia.
Conclusions: Malnutrition was prevalent among children with nephroblastoma. The prevalence of treatment-induced neutropenia was higher in those with poor nutritional status, identified by MUAC. Poor nutritional status according to MUAC was also linked to an increased frequency and duration of neutropenia. It is important to include MUAC in the nutritional assessment of children with nephroblastoma.

Keywords: cancer, children, malnutrition, nephroblastoma, treatment-related neutropenia

Introduction

Nephroblastoma is the most common renal malignancy in children,[1] and is the fourth most common paediatric cancer in South Africa (SA), accounting for 12% of all paediatric cancers.[2]

Current treatment protocols in Europe and North America are moving away from the simple objective of maximising cure, to maintaining high cure rates, whilst reducing treatment-related toxicities.[1,3] However, 80% of children with nephroblastoma live in poor countries and present at an advanced stage of disease, with malnutrition and associated co-morbidities, and face much lower survival rates.[4] Adequate and appropriate nutrition in paediatric oncology patients is essential for maintaining growth and development. It may also improve survival, decrease treatment-related toxicity, and improve quality of life.[5,6] Malnutrition represents a treatable co-morbidity in children with cancer, including those with nephroblastoma,[7,8] and assessment of nutritional status at presentation allows appropriate management strategies to be implemented.[9]

Malnutrition is associated with impaired immunocompetence, including depressed cell-mediated immunity, reduced mucosal secretory antibody response and lower antibody affinity,[10] suggesting a synergistic relationship with infections, which impacts on child mortality.[11] Calorie provision can be individualised in order to maintain weight during treatment and prevent weight loss associated with cancer.[12] Nutrient requirements may be altered by many different factors during treatment, including the effect of the disease on host metabolism, catabolic effects of cancer therapy and physiological stress caused by surgery, fever, malabsorption and infection.[12] Tailored nutritional support is justified in the management of these children in order to avoid adverse outcomes.[13]

Malnutrition has been inconsistently described and defined and no consensus exists regarding a specific definition to identify children at risk.[13] Several factors influence the recorded prevalence of malnutrition in children with cancer. These include: (1) different techniques used to assess nutritional status; (2) histological type and staging of malignancy during assessment; (3) the child's individual susceptibility to malnutrition in the hospital ward and anticancer treatments; and lastly (4) the non-specific definition of malnutrition.[13] As a result, the reported prevalence of malnutrition in children with cancer varies widely.[13]

Both chemotherapy and radiotherapy can cause side effects such as nausea, vomiting, anorexia, mucositis, dysphagia and changes in bowel function. Each of these may result in poor dietary intake resulting in malnutrition.[14] Children with cancer and concurrent malnutrition may be negatively affected by reduced chemotherapy delivery due to impaired tolerance, which may impact on overall survival and quality of life.[15,16] The effect of sub-optimal nutritional status on disease progression or on the distribution and excretion of chemotherapeutic drugs has not been widely studied. Studies from South Africa and Malawi suggest that there is an increased mortality rate amongst patients who are severely nutritionally depleted, allied to an increased toxicity of therapeutic drugs.[15,17,18] There is a narrow therapeutic index for such drugs that may be further narrowed by malnutrition.[19]

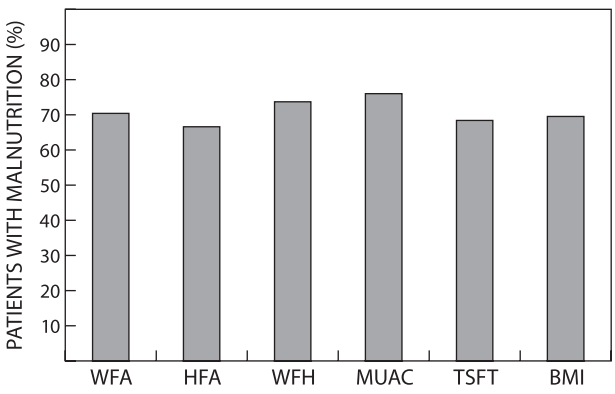
Although nutritional support is an important part of oncology care, few studies have evaluated the possible role that nutrition plays in treatment toxicity. This study aimed to determine the relationship between nutritional status and the prevalence, frequency and duration of treatment-related neutropenia in South African children with nephroblastoma, admitted to IALCH between 2004 and 2012.

