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Children's Oncology Group (COG) Nutrition Committee

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The Children's Oncology Group (COG) Nutrition Committee was established to further the knowledge of nutrition in children with cancer by education and the conduct of clinical trials. A survey of COG institutions revealed lack of conformity in evaluation and categorization of nutritional status, and criteria for nutritional intervention. The Committee subsequently established specific categories of malnutrition (Underweight and Overweight) based on ideal body weight or body mass index. An algorithm was developed as a guideline for nutritional intervention as well as references and resources for determining estimated needs. The Committee embarked on concepts for clinical trials of nutritional interventions. The first pilot study, evaluating the feasibility of using an immunoneutraceutical precursor for glutathione production, has been completed. This study showed weight gain and improvement in glutathione status. A pilot trial of proactive enteral feeding for patients at high risk of malnutrition has commenced. The Committee believes that nutrition is relevant to all aspects of cancer control. The paucity of nutritional investigation in children with cancer needs to be rectified. Pediatr Blood Cancer 2008;50:447–450.

Key words: cancer; children; nutrition

INTRODUCTION

The purpose of the Children's Oncology Group (COG) Nutrition Committee is to initiate and facilitate collaboration between basic scientists and health care professionals so as to improve the knowledge of nutrition pertinent to pediatric oncology. COG is an international co-operative clinical trials and biological study group for pediatric cancers with over 230 centers contributing. The Committee desires to promote and conduct clinical studies in order that nutritional assessment and nutritional interventions for children with cancer are evidence-based and not opinion-based as is the current status.

Aims of the Nutrition Committee:

(1) To develop a forum for hypothesis-driven studies relating to nutrition within all of the areas encompassed by cancer control.
(2) To improve or maintain nutritional status, to support normal growth and development, to limit therapeutic toxicity, and to maximize quality of life for children with cancer through the conduct of interventional studies and educational processes.

Nutrition of the pediatric cancer patient encompasses all the elements of cancer control; in particular prevention, treatment, supportive care, delayed effects, and even palliative care. Intensive multi-modal therapy (chemotherapy, surgery, radiation, stem cell transplantation) has resulted in increased survival for children with cancer, but therapy-related side effects frequently result in suboptimal nutritional status and quality of life [1].

The criteria used to define and categorize malnutrition vary widely in the pediatric literature, as described by Pietsch and Ford [2]. A commonly used technique is the Waterlow Criteria for determining percent ideal body weight (IBW) for height [3]. More recently body mass index (BMI) has been used to determine nutritional status [4]. Growth charts are available at www.cdc.gov/growthcharts/.

The causes of malnutrition are insufficient quantity or quality of food, increased requirements, increased energy expenditure or inadequate utilization. A child's metabolic rate can be affected by nutritional status, age, sex, hormones, pathological conditions, the treatment of cancer and the complications thereof. The cancer cachexia syndrome seen in the pediatric patient is a multifactorial interaction of host, disease and treatment [5].

In order to identify the standards of practice in the nutritional management of a child with cancer, the COG Nutrition Committee conducted a survey of institutions that are part of the COG consortium [6]. Surveys were submitted to 233 participating institutions. One member of each of three disciplines was requested to complete the survey: physician, registered dietitian, nurse or nurse practitioner. Fifty-four percent of institutions responded to the survey.

The results of this survey demonstrated that there is no uniform approach to nutritional assessment or intervention. Despite a number of publicized guidelines suggesting effective approaches of nutritional intervention [7,8], there are no clinical studies testing the efficacy of any of these guidelines for children with cancer. Assessment of nutritional status does not occur routinely in all institutions and different indices are employed to indicate the nutritional status of a patient. Institutions also rely upon different guidelines when categorizing nutritional status. Nutritional intervention was also inconsistent with a variety of approaches utilized. Additionally, this survey did not find standardized nutritional protocols being employed in this population. The effects of varied nutritional practices on the quality of life, toxicity, and outcome in children with cancer are unknown.

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CATEGORIES OF NUTRITIONAL STATUS

Based on the results of the questionnaire, the Nutrition Committee decided that it was imperative to develop standardized nutritional guidelines for children on COG clinical trials. The Committee developed a Nutritional Algorithm (Appendix 1) and categories for nutritional status (Table I) with references and equations to assist clinicians in utilizing these documents (Appendix 2–4). The objectives of the algorithm and categories are to create a uniform approach to the nutritional assessment of and intervention for children with cancer so as to provide and to collect standardized data to aid future research initiatives.

