Nutritional Support in Pediatric Cancer Patients

M. Roulet\textsuperscript{a}, N. Bianchi\textsuperscript{a}, A. Garcia Aristizabal\textsuperscript{b}, and M. Nenadov-Beck\textsuperscript{b}

\textit{Units of \textsuperscript{a}Clinical Nutrition and \textsuperscript{b}Pediatric Oncology, University Hospital, Lausanne, Switzerland}

Specific Aspects of Pediatric Cancer

Cancer is the second most common cause of death after accidents in children. The types of malignancies are very different from those in adults. The most prevalent cancers are leukemia and lymphoma, brain tumor, soft-tissue sarcoma, neuroblastoma, Wilm's tumor, and bone cancer. Childhood cancers are usually very susceptible to chemotherapy, combined or not with surgery or radiotherapy. In general the outcome is much better for children than for adults. For instance the cure rate of acute lymphocytic leukemia, which is the most frequent cancer in children, is now approximately 80%. The prognosis for many childhood cancers has steadily improved in the last 20 years and the role of nutritional support in the medical management of these children has kept pace with this progress. Most cancers in children are of acute onset and, for this reason, weight loss is a relatively rare finding in children with newly diagnosed tumors. Malnutrition has been seen at the time of diagnosis in only 6% of our patients in the last five years. In contrast, malnutrition is often a presenting symptom in adults with cancer. The prevalence of weight loss ranged from 31 to 87% in 3,047 adult patients according to the type of tumor [1]. Therefore malnutrition in pediatric cancer patients is most often due to therapy or tumor progression. Cachexia is actually very rare in a child with cancer, except near the time of death in the case of therapeutic failure.
Cancer Malnutrition-Cachexia

Pathogenesis
The pathophysiological mechanisms of cancer anorexia and cachexia have been reviewed by several authors over the last four years [2–7]. The pathogenesis of cancer malnutrition-cachexia is still unclear. Anorexia plays an early and central role, but cancer malnutrition-cachexia is more complex than simple chronic starvation. Firstly, anorexia in cancer patients may have many different causes, for instance appetite-depressing factors produced by the tumor cells themselves or by the immune cells of the host, chemotherapy, radiotherapy, surgery, recurrent infections, nausea, uncontrolled pain, changes in smell and taste perception, intestinal motility disorders, early satiety, low physical activity, and psychological factors. Low protein-calorie intake related to anorexia may be aggravated by loss of nutrients by vomiting and malabsorption. Stomatitis, xerostomia, dental problems, and dysphagia may also contribute to a low protein-calorie intake. Secondly, complex metabolic abnormalities are involved in cancer malnutrition-cachexia, in particular an equal mobilization of fat and skeletal muscle, an increase in neoglucogenesis, high glucose recycling, insulin resistance, and an increase in resting energy expenditure. Cytokines, e.g., TNF-α, IL-1, IL-6, and γ-interferon, play an essential pathogenic role in anorexia and the metabolic syndrome observed in cancer malnutrition-cachexia. Furthermore, anticancer treatments can alter substrate utilization. Finally, cancer malnutrition is too often not seen by oncologists as a symptom requiring management in such a proactive manner as pain or nausea. This is bad, since anorexia may be largely bypassed by nutritional support and, perhaps in the near future, metabolic abnormalities may be treated by drugs. By chance, pediatricians have been aware of malnutrition for more than 50 years, and this might be another reason why malnutrition is less frequent in children with cancer than in adults.

