Effects of Therapy on Nutritional Status of the Pediatric Cancer Patient

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Abstract

Children with cancer are at high risk for major nutritional problems both from the tumor itself and from the treatment administered. Overt malnutrition is seen in as many as 17% of children with newly diagnosed localized tumors and 37% of those with metastatic disease. Weight loss in children with cancer is directly correlated with a poor nutritional status at the time of diagnosis and with a low serum albumin. Massive surgical resections are a common source of nutritional problems and are usually not indicated as primary therapy in children with cancer. Both radiotherapy and chemotherapy are associated with recognized acute and long-term complications which may have an impact upon the nutritional status of the child. The majority of childhood cancers are best managed by a multidisciplinary approach including limited surgery, irradiation, and chemotherapy. This combined modality approach requires careful management including monitoring for known sequelae such that optimistic cure rates can be achieved without compromising the nutritional status of a child with cancer.

There is a paucity of information relating to the nutritional status of children with cancer, and few data differentiating the nutritional impact of the disease itself from that of the treatment administered. Modern pediatric cancer treatment affects normal tissues as well as malignant tissues and in so doing has the potential to create specific nutritional problems. In addition, a significant number of children are found to be malnourished at the time when their malignant disease is diagnosed. Thus, nutritional problems from the disease itself may soon be intensified by iatrogenic nutritional problems resulting from surgery, chemotherapy, and/or radiotherapy used to treat the cancer. The purpose of this review is to identify the effects of these modalities in an attempt to elucidate the areas of clinical and laboratory research which still require investigation with respect to nutritional studies in children with cancer.

Effects of Malignant Disease on Nutritional Status

While pediatric tumors are, as a group, responsive to therapy, it is well recognized that children with cancer often become ill rapidly and usually respond to treatment rapidly. A relatively brief period of symptoms related to the tumor may contribute to major nutritional sequelae leading to overt malnutrition in a surprisingly high percentage of children. Malnutrition in the pediatric population is generally considered to be present if there is inadequate growth, with a weight:height ratio below the 20th percentile of the national standard and/or a serum albumin value <3.0 g/dl (53).

The Diet, Nutrition, and Cancer Program of the NIH sponsored a cooperative randomized clinical trial which tested the value of hyperalimentation among 2 groups of children with cancer. One group included newly diagnosed children known to have abdominal or pelvic tumors. The incidence of malnutrition among these children was 7 of 40 (17.5%) (50). The second group included children known to have metastatic disease to or from the bone. Among 40 children in this group, overt malnutrition was diagnosed in 15 (37.5%) (50). Thus, overt malnutrition is not uncommon among children with cancer. The incidence is higher among those with advanced disease, but it is not limited to this group. Thus, at the outset, even before therapeutic programs are initiated, a significant number of children are found to be malnourished from the effects of malignant disease. Thus, these unfortunate children often enter aggressive therapeutic programs with the additional insult of little or no nutritional reserve.

The etiology of protein calorie malnutrition is inadequate intake for one’s caloric demands. Inadequate intake in a child with cancer often relates to the symptoms of the disease. A review of 244 pediatric cancer patients studied with respect to their nutritional status at the time of referral to pediatric cancer centers revealed a correlation between initial signs and symptoms of the disease and nutritional status. Various variables were evaluated as shown in Chart 1. It was seen that relationships among variables connected with a solid line were correlated positively, with the presence of one factor being associated with the presence of another. Thus, weight loss was directly correlated with a low nutritional status and with a low serum albumin. However, a low serum albumin and nutritional status at the time of first referral were not correlated. Fever and fatigue were directly correlated as common presenting symptoms of leukemia but were inversely correlated with abdominal mass. The constellation of symptoms of weight loss, anorexia, and poor nutritional intake (early satiety) as direct correlates relate to all pediatric tumors. Other causes of malnutrition in children include psychological factors, with learned food aversions associated with chemotherapy; malabsorption from radiotherapy or chemotherapy; excessive nutrient loss as with persistent nausea and vomiting, severe renal protein loss or steroid-induced diabetes; and major increases in caloric demands from the tumor itself.