Correlation of IBW and BMI in the Evaluation of Nutritional Status

Ideal body weight and BMI are commonly used indices in the assessment of nutritional status, but it has been unclear as to whether there is a correlation between the two indices. The relationship of BMI to IBW was assessed in a study of 227 children with sarcomas treated at Children's Hospital of Philadelphia. BMI was assessed using the formula: *weight (kilograms)/height (meters)*^{2}. Age and gender standardized BMI z-scores were calculated for each study patient using height, weight, gender, and age data based on the Centers for Disease Control and Prevention (CDC) National Center for Health Statistics (NCHS) growth curves [9].

Correlations were assessed at multiple points during treatment using Pearson r correlation coefficients. Both IBW and BMI were approximately normally distributed at each point of assessment. At each of the time points, BMI exhibited a substantial and statistically significant correlation with IBW. The specific correlation coefficients by time point are listed as follows: (a) at first referral ($r = 0.80$, $P < 0.0001$, $n = 187$); (b) at lowest weight during therapy ($r = 0.84$, $P < 0.0001$, $n = 185$); c) at end of therapy ($r = 0.79$, $P < 0.0001$, $n = 181$); and (d) after amputation corrected for lost body part ($r = 0.87$, $P < 0.0001$, $n = 35$). These findings indicate that IBW and BMI yield comparable findings throughout therapy.

Research Methods of Body Composition

The use of dual energy X-ray absorptiometry (DXA) is becoming widely accepted as the gold standard for assessing body composition in the pediatric population as detailed in this series of papers (e.g., Kaste et al., [10]). Accurate assessment of body composition is fundamental to assessing nutritional status in both health and disease. Body composition changes during normal development in childhood and adolescence and is influenced by nutrition, genetics, age, gender, pubertal status, disease and physical activity.

Due to the epidemic of obesity that also affects children with cancer [11] there has been interest in validating the DXA measurements of fat and fat free mass. It is important to understand that each DXA system has differences and the value for any given body compartment may differ appreciably between instruments. Comparison to 4 component models in healthy children has shown both overestimates and underestimates of percent body fat [12]. Overall there is good correlation between body thickness and fatness with a strong predictable relationship of the DXA body composition measurements, supporting its acceptability in longitudinal studies.

It is also important to establish the relationship between nutritional status and morbidity and mortality in children with cancer. Obesity and malnutrition (under nutrition) are significant risk factors in childhood cancer. There are too few studies reporting the use of DXA as a measurement of body composition to assess nutritional status in childhood cancer. Long-term follow up programs have provided the most information regarding body composition in the pediatric cancer patient. Most studies are from single institution studies with small numbers and include mostly acute lymphoblastic leukemia (ALL) patients. The most frequently reported finding is an increase in body fat after completion of therapy. The propensity for obesity has been shown especially in females treated for ALL, particularly in those receiving cranial irradiation [13]. An increase in percent body fat has been reported also in children receiving glucocorticoids and intravenous high dose methotrexate. Body composition studies using DXA during therapy

TABLE I. Categories of Nutritional Status for the Pediatric Oncology Patient

Identify appropriate category			
Age >2 years—choose either			
Body mass index—percentile (BMI)[21] or			
Ideal body weight (IBW for height or length—percentile)[22]			
Age <2 years—choose either:			
WT/LT (Weight for Length—percentile) or			
Ideal body weight (IBW for height or length—percentile)[22]			
Underweight	Normal	Risk of overweight/overweight	
Weight loss/gain may or may not be present			
BMI			
<5th percentile	5–85th percentile	>85–95th percentile	>95th percentile
WT/LT			
<10th percentile	10–90th percentile		>90th percentile
IBW			
<70% severe	>90–110%	>110–120%	>120%
>70–80%			
Moderate			
>80–90% Mild			

are limited to two studies in children with ALL. The longitudinal studies during therapy showed lower lean body mass at diagnosis that persisted during therapy in conjunction with an increase in fat mass on therapy [14,15]. There are no reports on the use of DXA for measurement of body composition in children during treatment for solid tumors. Development of normative reference data and validation of precision and accuracy of fat and fat free mass measurements will enhance the use of DXA as a tool for the assessment of body composition in children with cancer. A longitudinal study of bone density and body composition in ALL patients for 4 years from diagnosis is being undertaken currently in Canada funded by the Canadian Institutes of Health Research (Dr. Leanne Ward, principal investigator).

PROPOSED TRIAL CONCEPTS

Evaluation of a Nutraceutical Cysteine Delivery Agent in the Management of Wasting in High-Risk Childhood Cancer Patients

This study examines the hypothesis that depletion of intracellular glutathione (GSH) levels in high-risk pediatric cancer patients is a causative factor of cachexia; that the supplementation of the subject's nutritional regimen with un-denatured whey protein derivative (Immunocal®) provides GSH precursors that can be utilized optimally by cells, and will increase cellular GSH levels and ameliorate cachexia and the toxicity of chemotherapy [16].