Consequences
The normal adaptive response to starvation is to draw on energy-dense lipid stores while sparing lean tissue. In contrast, cachectic cancer patients experience severe lean tissue wasting with a relative sparing of adipose tissue. Cancer malnutrition-cachexia has multiple functional consequences, such as muscular weakness, impairment of immune defenses, retarded wound healing, increase in postoperative complications, high sensitivity to cold, asthenia, decreased mental skill, decline in attention span and concentration abilities, and mental depression. Malnutrition is also responsible for growth retardation and dwarfism in children. Furthermore, it can also affect the body image and impair the quality of life. Adolescents are typically distressed by the change in the appearance that their weight loss causes. Cancer-induced weight loss prior to therapy has been shown to be an independent adverse prognostic factor in adults [1]. It is also a predictor of increased toxicity following chemotherapy, prolonging delays between the cures of antimitic drugs and thus impairing tumor response.
Nausea, vomiting, mucositis, pain, learned food aversions (acquired aversions when a food is given simultaneously with painful or emetogenic treatments), changes in taste and smell perception, anticipatory nausea and vomiting (symptoms which are paired with anxiety-producing stimuli such as scheduled chemotherapy), behavior and emotional problems are common causes that prevent a child from eating normally. During treatment most of the cancer children may eat “junk” foods for days or weeks. Such an eating disorder often leads to conflict with the parents, who often consider appetite, eating behavior and weight status indicative of their child’s response to therapy. Doctors, nurses, dietitians, and psychologists with a large professional experience in pediatrics have to be involved to counsel the child and his or her parents. Early introduction of the essential role of nutrition in the child’s therapy helps to establish its importance in the minds of the child and parents. Before considering nutritional support in a particular child, favorite and nutrient-dense foods must be offered, learned food aversions avoided, and high-energy high-protein oral liquid supplements prescribed. An exercise program aimed at maintaining muscle mass should be recommended. Successful weight maintenance and rehabilitation with a volitional oral feeding program may be extremely difficult, but is not impossible.

Nutritional support includes forced enteral nutrition or parenteral nutrition [8, 9]. Numerous prospective randomized controlled trials have failed to demonstrate the clinical efficacy of providing nutritional support in malnourished adult cancer patients in terms of morbidity, mortality and duration of hospitalization. This disappointing phenomenon has been reported principally with parenteral nutrition [10]. Therefore to restore weight, which is a long and often impossible task in cancer patients stressed by therapy, is not sufficient. As a consequence, the problem has to be considered differently. Since pretreatment weight loss is quoted as a major indicator of poor prognosis, nutritional intervention has to be seen as a way to maintain weight and body functions [11]. This means that nutritional assessments have to be done at frequent intervals and followed, if necessary, by an early aggressive nutritional approach, such as enteral and parenteral nutrition. No long period of starvation should be allowed at any stage of disease. Malnutrition is no more acceptable in a child with cancer than in a child with cystic fibrosis or Crohn’s disease. A weight loss around 5–10% is acceptable during chemotherapy without taking aggressive nutritional measures to stop it. However, such a weight loss should be recovered between two courses.

Short-term nutritional support (5–10 days) is usual in pediatric cancer patients with temporary impairment of oral nutritional intake. Its principal aim is to cover water and electrolyte needs and to provide some protein-calorie intake with the hope of a protein-sparing effect. Such a short-term nutritional support is less common in adult cancer patients because their rate of dehydration and weight loss is much less rapid. Long-term nutritional support (several weeks) is indicated when a
low oral intake is expected for a long time according to the type of cancer and the therapeutic protocol. Once again, it is not necessary to wait until the child is severely malnourished. To prevent malnutrition by early nutritional intervention is much better than to institute nutritional support when the child is already malnourished. This requires knowledge of which tumors result in a high risk for malnutrition either from the tumor itself or from the intensive treatment planned. For instance, the nutritional risk for children with acute lymphocytic leukemia is minimal. In contrast, children with disseminated neuroblastoma need very aggressive anticancer treatments and consequently the nutritional risk is extremely high. Pediatric cancers with a high nutritional risk are brain tumors, advanced lymphoma, disseminated neuroblastoma, Ewing’s sarcoma, and rhabdomyosarcoma. Bone marrow transplantation and stem cell reinfusion are treatments with very high nutritional risk. A detailed and careful nutritional assessment at the time of diagnosis is highly recommended and must be regularly repeated in children with such cancers. A simple measure of weight and height, including calculation of weight for height ratio, is not sufficient. Edema or large tumor mass may mask diminished body weight. Moreover fat and fluid may fill the space left by muscle wasting [12].

