Nutrition and the child with cancer: where do we stand and where do we need to go?

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Abstract

As a result of ongoing research and better supportive care, the treatment of childhood malignancies has dramatically improved survival in developed countries. The same cannot be said about the all important nutritional care of the child with cancer as much still needs to be done to reach the ultimate goal, namely to provide evidence based nutritional intervention that will contribute to further improvements in optimal outcomes. Furthermore, in developing countries, especially in Low Income Countries, malnutrition is only one aspect of socioeconomic disadvantages that are associated negatively with many components of cancer control, from access to care, through to treatment compliance, to long-term follow-up. In these settings economic evaluations of nutritional support in the form of cost-effectiveness and cost-utility analyses, would be logical undertakings.

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Introduction

Over the last decades, the survival of children diagnosed with cancer in developed countries has increased substantially. Although individual prognosis varies according to type of cancer, available US data indicates that between 1975 and 1995 mortality from childhood cancer declined with almost 40%.[1] The five-year survival rate of all combined childhood cancers is now approximately 80%. However, in developing countries the cure rate is much lower, due to multiple factors, including late diagnosis, under-diagnosis and advanced treatments not always being available. A lack of accurate epidemiological data makes the exact rate unknown. [2] HIV-related immunosuppression further increases the incidence of certain types of cancers in children, e.g. Kaposi's sarcoma and lymphomas. HIV-infection and its co-morbidities such as tuberculosis (TB) make it more difficult to treat diagnosed malignancies.[3]

Adequate nutrition during cancer plays an important role in clinical outcome measures, such as treatment response, quality of life and cost of care. However, in a recent critical review of important aspects of nutrition in children with cancer it was found that the importance of nutrition in children and young adults with malignancies is still underestimated.[4] Between 5 and 50% of children and young adults with cancer experience malnutrition at diagnosis, depending on the diagnosis and the malnutrition criteria used. This is due to tumour- and treatment-related factors.[5] During treatment this figure can increase with 40 -80%.[6] Children are particularly vulnerable to malnutrition due to increased substrate needs related to the disease, treatment and limited reserves. At the same time, children have increased energy and nutrient requirements to attain appropriate growth and development.

On the other side of the coin is the growing population of childhood cancer survivors. Children with malignancies tolerate the acute side-effects of antineoplastic agents better than adults, but the growing child is more susceptible to long-term diseases that have implications for later life.[1] In a recent report comparing the health status of 10 397 survivors of childhood cancer treated from 1970 to 1986 with 3 034 of their siblings, 62% of the survivors had at least one chronic health condition, and 27% had a serious or life-threatening condition such as stroke, heart disease or kidney failure. Survivors were 15 times more likely to develop a second malignancy than their siblings. Adverse health behaviours later in life, such as smoking, drinking, poor diet and lack of exercise may increase the risk of developing some of these complications.[7]

Malnutrition in childhood cancer

The Free Medical Dictionary defines malnutrition as "the condition that develops when the body does not get the right amount of the vitamins, minerals, and other nutrients it needs to maintain healthy tissues and organ function".[8] Other definitions focus on protein-energy imbalances. More recently the American Society for Parenteral and Enteral Nutrition (ASPEN) has accepted Soeters and Schols's[9] umbrella definition of malnutrition: "A subacute or chronic state of nutrition, in which a combination of varying degrees of overnutrition or undernutrition and inflammatory activity has led to a change in body composition and diminished function."[10]