A pilot feasibility study was conducted through the COG Nutrition Committee [17]. The study was a 90-day, two dose evaluation of Immunocal® (0.5 g/kg/day vs. 1.0 g/kg/day) added to the standard institutional nutritional regimen. Twelve patients with high-risk tumors with $\geq$5% weight loss from the time of diagnosis were entered on study. Clinical and biochemical data were assessed at baseline and days 0, 45, and 90. Immunocal® was administered successfully by one or more of three routines (oral, gastric tube and nasogastric tube) and was generally well tolerated with overall good compliance. All but 4 patients gained weight ranging from 7.1% to 26.9% from their pre-study weight. Though not statistically significant, GSH levels were increased and oxidized glutathione (GSSG) levels decreased in all but one patient. Other observations included the amelioration of severe mucositis in two patients and abatement of nausea and vomiting in two patients. The study concluded that Immunocal® was well tolerated and can be given safely to the majority of children with cancer. These results established the end-points for a double-blind placebo-controlled evaluation of the efficacy of Immunocal® as a nutritional supplement in the management of patients on cancer treatment [17].

Pro-Active Enteral Feeding for at-Risk Patients

Pediatric cancer patients with advanced disease or on intensive chemotherapeutic protocols are at high risk of losing weight and becoming malnourished [1]. The primary objective of this pilot clinical trial is to determine the feasibility and acceptance of pro-active enteral tube feedings. The secondary objective is to determine the safety of pro-active enteral nutrition in children receiving chemotherapy for newly diagnosed acute myeloid leukemia/myelodysplastic syndrome, primary cancers of the central nervous system or high risk solid tumors. Patients between 1 and 21 years of age, who are newly diagnosed and who have no contraindication for enteral feeding, will be eligible for participation. Participants will be fed on the basis of a calculation of estimated caloric requirements; feedings will be delivered via an enteral feeding tube and continued during the period of hospitalization and at home until adequate oral intake is established. Participants will be followed from the time of enrollment on the feeding study until they complete all of their chemotherapy. If the pilot study indicates feasibility, a randomized trial will be proposed to evaluate if pro-active enteral feeding results in maintenance of weight or weight gain and a decrease of treatment-related morbidity.

Antioxidants to Ameliorate Toxicity in Patients With Central Nervous System (CNS) Tumors Directly After Therapy and SCT (Stem Cell Transplant) Patients Directly After Transplantation

In a systematic review of the literature antioxidant levels decline in patients receiving chemotherapy, particularly in those undergoing conditioning regimens prior to blood and marrow transplantation (BMT) and receiving radiation therapy [18,19]. A prospective study in 107 children with ALL found that sub-optimal total antioxidant status whilst on treatment was associated with significantly increased toxicity from chemotherapy [20]. The benefit of nutritional supplements to improve nutritional and antioxidant status and reduce the toxicity associated with chemotherapy has been reported inconsistently [18]. CNS tumor patients and BMT patients have significant treatment-related toxicity. A proposal is currently being planned by the COG Nutrition Committee to test the hypothesis that a mixture of vitamins and exogenous nutrients which includes antioxidants will reduce regimen-related toxicity in children undergoing BMT.

CONCLUSION

Research into the relevance of nutrition in all aspects of cancer control is required for children with cancer. A standardized nutritional assessment and algorithm of nutritional intervention will decrease the variability of nutritional practice that may well affect the outcome (mortality and toxicity) of therapeutic clinical trials.

REFERENCES

1. Mauer AM, Burgess JB, Donaldson SS, et al. Special nutritional needs of children with cancer. JPEN 1990;14:315–324.
2. Pietsch JB, Ford C. Children with cancer: Measurements of nutritional status at diagnosis. Nutr Clin Pract 2000;15:185–188.
3. Waterlow JC. Classification and definition of protein-calorie malnutrition. BMJ 1972;3:566–569.
4. Hammer LD, Kraemer HC, Wilson DM, et al. Standardized percentile curves of body-mass index for children and adolescents. Am J Dis Child 1991;145:259–263.
5. Sala A, Pencharz P, Barr RD. Children, cancer, and nutrition—A dynamic triangle in review. Cancer 2004;100:677–687.