Based on the types of tumors (histology, grading, staging, localization and size) and on the specific treatment protocols planned, we have classified 46 consecutive patients with a low (63%), moderate (15%), and high risk (22%) of malnutrition at the time of diagnosis. By following these patients at 3-month intervals for at least two years, we have observed 0% malnutrition in the low-, 28% in the moderate-, and 50% in high-risk group, malnutrition being defined as a weight for height ratio of <85%. Firstly, this observation has shown that malnutrition can be easily predicted. It has also shown that children with lymphocytic leukemia do not need to be followed by nutritionists, which is a way to give priority to efforts in the future.

In case of a moderate and high risk of malnutrition, it is essential to explain as soon as possible to the child and his or her parents that nutritional support is an indispensable part of the treatment protocol. This is done systematically by our oncologist within the first days after diagnosis and resumed some days later by the dietitian or the nutritionist. As a consequence, enteral nutrition is almost never refused and well tolerated. This was not at all the case in the past when enteral nutrition was proposed only when the child was very sick and malnourished. Anticipation of nutritional problems is also a way to diminish the conflict between parents and the child, if they are aware that enteral nutrition support is available as a backup in case of inadequate oral intake. Cycling the nutritional support at nighttime is another method for better acceptance. This allows the child to be more mobile and eventually to go back to school.

In the last two years, after several cases of cachexia in our pediatric cancer patients, we have decided to perform serial nutritional assessments and favor early nutritional support. We are presently following 50 children, 16 of whom
have acute lymphocytic leukemia. Moderate malnutrition with a weight for height ratio between 90 and 85% is present in 6 patients. Only one child is severely malnourished with a weight for height ratio of 81%. He has neuroblastoma and treatment-related deafness. He had percutaneous endoscopic gastrostomy (PEG) when his weight for height ratio was 75%, but he refuses to use it now after having changed his body image by gaining some muscle mass!

One important concern continues to be the potential harm of nutritional support in cancer patients. Increased tumor growth has been seen in animal models by correction of protein-calorie deficit. Human studies are much less convincing regarding the ability of nutritional support to promote tumor growth. Furthermore it has been demonstrated that nutritional support may enhance the response to cell cycle-specific chemotherapy by increasing the percentage of tumor cells in the S phase [13].

**Enteral Nutrition**

If a nutritional support is necessary to maintain weight, tube feeding via the gut should be the method preferred. Enteral nutrition is the least invasive and most physiological method. It maintains the anatomic and immunologic gut-mucosa intestinal barrier, impairing bacterial and toxin translocation triggered by many factors in cancer patients. It also has many advantages in terms of feasibility, cost (about 10% of those for parenteral nutrition), and quality of life. Enteral nutrition can provide nutritional support in cancer children with adequate gastrointestinal function and suboptimal oral intake [14]. Nasogastric tubes are most frequently used, but are badly tolerated for more than 6-8 weeks in our experience. PEG and button devices are optimal for long-term feedings or when the nasopharynx must be bypassed. PEG is used more and more often in cancer children with a functional gastrointestinal tract. It has been shown to be a safe and effective method of reversing malnutrition in children with cancer [15, 16]. Acceptance is good once the child and parents realize its esthetic benefit as compared to a nasogastric tube. Initial resistance decreases when the family learns the simplicity of feeding via a PEG. The most common complication is local inflammation at the PEG site during periods of severe neutropenia. Systemic infection from the PEG site has rarely been reported, and we have never observed this problem. Home-care organizations enable families to administer enteral nutrition at home, a good way to increase the independence of the child.