Finally, the location of the tumor itself may have an impact on nutritional status. As the hypothalamus controls the regulation of food intake, it can be shown experimentally that destruction of the ventromedial hypothalamus causes hyperphagia and obesity, while destruction of the ventrolateral hypothalamus causes aphagia (2). Thus, tumors impinging in these areas produce similar results; children with hypothalamic

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tumors not infrequently present with this symptomatology. Diabetes insipidus is a presenting symptom of Hand-Schüller-Christian syndrome, and it is recognized to be associated with decreased food intake because of large volumes of fluid necessary to maintain water balance. An additional impact is the use of large numbers of calories to bring large volumes of cold water intake to body temperature. Such a caloric load may be a significant fraction of one's dietary intake (32).

Specific substances produced by endocrine glands or paracrine tumors may have nutritional consequences in children. Vasoactive intestinal peptide has been associated with a syndrome of watery diarrhea due to stimulation of small bowel secretions by the peptide hormone and is responsible for a syndrome of diarrhea with weight loss seen in children with neuroblastoma (54). In general, the patients with identifiable vasoactive intestinal peptide have had neuroblastoma or ganglioneuroblastoma with excretion of large amounts of catecholamine metabolites.

Effects of Surgery

The nutritional sequelae of surgical resection in the cancer patient have been reviewed in detail by Lawrence (31) and Shils (45, 46). Although the bulk of the literature has been directed to surgical procedures in the adult, identical observations will be seen in children when these procedures are applied to a pediatric population. However, because cancers in children are quite distinct from those neoplasms seen in the older age group, the appropriate surgical procedures for childhood cancers vary from those operations necessary for adult tumors.

The most common form of adult cancer in the United States is carcinoma of the gastrointestinal tract. Surgical resection is currently the primary approach to patient management of gastrointestinal tract tumors. Resection of the thoracic esophagus or stomach will invariably produce varied forms of malabsorption, particularly of ingested fat, but will also be accompanied by a reduction of caloric intake, which plays a primary role in leading to the malnutrition accompanying such operations. Massive small bowel resection inevitably is accompanied by major nutritional sequelae. The blind-loop syndrome which may accompany small intestine resection may lead to diarrhea, steatorrhea, anemia, weight loss, and multiple vitamin deficiencies. Large bowel resections may contribute to water and electrolyte loss. The recognized nutritional effects of these procedures include stasis, hypochlorhydria, diarrhea, steatorrhea, dumping syndrome, hypoglycemia, vitamin deficiency, fluid and electrolyte imbalance, acute and chronic malabsorption. Fortunately, primary gastrointestinal cancers in children are extremely rare; thus, these operative procedures are not applicable to a pediatric population. Nutritional consequences from major pancreatic or biliary surgery may be severe and associated with pancreatic exocrine and endocrine insufficiency; however, these procedures also are rarely, if ever, indicated in a pediatric population inasmuch as primary tumors in such organs are extremely uncommon in youngsters.

Major hepatic resection for malignant tumors imposes metabolic problems. Malignant liver tumors in infants, children, and adults require primary resection; however, still the survival rates are poor. Following hepatic resection, approximately only 36% of adults will survive (20). Hepatoma in infants and children is said to be less likely to metastasize than is the adult form of primary liver cancer. Operative death rate in infants and children is in the range of 23% with a 5-year survival of 33% (20). Patients with localized and solitary hepatic metastasis from other primary sites, such as primary Wilms' tumor, may also be candidates for partial hepatic resection. In addition, children may require partial hepatic resection for nonmalignant conditions such as hamartomas and hemangiomas.