An adequate protein-energy balance is needed to sustain age-appropriate growth and maintenance. Although there is currently no consensus definition for malnutrition, weight and height parameters are most often used as indicators for malnutrition, but these are

not necessarily appropriate for children with cancer. Those with solid abdominal masses (neuroblastoma, hepatoblastoma, Wilms tumour) may present with normal weights due to the mass of the tumour. Furthermore, undetectable nutritional depletion of one or more micronutrients occurs in normal-, under- and/or over-weight children. Current data regarding the prevalence of malnutrition in children with cancer is influenced by different diagnostic techniques used in nutrition assessment, type and stage of cancer during assessment, the child's individual susceptibility toward malnutrition and treatment regimens as well as the non-specific definition of malnutrition.[4] Pathophysiological mechanisms that contribute to the development of malignancy induced malnutrition and growth failure include: i) complex interactions between energy and substrate metabolism; ii) hormonal and inflammatory components; and iii) alterations in metabolic compartments resulting in increased mobilization and oxidation of substrates and loss of body proteins. The type, stage and metastatic status of the disease and treatment modalities are some of the main risk factors for malnutrition.[4]

Malnutrition in cancer patients is further aggravated by cancer cachexia. In contrast to simple starvation where there is a relative maintenance of lean body mass at the expense of body fat, cancer cachexia is characterized by profound and progressive loss of both lean body mass and body fat. Although malignancy induced cachexia is not yet fully understood, it seems that the body's compensatory mechanisms to conserve protein during simple starvation and decrease energy expenditure to allow prolonged survival are either lost or inhibited in certain cancers.[4,11,12]

Management of malnutrition in the paediatric cancer survivor

The challenge in the management of children with malignancy is to assess the nutritional needs of the paediatric oncology patient to provide the optimal nutrition intervention to prevent or treat malnutrition and prevent its consequences. Short-term consequences include muscle and fat wasting with changed body composition, decreased tolerance and response to chemotherapy, treatment delays, biochemical disturbances such as anaemia and hypoalbuminaemia and higher susceptibility to infections. Long-term consequences include growth impairment, impaired neurodevelopment, abnormal bone density, decreased quality of life and increased risk for secondary cancers.[4]

In summary we therefore can say that we know where we stand, in that:

- Many of newly diagnosed children with cancer will be mal-nourished or become malnourished during the course of treatment.
- Malnutrition (over- and under-nutrition) will negatively impact on the course of the disease and its treatment due to changes in body composition.
- Malnutrition, in many cases, impacts on the long-term human potential and quality of life of the survivor of childhood cancer.

Nutritional assessment

"Adequate nutrition assessment is paramount for the decision making process of nutritional intervention".[6] The A, B, C, D of nutritional assessment must be followed, but obstacles will be faced along the way.

***A**nthropometrics:* Weight is not a reliable indicator in an acute care setting due to dehydration, over-hydration, and disease mass and is not an indicator of muscle loss. Arm anthropometry is recommended as it offers advantages over measures of height and weight and provides useful assessment of nutritional status, especially in developing countries.[13] The question however remains which standard references to use in the childhood cancer setting.

***B**iochemical data:* Although data of blood concentration of nutrients and proteins can serve as a proxy of a patient's current nutritional status, they need to be interpreted with current hydration status, medications and drug-nutrient interactions in mind. For instance, serum albumin, a marker of protein status during starvation, is not useful during acute disease, because it is a negative phase protein that decreases during the acute phase response. Nevertheless, as a marker of inflammation and acute illness, which is usually associated with reduced appetite and nutrient intake, hypoalbuminemia still suggests a need for nutritional intervention. As such, albumin is often monitored together with C-reactive protein (CRP) to distinguish between nutritional and inflammatory causes of low albumin and as a means to assess recovery from, for instance, an acute infection.[1,14] As another example, lower antioxidant levels have been documented and are associated with increased risk of toxicity (dose reductions), infections, chemotherapy delays, days spent in the hospital and decreased quality of life.[6] A lower dietary intake of antioxidants had similar effects.[15,16]

***C**linical assessment:* This is particularly important in children who should be assessed for clinical signs and symptoms of depleted muscle and fat stores as well as micronutrient deficiencies.[17]