Methods

The Biomedical Research Ethics Committee of the University of KwaZulu-Natal approved this study (BE025/13). This prospective, observational study, which used a cohort study design, was conducted at Inkosi Albert Luthuli Central Hospital, a tertiary and quaternary level hospital in Durban, KwaZulu-Natal (KZN). IALCH provides care to the whole of KZN and part of the Eastern Cape (EC), thus servicing over 10 million people.[20] The study population consisted of newly diagnosed patients aged 1–12 years with nephroblastoma admitted to the Paediatric Surgical Oncology service at IALCH, between 2004 and 2012. IALCH was the only state hospital treating newly diagnosed nephroblastoma patients in KZN at this time. Patients with incorrectly recorded anthropometric measurements or those not measured before treatment commenced were excluded. Of the 161 newly diagnosed patients with nephroblastoma admitted to IALCH between 2004 and 2012, 77 fulfilled the inclusion criteria. Of the patients who were excluded from the study, 73 children did not have full anthropometric data recorded, 10 patients' files could not be located and in one case measurements were only made once treatment had started.

Anthropometry

The registered dietitian assigned to the paediatric surgical oncology ward took anthropometric measurements before any treatment commenced (nutritional supplementation, chemotherapy or radiotherapy). Weight (recorded to the nearest 100 g) and height measurements (recorded to the nearest 1 cm) were taken using an electronic weight and height scale (Nagata BW-1122H), while the subjects wore minimal clothing and no shoes. Height measurements were taken with the subject standing, looking forward and with the back against the stadiometer. Infants were weighed using an electronic baby scale (Nagata BW-20; Nagata Scale Co, Taiwan, ROC) and length was taken with a non-stretch, flexible tape while supine. A corrected weight, which was calculated for each subject by subtracting the tumour weight from the weight on admission, was used for statistical analysis. For the MUAC measurement, the mid-point between the tip of the acromion process and the olecranon process was located, with the left forearm bent at a right angle. A non-stretch, flexible measuring tape was used to take the measurements to the nearest 0.1 cm, while the arm hung straight down. Triceps skinfold measurements were taken to the nearest 0.1 cm at the same midpoint, using a Harpenden skinfold calliper (Assist Creative Resources Ltd., Wrexham, UK). All measurements were taken in triplicate and an average was recorded and used in subsequent calculations. Weight for age (WFA), height for age (HFA), weight for height (WFH) and body mass index (BMI) were classified according to age (including month) and gender-matched norms, employing the STATGrowthChartsapp.[21] This classifies subjects according to Z-scores using the WHO (World Health Organization) growth charts. Mid-upper arm circumference and TSFT measurements were used to classify patients as normal or underweight, using standards developed by Frischanco 1981.[22]



Notes: WFA = weight for age; HFA = height for age; WFH = weight for height; MUAC = mid-upper arm circumference; TSFT = triceps skinfold thickness; BMI = body mass index.
Figure 1: Patients with malnutrition according to different anthropometric parameters

Biochemistry

All blood samples were analysed for serum albumin on admission, at the National Health Laboratory Service at IALCH. The method used involved the use of bromocresol green solution (BCG) as a binding dye.[23] A serum albumin value of > 32 g/l was regarded as normal.

Treatment-related neutropenia

Patients were classified as having grade four neutropenia if they received Filgastrim (Neupogen® Roche, Amgen South Africa). Filgastrim (Neupogen®) is a colony-stimulating factor used to stimulate granulocyte production in bone marrow when the neutrophil count has dropped due to the toxic effects of chemotherapy. Neutropenia, with its attendant increased risk of infection, must be reversed before further chemotherapy can be given and treatment delays jeopardise the success of the regimen. Blood counts were checked before and after each chemotherapy administration with the intention of recognising neutropenia, should it occur. The protocol in use at the time of the study required the administration of Filgastrim when the patient experienced an absolute neutrophil count (ANC) of below 1×10^9/l. The standard dose given to patients was 5 micrograms/kg daily. The frequency and prevalence of neutropenia was determined using the number of episodes of neutropenia during treatment at IALCH. Duration of neutropenia was measured as the number of days for which neutropenia was present during treatment in each patient.