Patients with primary or metastatic liver disease present in an undernourished state and require preoperative nutritional support as well as post-operative support with albumin and carbohydrate, to avoid the life-threatening biochemical and metabolic changes which can accompany major resection. McDermott et al. (33) have reported a significant drop in blood sugar following hepatic resections of 70% or more, and severe hypoglycemia has been noted in patients following total hepatectomy and liver transplantation. Others (1, 37) have noted less profound blood sugar changes following resection, perhaps because of the routine use of postoperative glucose infusion. It seems clear that the danger of hypoglycemia can be avoided by careful monitoring of blood sugar and continuous infusion in the early postoperative period. In addition, as the liver is the site of albumin synthesis, a significant hypoalbuminemia will occur unless replaced by parenteral administration. Failure to replace albumin will lead to a progressive fall in osmotic pressure in the vascular compartment and accumulation of marked interstitial fluid with increased vascular load and danger of pulmonary edema. Attention must be given to fibrinogen, prothrombin, and clotting factors synthesized by the liver which may fall following resection. The liver has a tremendous capacity for regeneration, allowing for major resections of up to 90% of the organ to be undertaken successfully. Optimal hepatic regeneration requires adequate nutritional support during this hypertrophic period when regeneration is at its maximum. Glucose, albumin, and vitamin levels generally return to normal as hepatic regeneration progresses.

Major surgery to the genitourinary tract may be accompanied by metabolic and nutritional sequelae. Urinary diversion and cystectomy for pelvic tumors may be associated with infection and electrolyte disorders. The procedure of ureterosigmoidostomy with implantation of the ureters was at one time fashionable for management of pelvic cancer in children. This procedure was often associated with ureteral obstruction and pyelonephritis, and often with hyperchloremia and acidosis. A clinical syndrome of thirst, anorexia, vomiting, fatigue, malaise, failure to grow, and vitamin D-resistant rickets with hyperchlo-
remic acidosis, hypophosphatemia, and hypokalemia was observed. Because of the metabolic and nutritional sequelae, ureterosigmoidostomy was replaced by cutaneous ureteroneocystostomy (ileal conduit). This procedure carries with it fewer metabolic problems as compared with ureterosigmoidostomy. Today, however, with childhood cancer which involves the pelvis and/or genitourinary tract, emphasis is upon "reasonable surgery" with maintenance of function and cosmesis. No longer is it appropriate to perform pelvic exenterations and major pelvic resections resulting in the sequelae described. Most retroperitoneal and pelvic neoplasms of childhood which once were managed by major surgical resections are now optimally managed with a multidisciplinary approach using minimal surgery, radiation therapy, and chemotherapy in an attempt to avoid these mutilating and deforming major resections.

Radical surgery for head and neck cancers is inevitably accompanied by mechanical alterations leading to chewing, taste, and swallowing problems with subsequent anorexia and diminished p.o. intake. Aspiration of food and problems with p.o. secretions lead to infection. No longer is it defensible to approach children with primary head and neck cancers with major surgical resection. Such difficult tumors of childhood, usually sarcomas, are optimally managed with a multidisciplinary approach involving limited surgery, radiotherapy, and chemotherapy. With such combined modality therapy, local control of tumors will be achieved in 89% of children, and three-fourths will be long-term survivors (13). Thus, as multi-disciplinary treatment programs are more widely used, nutritional problems related to surgery alone are less frequently observed.

Effects of Chemotherapy

Cancer chemotherapeutic agents are used today in the treatment of nearly all childhood neoplasms. The various agents available each affect host cells in individual ways providing a variety of side effects, e.g., nausea and vomiting, oral pain, diarrhea, anorexia, and weakness. Because many of the agents known to be effective today have differing side effects, multi-agent therapy is routinely used as primary management. Each of these antineoplastic agents produces biochemical and histological injuries to major organ systems, which may leave a child in a state of profound nutritional insufficiency. There has been surprisingly little attention given to the nutritional and metabolic consequences of modern chemotherapy as used in the treatment of childhood cancer. The nutritional sequelae of cancer chemotherapy as applied to the adult population have recently been reviewed (36). Thus, this paper is restricted to those agents used in the treatment of childhood cancer. It is particularly important to look critically at the acute and long-term effects of these drugs in terms of nutritional alterations that they may produce, because all children with cancer should be treated with curative potential. The majority of these will be long-term survivors.