***D**iet history:* Apart from the usual information gathered during a diet history, the Children's Oncology Group (COG) recommends that the history must also include information about the use of supplements, herbs, or alternative therapies.[17] It is estimated that up to 85% of the pediatric oncology population use some form of alternative medicine, including dietary supplements. Although some such supplements may be beneficial, others may interact with medications or cause adverse effects. Patients and their families may not always feel comfortable to share their use of alternative, often cultural medical and/or food practices. Therefore an open and non-judgemental approach is needed to encourage families to share such practices so as to allow alternative modalities that are deemed safe and appropriate to be integrated in the patient's treatment. Well- designed research on the use of alternative dietary therapies in the paediatric oncology patients is however lacking and is needed to make sound recommendations.[1]

Nutrition support for children with cancer

A relative paucity of data on best practices contributes to the challenges in achieving the goals of nutrition support (Table I).

Table I: Goals of nutrition support in children with cancer

Sustain and promote normal growth[17]
Reverse malnutrition, if present[17]
Prevent future malnutrition[17]
Promote normal eating behaviours[1]
Improve quality of life[1]

Criteria for intervention

Currently there are no universally agreed guidelines for nutrition intervention in the paediatric oncology population. In an international survey conducted by the COG, it was found that no standardized nutrition protocols were being employed for nutrition intervention. The effect of the varied and variable nutrition practices on the quality of life, toxicity of cancer treatments and outcome in children with cancer remains largely unknown. As a result of this the COG Nutrition Committee developed an algorithm as a general guideline for nutrition intervention in an effort to establish a base for appropriate clinical trials about nutrition and its impact on the child with cancer.[18]

Nutrient requirements

There are no specific guidelines for nutrient requirements or the changes that occur in the paediatric oncology population. Several tools are available to estimate energy and nutrient needs of the child with cancer, including age appropriate Dietary Reference Intakes (DRIs) and the World Health Organization's (WHO) equations for basal metabolic rate. The difficulty in estimating nutrient requirements is further augmented by the wide age range of paediatric patients and age specific requirements, ranging from an infant weighing about 3 kg with minimal reserves to an obese adolescent weighing 100 kg.[1,4,17,18] The COG recommends that (i) cancer treatment may increase energy needs by approximately 20% and protein needs by as much as 50%; (ii) poor treatment related dietary intake may necessitate a daily multivitamin and mineral supplement to meet daily recommended intake; and (iii) fluid status should be assessed and monitored to ensure proper hydration.[1]

Enteral or parenteral nutrition support?[1]

When oral intake remains inadequate to support growth or nutrition repletion in a child with cancer, enteral nutrition (EN) should be considered before the initiation of parenteral nutrition (PN). EN, in the presence of an intact gastrointestinal tract, preserves gut integrity and prevents bacterial translocation, enhances immune response and reduces the risk of infections.[13,17] Studies in paediatric oncology patients have demonstrated that EN is successful in maintaining adequate nutritional status and in reversing malnutrition. Unfortunately, the use of EN is inconsistent.[19] Some of the treatment related side effects, such as mucositis discourage the use of EN. In addition, children may have neutropenia or thrombocytopenia that can increase their risk for bleeding when the tube is inserted; however, clinical trials have not supported these theoretical risks.[5,20,21] There is currently no evidence-based guidelines about the particular composition of EN in the paediatric oncology population. The three-way diet–chemotherapy–cancer interaction needs to be explored to answer questions about key gene expression and genetic pathway alterations by specific nutrients and/or combinations of nutrients.[22] Supplementation with glutamine is reported to relieve severe mucositis, but clear evidence remains in need of confirmation.[23-25] Equally, there is no consistent of confirmed evidence regarding the use of pre- and probiotics in this patient population. The American Academy of Paediatrics (AAP) does not recommend their use in seriously or chronically ill children until the safety of administration has been established.[26] Pre- and probiotics may further alter anticancer drugs' pharmacokinetics.[22] The use of anti-oxidants is controversial as there are arguments for and against their inclusion in cancer treatment regimes. The findings of such small scale studies with many uncontrolled variables are inconsistent and in adequate to guide clinical practice.[27]

