The Relevance of Nutrition to Pediatric Oncology

Nutrition is an under acknowledged topic within paediatric oncology. Nutrition is relevant to most of the components within the broad meaning of cancer control. These include epidemiology, prevention, biology and pathogenesis of cancer in children, treatment of the cancer and obviously supportive care during cancer treatment. This presentation will attempt to highlight why we need to think of nutrition as a fundamental aspect of cancer control and raise questions that we paediatric oncologists need to address.

There is minimal research undertaken on the epidemiology and potential prevention of childhood cancers from the perspective of malnutrition during preconception, pregnancy and the different phases of childhood growth & development. Folic supplementation during pregnancy has been associated with a decreased risk of acute lymphoblastic leukemia. There is possibly an association of folic acid deficiency with neuroblastoma and brain tumors. Mechanisms that could explain association between folic acid deficiency and increased cancer risk are changes in DNA methylation and impaired DNA synthesis and repair. It is probable that there maybe other nutrient deficiencies during pregnancy and early childhood development leading to gene pathway deregulation. Impaired nutrition is causatively involved in many other diseases in childhood and subsequently in adulthood. Cancer is one of those pathological conditions related to impaired nutrition in adults but poorly understood for pediatric malignancies. In adults the epidemiological evidence for nutrition related cancers is growing and potential preventative strategy for adult cancers should begin in childhood. We need to focus on the nutrition of the mother, fetus, neonate and the young child and the potential impact of nutrition on the life long risk of cancer. The World Cancer Research Fund UK has set their research priorities as follows

- Studies that focus on nutrition of the mother, fetus, neonate and young child and lifelong risk of cancer
- Studies investigating energy intake and expenditure, body composition, body weight and cancer risk
- Studies investigating the role of physical activity /inactivity and cancer risk
- Projects focusing on countries in transition from developing to developed economic status in order to study the relationship between food, nutrition, physical activity and cancer.
- Studies investigating the interventions aimed at changing eating habits, physical activity or nutrition status at individual, community or population levels.

These population based research questions need to be embraced by paediatricians.

The understanding of the biology of pediatric malignancies is rapidly evolving. Nutrition may have an effect on the biochemical and gene signalling pathways that are relevant to promoting or inhibiting cancer development. Research into the effects of nutrients on the expression of specific genes associated with apoptosis, cell proliferation, angiogenesis, adhesions molecules, cytokines and cytokine receptor expression is taking place. Animal models have shown that changes in diet can affect DNA methylation. Dietary supplementation of the glutathione system leads to a diminution of reactive oxygen species and the down regulation of the NF-kappaB which confers a variety of benefits including inhibition of pro-inflammatory cytokines and sensitisation of cancer cells to chemotherapy. These are exciting developments that may well have practical relevance.
As paediatricians we recognise the importance of good nutrition on normal growth and development and the maintenance of normal physiological homeostasis. There are clearly described pathological disorders that are evident in nutritional deficiencies such as protein calorie malnutrition, vitamin deficiencies and trace element deficiencies. Oncogenesis is highly complex and the hypothesis that the initiation, promotion, and progression of oncological disease in a growing child may be influenced by the nutritional state at preconception, gestation, neonatal and periods of growth is plausible. The concept definitely needs further research.

There is an association between nutrition and immune status. There is a growing field of immune nutrition that is investigating functional foods or nutraceuticals that may influence immunological response mechanisms. Functional foods are foods containing natural, bioactive chemical compounds that have health promoting, disease preventing or medicinal properties (polyphenols, phytoestrogens, fish oils, carotenoids, phytosterols, soy isoflavones, vitamins and trace elements). Nutraceuticals are products that are isolated or purified from functional foods and prepared in pharmaceutical forms (glutamine, omega-3 fatty acids, arginine, and ribonucleic acids, N-acetylcysteine). Immunonutrients may act as pharmacologic agents since these nutritive agents have the potential to modulate the immune response at a molecular level and thus their effects may be disease-state specific. Evaluating single nutrients in the same methodology as small molecule drugs is probably flawed as nutrients rarely function in isolation. The immunonutrition approach may well have relevance to cancer prevention, cancer therapy and supportive care during therapy.

The prevalence of malnutrition as defined by protein calorie malnutrition (PCM) ranges from 50-60% depending on diagnoses, stage, treatment and social economical status. Nutritional status at diagnosis and its relevance to overall survival and disease outcome is controversial. There are reports that under nutrition is associated with poorer survival especially in countries where malnutrition is prevalent. In developed countries this does not always appear to be a prognostic factor. Malnutrition does appear to be associated with impaired intolerance to chemotherapy, impaired immune status with increased risk complications to therapy such as infection, marrow suppression and altered treatment schedules. Improving nutritional status does enhance the feeling of well being. The pharmokinetics of drugs are affected by PEM with decreased clearance and alternate distribution of drugs. This has been well described for Methotrexate.

A recent view of the Children’s Oncology Group nutrition committee reported a wide disparity of nutritional practice in the assessment and nutritional intervention for children on therapy. This report showed that assessment of nutritional status does not occur on a consistent basis and when it does it is mostly based on weight change alone. Consistency is required for the assessment of nutritional status, categorization thereof and the use of clinical pathways for intervention. While the impact of nutritional intervention in children with cancer is uncertain with respect to the cancer outcome, we as pediatricians accept that adequate nutrition is essential for growth, development and well being of children without disease. Thus it seems prudent and rational that adequate nutrition should be ensured for children with cancer.