The most common side effects of the agents used in treatment of childhood cancer are nausea and vomiting. These symptoms from antineoplastic agents are mediated by the chemoreceptor trigger zone located in the area postrema of the fourth ventricle (4, 10). This complication occurs with almost every major class of compounds including a majority of alkylating agents, the nitrosoureas, folate analogs, purine analogs, pyrimidine analogs, derivatives of hydrazine, anthracycline antibiotics, and other antibiotics and enzymes including asparaginase. Nausea and vomiting may be particularly violent and prolonged after procarbazine (6, 22, 47, 48), cis-diaminedichloroplatinum (24), and 5-azacytidine (29, 52) and may be dose limiting (Table 1). The presently available antiemetics are not wholly effective in the control of this drug-induced vomiting, and often vigorous sedation is useful. Vomiting caused by chemotherapy has responded to p.o. tetrahydrocannabinol (43). Its usefulness is currently under large-scale testing. There are only a few cancer chemotherapeutic agents in common use in pediatric oncology today which are not associated with nausea and vomiting. These include vincristine, steroids, and some of the alkylating agents.

Nausea and vomiting are accompanied by anorexia which results in decreased p.o. intake and also with fluid and electrolyte imbalance, weakness, and weight loss. Often these symptoms are accumulating through a course of chemotherapy. Many drugs are anorectogenic by causing an abnormality in taste. Disruption of the mucosa of the oral cavity, oropharynx, and upper gastrointestinal tract as seen with mucositis, cheilosis, glossitis, stomatitis, and esophagitis painfully interferes with ingestion of nutrients. Dose-limiting oral mucosal toxicities occur following administration of actinomycin D (30, 44, 49) and methotrexate (11). Severe oral toxicity also occurs with Adriamycin, daunorubicin, and 5-fluorouracil. Certain phases of the cell cycle are more sensitive to the cytotoxic effects of these drugs, although the cycle-nonspecific drugs also have greater effects on cells undergoing rapid turnover such as the epithelial cells of the gastrointestinal mucosa. Continual mucosal toxicity manifest as diarrhea may occur following actinomycin D, 5-fluorouracil, methotrexate, and 5-azacytidine. In severe cases, there may be proctitis, mucosal

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ulceration, and bleeding. Vincristine and vinblastine may cause constipation and even adynamic ileus.

Other significant chemotherapeutic toxicities which affect nutritional status include organ damage, particularly to the liver and pancreas. Anorexia is particularly common after hepatic injury. Malnutrition presenting with hypoalbuminemia is commonly seen with diffuse hepatocellular damage. Hepatic dysfunction is common after methotrexate (42), mithramycin (5), asparaginase (7, 8, 27, 35), and glutamine antagonists, such as azaserine and duazomycin (18). Jaundice related to 6-mercaptopurine has been reported in as many as one-third of the patients (17, 19). Several cases of hepatic fibrosis and cirrhosis have been reported in children after long-term therapy with methotrexate for leukemia and following treatment for psoriasis (42). In addition, asparaginase has been associated with 20% loss of body weight (36) and with pancreatitis. The toxic effects of host L-asparagine depletion by Escherichia coli asparaginase on the liver and pancreas are the result of inhibition of protein synthesis in these organs. Patients are observed to have biochemical evidence of hepatic functional impairment with hypoalbuminemia, hypocholesterolemia, and diminished blood-clotting proteins. The liver may show a fatty metamorphosis. It also can cause toxic effects on the central nervous sytem ranging from drowsiness to coma, thus compounding one’s inadequate nutritional intake.

With many of these agents, the clinical toxicity is closely related to the dose of the drug received and the duration of the administration. When methotrexate is given in high doses, one can obtain an enhanced therapeutic response by delivering high doses to the tumor while simultaneously sparing the patient from clinical toxicity by the adminstration of leucovorin rescue (21).