Data analysis

The Statistical Package for Social Sciences (SPSS®) version 17 (SPSS Inc, Chicago, IL, USA) was used for analysis of the data and a p-value of < 0.05 was considered significant. An independent samples t-test was used to determine the influence of malnutrition as measured using serum albumin on the prevalence of treatment-related neutropenia. A non-parametric Kruskal–Wallis test was applied to the categorical indices, MUAC, TSFT, WFA, HFA, WFH and BMI.

Results

The mean age was 4.7 years (SD ± 2.9) and the median age was 3.8 years (IQR = 37.32 months). There was an even gender distribution (male = 49.4%; female = 50.6%).

Malnutrition and treatment-related neutropenia

The percentage of patients with malnutrition according to the different anthropometric parameters is shown in Figure 1. When MUAC was used, 76% of the patients were classified as malnourished.

Table 1: Group statistics for serum albumin and neutropenia

Neutropenia	*n*	Serum albumin (g/dl) (Mean ± SD)	*p*-value
Present	50	37.76 ± 5.99	> 0.05
Absent	27	40.11 ± 5.28	> 0.05

With BMI and TSFT, 69.5% and 68.4% were malnourished, respectively. A significant number of those with normal MUAC measurements did not experience neutropenia (p = 0.026).

In all, 65% of the patients classified as malnourished using all parameters (WFA, HFA, WFH, MUAC, TSFT, BMI and serum albumin) experienced neutropenia. The frequency of neutropenia ($p = 0.032$) and duration of neutropenia ($p = 0.013$) was significantly higher in those classified as malnourished, using MUAC. The group with normal nutritional status experienced neutropenia for an average of three days while those classified as malnourished experienced neutropenia for an average of six days. Frequency and duration of neutropenia were positively correlated ($r = 0.225$, $p = 0.025$).

There was no significant difference in the serum albumin measurements between those with and without neutropenia ($p > 0.05$). The group statistics for serum albumin and treatment-related neutropenia are given in Table 1.

Discussion

Serum albumin is known to be a poor indicator of nutritional status in children with cancer, as it may be affected by various factors such as hydration status, sepsis, stress and acute illness.[24,25] In this study, 70% of the patients were classified as well-nourished when albumin was used in isolation, and only 14% of patients had a serum albumin of < 32 g/l. This is consistent with another report, which showed that only 13% (16 out of 127) of children with cancer aged 0–18 years were found to have a serum albumin of < 32 g/l.[9] There was a statistically significant relationship between neutropenia and malnutrition, when malnutrition was identified using MUAC. Israëls *et al*. (2012) observed neutropenia in malnourished Malawian children with nephroblastoma, where 40% of the patients were stunted, indicating chronic malnutrition.[15] Israëls *et al*. (2010) showed that the malnutrition experienced by these patients was associated with significantly decreased clearance and higher serum levels of chemotherapy drugs,[17] which may explain in part why malnourished patients experience increased chemotherapy-related toxicity.[15] Dose reductions need to be considered for patients that present with malnutrition, in order to prevent an increased incidence and severity of toxicity.[15,17] Dose reduction of neoadjuvant chemotherapy may allow a period in which to improve the nutritional status of malnourished patients.[15,19] This study showed that the frequency and duration of treatment-related neutropenia was significantly higher in patients classified as malnourished by MUAC on admission. With an increase in frequency of neutropenia, there was a concurrent increase in the duration of neutropenia. Early nutritional intervention has been shown to improve immune competence and tolerance to treatment.[26] By providing nutritional support from admission and throughout treatment the frequency and duration of neutropenia may be reduced. It is also strongly recommended that MUAC be routinely measured in order to obtain an accurate assessment of nutritional status. This would help to ensure that adequate nutrition is continually provided.

Conclusion

In children with nephroblastoma, poor nutritional status as identified by MUAC is associated with an increased frequency and duration of treatment-related neutropenia. The results of this study emphasise the pivotal role of MUAC in the assessment of nutritional status in children with solid tumours and suggest one mechanism whereby nutritional status might affect outcome. Implementation of nutritional support on admission and throughout treatment to prevent or manage malnutrition is essential, in order to reduce the frequency and duration of treatment-related neutropenia.

Recommendations

Further studies should tease out the individual contribution of each element of treatment to the development of neutropenia, which would allow clinicians a more targeted response to neutropenia.

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