Contraindications to EN are similar to those in other diseases. If no EN is possible, PN is indicated without delay. A delay of three to seven days as suggested by some is thought to be detrimental to children with preadmission protein energy malnutrition (PEM) and/or history of poor dietary intake.[1,4,17,28] When considering PN the impact of specific lipid formulations should be considered. Recent knowledge about the immunomodulating actions of ω-3 polyunsaturated fatty acids indicates that eicosapentanoic acid and docosahexanoic acid may have different effects on the function and gene expression of immune cells.[29,30] Furthermore, parenteral nutrition–associated liver disease (PNLD) remains a dreaded complication of PN in children.[31] New intravenous lipid emulsions containing fish oil have been shown to be beneficial and safe in the management of PNLD in paediatrics, but their impact on cancer treatments need to be further explored.[22,32,33] Whichever route of nutritional repletion is used, it needs to be borne in mind that the malnourished child with cancer is at risk of refeeding syndrome, should aggressive nutritional rehabilitation be implemented.[17]

In a recent Cochrane Review to determine the effects of any form of PN or EN support in children and young people with cancer undergoing chemotherapy, the authors concluded that there is limited evidence from individual trials to suggest that PN is more effective than EN in well-nourished children and young people with cancer undergoing chemotherapy. The evidence for other methods of nutritional support remains unclear. No studies were identified comparing the nutritional content in the PN or EN groups of studies [34]

Where do we need to go?

Analysis of childhood cancer statistics in the US has shown that the rate of decline in mortality from most cancers has decreased. This latter has been attributed to the consistent improvements in outcome from sequential clinical trials by optimizing delivery of standard cytotoxic agents and other conventional therapeutic approaches (surgery, radiation therapy, and hematopoietic stem-cell transplantation). With the advent of targeted therapeutics, which is currently in its infancy, further improvements can be expected.[35] At the same time it has been acknowledged that there is paucity of nutritional investigation in children with cancer that needs to be addressed.[18] Some of the areas to explore include the biological modification of disease by nutrients, improved tolerance of chemotherapy and amelioration of

toxicity.[6] Examples of nutrients being investigated are glutamine, ω-3 polyunsaturated fatty acids, pre- and probiotics that are therapeutic factors that potentially modulate gastrointestinal toxicity related to cancer treatments. Mechanisms underlying the action of these nutrients are being unravelled and will lead to the better understanding of their potential clinical benefit or detriment. Optimal strategies to translate these findings into clinical care however still remain to be elucidated.[22] Furthermore, cancer cachexia is another area of ongoing research, and current treatment options for cancer malnutrition in adults, including drugs and anabolic agents are of limited use in the paediatric cancer population due to adverse effects in a growing and immature child and need to be further investigated.[4]

The identified knowledge gaps are being addressed in the developed world and will no doubt further improve clinical outcomes among the children of the developed world, in so-called High Income Countries (HIC). But where do we have to go in the developing world, in Middle (MIC) and Low Income Countries (LIC), in which 80% of the world's children live, and where poverty, lack of public health infrastructure, high under 5-year mortality rates, and low childhood cancer cure rates are pervasive?[36] The challenging question often asked is: "Can or should cancer treatment and supportive care take precedence over much bigger health problems facing children in LIC"?

Last but not least: where do we need to go with survivors of childhood cancers?

We are in the era where survivors of childhood cancers has increased to up to 80% of cases due to the introduction of chemotherapy and improved associated treatment modalities. The increasing number of cancer survivors has brought to the fore the need and importance of identifying appropriate nutrition interventions not only to improve cancer outcomes but also to prevent and/or manage chronic health issues, improve quality of life, and decrease health care costs. This change in the landscape of paediatric oncology underscores the need for further research to support the development of evidence-based nutrition guidelines for cancer survivors.[37]

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