The corticosteroid hormones have known nutritional consequences, particularly evidenced after long-term administration. They exert an endocrine effect resulting in polyphagia, hyperglycemia and glycosuria as well as obesity. Fluid and electrolyte disturbances including edema and hypokalemic alkalosis may occur. Specific gastrointestinal toxicity includes peptic ulceration and acute pancreatitis. Thus, this class of drug, the hallmark of therapy for childhood leukemia, has important nutritional side effects.

Effects of Radiotherapy

Little attention has been given to the nutritional consequences of radiotherapy in infants and children. The acute and late manifestations of radiation effect from head and neck, thoracic, and abdominal and pelvic radiotherapy in the adult have been reviewed in detail (12, 16). It is well recognized that anorexia, loss of taste, xerostomia, and mucositis may accompany head and neck irradiation; dysphagia, nausea, and vomiting may accompany thoracic and abdominal irradiation; and diarrhea may accompany pelvic irradiation (Table 2). These acute effects are generally reversible and when given adequate supportive management are generally not considered serious deterrence to irradiation in the adult. However, because children have less nutritional reserve and are often malnourished at the initiation of therapy, one must give serious consideration to these acute effects before embarking upon a therapeutic program. Furthermore, of greater concern are the late consequences of radiotherapy in a population undergoing active growth and development. Late effects of radiotherapy, which have a great nutritional impact, include trismus, mandibular necrosis, dental caries, ulcer, chronic enteritis-colitis, and fistula (Table 2). Although difficult to prove, there is increasing evidence suggesting a predictive correlation between the presence of early injury from radiation and possible late effects. In a retrospective analysis of children from the Institut Gustave-Roussy who were reviewed for degree of injury following abdominal irradiation, it was observed that no child developed delayed enteritis (defined as nausea and vomiting accompanying small bowel obstruction) who had not previously had early enteritis (nausea and vomiting during the period of radiotherapy) (15). The observation of excessive and enhanced early radiation reaction should draw attention to possible late effects in the same patient. When these effects are associated with nutritional sequelae, one may anticipate potential late nutritional consequences. Because much radiation injury can be prevented altogether by attention to detail and supportive therapy before, during, and following irradiation, it is essential that a radiotherapist be closely involved with the total management of the planning and administration of therapy and continual follow-up.

A child undergoing head and neck radiation needs help in maintenance of good oral hygiene, mouthwashes, prophylactic dental care, daily fluoride treatments, use of p.o. antibiotics, and dietary supportive care. Gastrointestinal side effects of radiotherapy can be minimized by specific medications including antiemetics, antispasmodic-anticholinergic compounds, and antiinflammatory drugs. Attention given to the details of radiotherapy such as time, dose, fractionation, field size, and use of multiple ports are the safest ways to minimize bowel damage. It is well known that radiation injury is a function of volume treated and dose administered. There is some evidence to suggest that prostaglandin inhibitors may decrease radiation reaction (34) and that antiinflammatory agents such as salicylazosulfapyridine are capable of decreasing severe bowel injury (23).

In children, the use of specific dietary therapy has been demonstrated to be effective in the management of severe radiation bowel injury and in the prevention of such injury (15). In this study, a group of 44 children who underwent whole

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**Table 2**

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<th>Region</th>
<th>Early</th>
<th>Late</th>
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<td>Vomiting</td>
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<tr>
<td>Head and Neck</td>
<td>Odynophagia</td>
<td>Ulcer</td>
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<td></td>
<td>Xerostomia</td>
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<td>Mucositis</td>
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* Modified in part from Ref. 16.
abdominal irradiation as therapy for their malignant disease were evaluated. Thirty-one of 44 children (70%) were found to experience early reactions including vomiting and diarrhea during radiotherapy, among which 13 (30%) were classified as severe reactions requiring i.v. infusion replacement therapy. Of the 14 long-term survivors of their disease, 5 children (36%) later developed delayed radiation enteritis, presenting as small bowel obstruction. The factors believed to be contributory in this high incidence of bowel damage included the number and extent of previous abdominal surgical procedures, a young age, and the presence of concomitant chemotherapy, particularly actinomycin D. The 5 children developing the severe delayed radiation enteritis were all managed by a fractionated or continuous specific low-residue, low-fat (0.5 to 1 g/kg/day) diet, free of gluten, milk, and milk products. All 5 treated children had radiographic and histological reversal of severe bowel damage coincident with specific dietary therapy alone. All treated children continue to survive free of malabsorption or other intestinal symptoms. Following this dramatic observation, investigators at the same institution began the initiation of "prophylactic" dietary therapy to all children receiving whole abdominal or hemiabdominal radiotherapy. Since the routine use of this supportive measure, there has been no case of severe acute enteritis and no case of delayed enteritis, suggesting that dietary therapy may be useful in preventing radiation-induced bowel injury. This observation has led to the need to investigate the use of prophylactic nutritional support in children undergoing aggressive therapy, particularly abdominal-pelvic radiotherapy with concomitant chemotherapy.