We placed seven PEGs in the last three years in cancer children with malnutrition. A weight gain of more than 10% was observed in each case after three months. Quality of life increased subjectively, and hospitalizations for dehydration were reduced. At the present time, about one fourth of our children with solid tumors have a PEG or a feeding button. All these children have a weight for height ratio of >85%.
Parenteral Nutrition

Parenteral nutrition is indicated when the child’s nutritional status cannot be maintained by the enteral route. This may occur for instance with tumors producing gastrointestinal tract obstruction or in cases of protracted nausea and vomiting. Reversal of energy deficit, improved weight gain, and an increase in serum albumin by parenteral nutrition have been reported. A usual indication for parenteral nutrition in oncology is bone marrow transplantation, which requires intensive treatments causing relevant gastrointestinal toxic effects. Morbidity and mortality rates are decreased by parenteral nutrition in this indication (see below, L-glutamine). However, its use should be strictly limited in other types of cancer, because a significant increase in infections and mechanical complications has been reported [17–19]. Central venous access must be obtained and employed only for nutrient infusion to reduce the risk of infection. We use, as much as possible, a one- or two-chamber implanted Port-A-Cath®.

Home-care organizations are useful in enabling a stable pediatric cancer patient with severe and long-term involvement of the gastrointestinal system to receive parenteral nutrition at home. With success we recently used home parenteral nutrition in two children with neuroblastoma and secondary chronic intestinal pseudo-obstruction.

Specific Nutrients

As stressed above, early nutritional support is encouraged, not only when severe malnutrition is present. Most pediatric cancer patients have not lost too much weight before diagnosis and thus are good candidates for such an early intervention. The failure of conventional nutritional support to improve clinical outcome in severely malnourished cancer patients, which has been reported principally in adults under parenteral nutrition, might be related to the fact that standard nutrients do not address or reverse metabolic abnormalities that result in cancer cachexia. For this reason, the use of specific nutrients is currently under consideration. L-Glutamine, L-arginine, and ω-3 polyunsaturated fatty acids, which are known to modulate the immunologic system, are the best studied. Until now these clinical trials have not been performed in children.

L-Glutamine

L-Glutamine is a nonessential amino acid synthesized by skeletal muscle. It is absolutely necessary for normal cellular proliferation, in particular for enterocytes and lymphocytes. Its role in maintaining gut mucosal integrity and function is essential. In contrast, tumor growth is strongly decreased in association with a significant increase in natural killer cell activity in rats receiving oral L-glutamine [20]. Furthermore L-glutamine has a potent antioxidant effect through the hepatic production of glutathione and may improve host tolerance to chemotherapy.
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L-Glutamine has been used with success in parenteral nutrition after allogeneic bone marrow transplantation for hematologic malignancies in adults. Better nitrogen balance, reduced incidence of clinical infection, lower rates of microbial colonization and shortened hospital stays have been reported in a double-blind randomized controlled clinical trial [22]. In another recent trial, oral and parenteral L-glutamine seemed to be of limited early benefit for patients having allogeneic or autologous stem cell transplantation for hematologic or solid malignancies, although long-term survival might be better [23]. L-Glutamine may also protect the intestinal mucosa from radiation therapy in an animal model. It may also prevent chemotherapy-induced stomatitis.

L-Arginine

L-Arginine is a nonessential amino acid in humans. Under certain circumstances, such as sepsis and severe trauma, it becomes an indispensable amino acid for adequate nitrogen balance and physiologic functions [24]. L-Arginine may play a role in the nutritional treatment of cancer patients in different ways, either by enhancing natural killer cell cytotoxicity, or by stimulating protein synthesis in tumors and increasing the response to chemotherapy, or by activating nitric oxide synthesis and inhibiting metastization by stimulating host defenses [25]. However, caution is mandatory since depletion of dietary L-arginine may inhibit growth of metastatic tumor [26].

ω-3 Polyunsaturated Fatty Acids

Dietary ω-3 polyunsaturated fatty acids from fish oil might restore immunodeficiency and prolong survival in severely ill patients with generalized malignancy [27]. It has also been suggested that a fish oil-enriched diet could reduce tumor-induced cachexia in an animal model [28]. However, caution is essential since ω-3 polyunsaturated fatty acids may promote colon cancer metastasis in the liver of rats [29]. This finding has serious implications for the treatment of cancer patients on a fish oil diet to fight cachexia.