6. Ladas EJ, Sacks N, Brophy P, et al. Standards of nutritional care in pediatric oncology: Results from a nationwide survey on the standards of practice in pediatric oncology. A Children's Oncology Group study. Pediatr Blood Cancer 2006;46:339–344.
7. ASPEN Board of Directors and the Clinical Guidelines Task Force. Guidelines for the use of parenteral and enteral nutrition in adult and pediatric patients. JPEN 2002;26:1SA–138SA.
8. Ladas EJ, Sacks N, Meacham LR, et al. A review of the nutritional practices for the pediatric oncology population: Assessment, intervention, nursing, pharmacology, quality of life, and survivorship. Nutr Clin Pract 2005;20:377–393.
9. Ogden C. Defining overweight in children using growth charts. Maryland Med 2004;5:19–21.
10. Wahner HW, Fogelman I. Total body bone mineral and body composition by absorptiometry. In: Fogelman I, editor. The evaluation of osteoporosis: Dual energy X-ray absorptiometry in clinical practice. London: Martin Dunitz Ltd 1994. pp. 196–218.
11. Rogers PC, Meacham LR, Oeffinger KC, et al. Review: Obesity in pediatric oncology. Pediatr Blood Cancer 2005;45: 881–891.
12. Sopher AB, Thornton JC, Wang J, et al. Measurement of percentage of body fat in 411 children and adolescents: A comparison of dual-energy absorptiometry with a four-compartment model. Pediatrics 2004;113:1285–1290.
13. Warner JT, Evans WD, Webb DKH, et al. Body composition of long-term survivors of acute lymphoblastic leukemia. Med Pediatr Oncol 2002;38:165–172.
14. Van der Sluis IM, van den Heuvel-Eibrink MM, Hablen K, et al. Altered bone mineral density and body composition and increased fracture risk in childhood acute lymphoblastic leukemia. J Pediatr 2002;141:204–210.
15. Halton JM, Atkinson SA, Barr RD. Growth and body composition in response to chemotherapy in children with acute lymphoblastic leukemia. Int J Cancer 1998;11:81–84.
16. Bounous G. Whey protein concentrate (wpc) and glutathione modulation in Cancer treatment. Anticancer Res 2000;20:4785–4792.
17. Melnick SJ, Rogers P, Sacks N, et al. A pilot limited institutional study to evaluate the safety and tolerability of Immunocal®, a nutraceutical cysteine delivery agent in the management of wasting in high-risk childhood cancer patients. 1st Annual Chicago Supportive Oncology Conference. Chicago, IL, 2005.
18. Ladas EJ, Jacobson JS, Kennedy DD, et al. Antioxidants and cancer therapy: A systemic review. J Clin Oncol 2004;22:517–528.
19. Block KI. Antioxidants and cancer therapy: Furthering the debate. Integr Cancer Therap 2004;3:342–348.
20. Kennedy DD, Ladas EJ, Rheingold SR, et al. Antioxidant status decreases in children with acute lymphoblastic leukemia during the first six months of chemotherapy treatment. Pediatr Blood Cancer 2005;44:378–385.
21. Motil KJ. Sensitive measures of nutritional status in children in hospital and in the field. Int J Cancer 1998;11:2–9.
22. Pietrobelli A, Faith MS, Allison DB, et al. Body mass index as a measure of adiposity among children and adolescents: A validation study. J Pediatr 1998;132:204–210.
23. St. Jude Children's Research Hospital, Department of Clinical Nutrition. Clinical Practice Guidelines, 2006.
24. Supportive Care of Children with Cancer. Current therapy and guidelines from the Children's Oncology Group. Altman AJ, editor. 3rd edition. The Johns Hopkins University Press 2004; 243–261.
25. Hamwi GJ. Therapy changing dietary concepts in diabetes mellitus: Diagnosis and treatment, Vol. 1. NY: American Dietetics Association. 1964. pp 73–78.
26. Traub SL, Johnson CE. Comparison of methods of estimating creatinine clearance in children. Am J Hosp Pharm 1980;37:195–201.
27. Devine BJ. Gentamicin therapy. Drug Intell Clin Pharm 1974; 8:650–655.
28. American Dietetic Association. Manual of dietetics. Adjustment in body weight for obese patients. Chicago: Chicago Dietetic Association and South Suburban Dietetic Association. 1989; Appendix 48:622–623.
29. Schofield WN. Predicting basal metabolic rate, new standards. Human Nutr Clin 1985;39 Suppl. 1:5–41.
30. Osterkamp LK. Current perspective on assessment of human body proportions of relevance to amputees. J Am Diet Assoc 1995;95: 215–218.
31. Dietary Reference Intakes: the Essential Guide to Nutrient Requirements. Institute of Medicine, National Academies of Science. Otten J, Hellwig JP, Meyers LD, editors. Washington, DC: The National Academies Press, 2006.
32. World Health Organization. Energy and protein requirements. Tech. Rep. Ser. 724. Geneva: WHO. 1985.
33. Amer\ican Dietetic Association. Children with special health care needs: Nutrition care handbook. Lucas BL, editor. 2004. p. 36.