Cancer cachexia is multifactorial both at the time of diagnosis and during treatment. It is critical to identify the interacting factors of host, tumor, treatment and complications thereof which may be contributing to malnutrition so that the appropriate interventions can be employed that may ameliorate some of those factors. While some of the contributing factors are recognized for cancer cachexia, many of the mechanisms are poorly understood and may well be different in the growing and developing pediatric patient compared with adult patients. Animal studies and the adult literature indicate pro inflammatory processes are implicated in the hypermetabolism and weight loss associated with cancer associated cachexia.

Nutrition assessment of the pediatric cancer patient is similar to the assessment of the nutritional status of any other pediatric patient. Assessments should be longitudinal so that trends can be ascertained. Practically, weight is the baseline measurement most frequently
undertaken and followed. Assessments based on weight alone can be misleading, especially in the acutely ill patient when fluid balance may be disturbed, or the presence of edema or mass disease. Additionally, weight may be maintained but lean body mass can be diminished. This can be the case in the patient who is obese at the onset of treatment. Weight for height is a widely used assessment of PEM. Body mass index (BMI) is considered a more reasonable parameter for assessment over the age of 2 years and ideal body weight (IBW) under the age of 2. BMI has to be interpreted relative to population reference data as BMI changes with age and differs between genders. It is considered a better proxy for body fat and lean body mass. It is the most appropriate index in assessing the other end of malnutrition i.e. obesity. Health care providers should measure and plot on the appropriate population charts, weight for age, height for age, weight for height, BMI, head circumference (under the age of three years) and mid arm circumference to better assess muscle wasting and triceps skinfold for estimation of adipose tissue. Evaluation of nutritional intake is a necessary component to try and predict those patients who are at risk of becoming undernourished. Biochemical measurements are of some use but interpretation can be difficult due to confounding factors such as sepsis and acute phase reactants during sepsis.

Cytotoxic therapy and sepsis may deplete the body of micronutrients. Decreased antioxidant levels have been reported following chemotherapy and trace elements may also be depleted, especially Zinc.

Nutritional intervention should be an active and continuous aspect of supportive care to sustain growth and development, plus improve well being and quality of life. Dietary intervention is the most commonly commenced if there is a weight loss, despite the limitation of weight being a sole criterion. A proactive approach is to identify patients that are at risk for malnutrition and intervene before there is significant weight loss and/or loss of lean body mass. Increasing oral intake should be the first approach. There is a wide variety of oral supplements available to increase calorie and/or protein intake. Enteral feeding can be increased by the use of tube feeding which may either be nasoduodenal, or the placement of percutaneous gastrostomy, duodenostomy or enterostomy tube. Many preconceptions exist about nasogastric (NG) tube feeding. There is a reluctance to place a NG tube as this is often seen as a punishment by the patients. NG tubes are frequently avoided in the neutropenic or thrombocytopenic patients, presence of mucositis, plus the concern of aspiration or sinusitis. These are all cited as reasons against the use of a NG tube. There is insufficient evidence either to support or dispute these perceptions. What is well described is the importance of maintaining gut integrity and the use of enteral trophic feeds are encouraged.

Specific designer nutritional supplements are available but further evidence is required before their routine use can be recommended. The Children’s Oncology Group Nutritional committee undertook a pilot study for patients on chemotherapy using an undenatured whey protein to enhance Cystine delivery, which is a precursor for glutathione production. The pilot study showed an increase of glutathione over the base level and weight gain in the majority of patients. A randomised study has been proposed. Glutamine supplements have been advocated to improve mucosal turnover, especially in stem cell transplant patients. The value of a neutropenic diet is uncertain but there is some evidence to indicate that it is of no value. Appetite stimulants are used but remain controversial.

Parenteral nutrition (PN) should be considered when all attempts for sufficient enteral feeding have failed or contraindicated such as presence of neutropenic entrocolitis (typhilitis) or gut that is not functional. PN is clearly associated with a significant increased risk of infection, hepatotoxicity and variety of metabolic abnormalities. The utility of PN has been best defined in stem cell transplant patients who have prolonged gut damage due to the preparative regimen, Graft-Versus-Host Disease and/or gut infection. If PN is required, when possible, minimal enteral feeding should continue to preserve gut integrity and function.

Nutritional supportive care for pediatric oncological patients should be undertaken with the same diligence as one does for other supportive care issues.
Obesity

In North America thirty percent of children over age six have a BMI greater than the 85% percentile. Pediatric Oncology patients have not been spared and reported in long-term follow up studies. The metabolic syndrome of impaired glucose tolerance, diabetes mellitus, insulin resistance, hypercholesterolemia, hypertension and cardiovascular disease is now being documented in children. Obese children tend to become obese adults. There is increased risk of the adult obese patient developing cancer and obese adult patients have a poorer outcome.

Obese paediatric patients with AML or ALL have a poorer outcome. An important aspect of obesity in children is the potential impact on the pharmacodynamics and pharmacokinetics of cytotoxic agents that may be altered in obese patients. Appropriate dosing for the overweight patient is unknown and does need further evaluation. Obesity is not only due to inappropriate nutrition but overall lifestyle. Obesity intervention is about prevention of which monitoring nutritional intake of both quantity and quality should be part of our every day care.

Conclusion

Nutrition and the overall impact on our patients deserves greater attention than is currently given. Such a fundamental component of life needs greater emphasis in our day to day care of our patients as well as our clinical and basic research programs.

References

3. Thompson JR, Gerald PF, Willoughby MLN, Armstrong BK. Maternal folate