Numerous clinical trials with an enteral formula containing ω-3 polyunsaturated fatty acids, L-arginine and nucleotides have been conducted in traumatized and surgical patients. Positive results were obtained in the majority of these clinical trials, in particular in the most recently published one [30]. These results encourage its use in cancer patients [31, 32].

Pharmacological Treatment of Anorexia-Cachexia

Pharmacological treatment of cancer anorexia-cachexia still remains disappointing. It includes appetite-stimulating drugs (corticosteroids and progestational agents), anabolic steroids, melatonin, insulin, growth hormone, insulin-like growth factor, and specific metabolic inhibitors and anti-cytokine drugs (thalid-
omide, pentoxifylline). The most studied drug is megestrol acetate, a progestational agent, which has resulted largely in the restoration of adipose tissue alone. This topic has recently been reviewed in detail by several authors [33, 34]. Since malnutrition and cachexia may be avoided in the vast majority of children with cancer, such drugs are not recommended for them.

**Conclusion**

In general, cancer malnutrition and cachexia are much less common in children than in adults. Moreover malnutrition is no longer acceptable in children with cancer in developed countries. Anticipation of problems and serial nutritional assessments from the time of diagnosis are essential. To maintain weight is the key to success. Restoring weight loss may be very difficult and as a consequence aggressive nutritional interventions, such as enteral nutrition and much more exceptionally parenteral nutrition, should as be considered early in the course of the disease and not be delayed for compassionate reasons. Initiation of feedings very early in the management may provide better improvement in outcome.

**References**

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Discussion

*Dr. Guesry:* What do you feed children to maintain their height growth after chemotherapy?

*Dr. Roulet:* We use special formulas for children less than 3 years old. Over 3 years we use the same formula that we use in adults. The energy and protein intake is increased to compensate for the weight gain in the recovery phase. During the first few weeks after chemotherapy, they receive at least 1.5–2 times the recommended amounts of energy and protein.
Dr. Guesry: My second question is related to the use of corticosteroids, particularly in acute lymphoblastic leukemia. These are known to impair height growth. What are the long-term height growth results in such cases?

Dr. Roulet: We are not particularly concerned with leukemia patients because they don’t have severe malnutrition, even if they are on corticosteroids, and their body composition is normal before they are treated with corticosteroids. I can only tell you that their growth is not very severely retarded by the treatment.

Dr. Jamal: As a comment on that, I find that the parents of children with acute leukemia are very happy with the induction treatment because the prednisolone actually improves their appetite. I have had no problems with malnutrition in leukemic children.

Dr. Vaithilingum: It pleases me as a pediatrician that you have pointed out the differences between adults and children, but it is also with great envy that I hear you say that only a very small proportion of them have significant malnutrition. We are of course looking after two completely different populations of patients, and I have a real problem with my patients presenting at diagnosis with significant malnutrition, often with weights of between 60 and 80% of the expected. Postulates might be that they present late with a much higher tumor burden, or that the population we look after may have a degree of underlying malnutrition which is just exacerbated by the onset of the malignancy. Because of the significant malnutrition, we anticipate major problems in terms of morbidity and mortality because of nosocomial infections and chemotherapeutic toxicity. What in your opinion would be the optimal management for patients with significant malnutrition, specifically those with acute lymphatic leukemia?

Dr. Roulet: I have no large experience with such malnourished leukemia patients, so I can’t answer that other than to say we would give such children short-term nutritional support, either by total parenteral nutrition or nasogastric tube, at the time of initial diagnosis and chemotherapy.

Dr. Vaithilingum: The impact of malnutrition on cognitive function is well known, but do you have any thoughts on the long-term effects of the added insult of cranial irradiation and intrathecal chemotherapy?

Dr. Roulet: We have too few patients to be able to answer that question definitively.

Dr. Jamal: From my personal experience, pediatricians in developing countries would like to work closely with dieticians, but we lack the resources and often do not have access to one.