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REVIEW ARTICLE

Importance of Nutrition in the Treatment of Leukemia in Children and Adolescents

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Background and Aims. Malnutrition has been identified as a prognostic factor in children and adolescents with leukemia.

Methods. A review of the data available on this topic has been carried out.

Results and Conclusions. In children and adolescents (0−19 years of age), acute lymphoblastic leukemia (ALL) is the commonest form of cancer worldwide and malnutrition is prevalent in this age group, especially in low- and middle-income countries where most of these young people live. Obesity, measured by body mass index, is associated with poorer survival rates in children and adolescents with ALL and acute myelogenous leukemia in high-income countries. In contrast, undernutrition is linked to poorer survival rates among young people with leukemia in low- and middle-income countries. © 2016 IMSS. Published by Elsevier Inc.

Key Words: Nutrition, Leukemia, Children, Treatment.

Introduction

In common parlance, the term 'malnutrition' connotes inadequate nourishment, although in clinical and epidemiological practice it often encompasses both overweight and obesity. Undernutrition has been defined as "a state of nutrition in which a deficiency of energy, protein and other nutrients causes measurable adverse effects on tissue/body form and function and clinical outcome" (1) and is categorized by the World Health Organization (WHO) as acute (wasting) or chronic (stunting). The former is based on measures of weight for height and the latter on height-for-age. Both wasting and stunting are prevalent in children in low- and middle income countries (LMICs), especially the former, as defined by the World Bank on the basis of Gross National Income (GNI) per capita (2). The corollary prevails in high-income countries (HICs) in which overweight and obesity, defined commonly by the measure of body mass index (BMI-wt. in kg/ht. in m^2) has become a major public health concern, notably in children and adolescents.

Both ends of the spectrum of perturbations of nutritional status, under- and over-nutrition, portend adverse consequences for young people with cancer, commanding international attention and resulting in the formation of expert groups focused on the challenges, exemplified by the Committee on Nutrition and Health in the International Society for Paediatric Oncology (SIOP) (3) and reflected in international workshops such as those convened in Puebla, Mexico (4,5).

Measurement of Nutritional Status and Body Composition

The first challenge is to determine the most appropriate measures to use in children and adolescents with cancer, particularly in LMICs where the great majority (>85%) live, undernutrition and co-morbidities are prevalent and resources often severely limited (6).

Limitations of the WHO categorization include underestimation of wasting in children with cancer in whom it has been known for at least 25 years that >10% of the body weight may be tumor (7), and overestimation of stunting

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in populations with genetically determined short stature such as some of the primitive peoples of equatorial southern Africa and, to a lesser extent, the Maya of Guatemala (8).

At the other end of the spectrum of the nutritional status, BMI does not distinguish between lean and fat mass, a real problem in patients with cancer who may be affected by the 'obesity paradox'. This circumstance occurs when fat mass is increased but lean body mass (notably skeletal muscle mass) is reduced (9) as a result of protein-energy malnutrition.

An approach to resolving the measurement of nutritional status in the clinical setting that is especially applicable in LMICs is arm anthropometry that owes much to the work of Frisancho (10). Measurement of mid-upper arm circumference (MUAC) and triceps skin fold thickness (TSFT) avoid the problems attendant on the WHO categorization. Moreover, MUAC offers an estimate of lean body mass (LBM) as TSFT does of fat mass (FM).

More precise and accurate measures of body composition are available (Table 1), but most are not suitable for clinical practice. Bio-electrical impedance assessment (BIA) and dual energy x-ray absorptiometry (DXA) are used in the clinical setting, BIA offering the advantage of instrumental portability but limitations in the face of aberrations in body water (11). With DXA, FM, fat-free mass/LBM and whole body bone mineral content add up almost exactly to total body weight measured directly (12).

DXA has been used to validate MUAC and TSFT as measures of LBM and FM, respectively, in children with cancer (13) and has been considered as a clinical 'gold standard' for measurement of body composition including in this population (14).

Assessment of Nutritional Status Along the Cancer Journey

Both over- and undernutrition impact clinical outcomes from diagnosis to long-term survivorship.

Nutritional Status at Diagnosis

Two landmark retrospective studies were performed by Lange and colleagues in the Children's Cancer Group (CCG). The first involved 768 children and adolescents with acute myeloid leukemia (AML) of whom 84 (10.9%) were underweight and 114 (14.8%) were overweight or obese, defined by BMI ($\leq 10^{th}$ percentile and $\geq 95^{th}$ percentile respectively). Both groups had significantly poorer survival than 'middle-weight' patients due to greater treatment-related mortality (TRM), the most common cause of which was infections during remission induction therapy (15).

In a subsequent report relating to >4000 children and adolescents with ALL, the CCG investigators focused on the effect of obesity, again as defined by BMI. The 5-year event free survival (EFS) was poorer and the relapse rate higher in obese (n = 343, 8%) compared to non-obese patients, but only in those 10 years of age and older (16). It is of note that >98.5% of the obese patients received doses of chemotherapy calculated on their actual body surface area; however, there was no excess of early toxicity in the obese group.

Such experiences in HICs do not translate readily to LMICs where the prevalence of overweight/obesity in young people with cancer is markedly lower. In the most extensive study conducted to date, a group of investigators in Central America and the Dominican Republic enrolled almost 3000 children and adolescents who were newly diagnosed with cancer. More than 60% had a battery of anthropometric measures made including BMI, MUAC and TSFT. Only 2.4% of the cohort were obese (BMI $>95^{th}$ percentile). According to BMI $<5^{th}$ percentile, 17% of the patients were undernourished. However, using MUAC and TSFT $<5^{th}$ percentile, 46% were severely depleted nutritionally, a figure that rose to 59% with the inclusion of hypoalbuminemia (17). The categories of nutritional status based on arm anthropometry are given in Table 2. Undernutrition was associated with a higher rate of abandonment of therapy and a lower 2-year EFS but no difference in TRM or rate of relapse (all diseases combined). A subsequent retrospective study of almost as many children was undertaken at the Tata Memorial Hospital in Mumbai, India using the categories of nutritional status developed in Central America (18). On this basis, >75% of children with cancer were severely nutritionally depleted, the inclusion of serum albumin having minimal additional value. In comparison, <18.5% were severely undernourished according to BMI, which categorized only 0.8% of children as obese. There was no report of the relationship between clinical outcomes and nutritional status in this study. Similar experiences have been reported from other LMICs including Turkey (19), Morocco (20) and Malawi (21), demonstrating greater sensitivity of arm anthropometry compared to measures based on height and weight.

Table 1. Measures of body composition

- Total body water (^{2}H or ^{18}O dilution)
- Estimation of ^{40}K (fat free mass)
- Neutron activation (not applicable to children)
- Bio-electrical impedance assessment
- Dual-energy x-ray absorptiometry

Table 2. Categories of nutritional status based on arm anthropometry

Adequately nourished: MUAC and TSFT $>10^{th}$ percentiles and serum albumin >35 g/L inadequately nourished

1.. Severely depleted: MUAC or TSFT $<5^{th}$ percentile or serum albumin <32 g/L.

2.. Moderately depleted: all others

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