Effects of Combined Modality Therapy

Modern pediatric oncological treatment today utilizes combined-modality therapy (surgery, chemotherapy, and radiotherapy) as initial planned therapy for virtually all children with malignant disease. The use of this combination therapy has pointed to the potential for interactions with or potentiation of the effects of single-modality therapy. These effects have been quantitated in terms of impact on critical normal tissues (38). There are, however, only limited data available on the nutritional complications of combined-modality therapy. Increased dermal and mucosal reactions have been observed when a range of antineoplastic agents are added to irradiation including actinomycin D (13), Adriamycin (14), methotrexate (3), and bleomycin (40). These reactions are particularly severe when drugs and irradiation are given concomitantly. Both actinomycin D and Adriamycin are capable of reactivating latent radiation effects with subsequent pulses of therapy, the so-called "recall phenomenon," which often severely limits nutrition during head and neck or esophageal irradiation. Severe esophagitis has been reported when combining irradiation with actinomycin D (26), and with vincristine-actinomycin D-Cytoxan chemotherapy (13). Severe reactions including esophageal stricture have been observed when utilizing radiation in combination with anthracycline compounds including Adriamycin and daunorubicin (25, 28).

Similar severe reactions have also been evidenced in the lower gastrointestinal tract in children, calling attention to the need for awareness of these enhanced reactions (9). The augmented radiation injury is most pronounced with the antineoplastic antibiotics, actinomycin D, bleomycin, and Adriamycin, all used frequently in the treatment of childhood cancers. The enhanced reactions of radiation and chemotherapy, each with independent cytotoxicity, in most cases display an additive reaction. However, actinomycin D and Adriamycin may be true radiation sensitizers and thus, when combined with radiation, may cause potentiation or synergism of their effects (39).

There is limited available information quantitating the augmentation of nutritional impairment that one should anticipate in children when chemotherapy and radiotherapy are used together. Experience with adults undergoing external-beam irradiation for head and neck cancers from Stanford University Medical Center revealed that 114 of 122 (93%) patients lost weight during a 6- to 8-week course of radiation, with an average weight loss of 3.7 kg (12). In another study of patients undergoing whole abdominal-pelvic radiation for non-Hodgkin's lymphoma at Stanford, 59 of 67 (88%) patients suffered weight loss during treatment with an average weight loss of 3.4 kg (12). Adult men undergoing combination chemotherapy of cis-platinum-vinblastine-bleomycin for Stage III nonseminomatous testicular carcinoma at Stanford, who required hospitalization between courses of chemotherapy for fever and neutropenia, exhibited a mean weight change of −2.9% body weight (16). This was more severe than in those who did not develop infection complicating the toxicity of mucositis and ileus from the chemotherapy.

Data relating to acute and long-term nutritional effects in children are even more sparse. The experience at the Institut Gustave Roussy among the children treated with whole abdominal irradiation and chemotherapy revealed that 24 of 44 (55%) lost weight during the course of radiation (15). A survey of the effects of leukemia treatment in children with acute lymphocytic leukemia at St. Jude's Children's Research Hospital revealed that, following systemic treatment and central nervous system prophylaxis, growth was slower than normal during the 2.5- to 3-year period of treatment (51). These investigators showed a delay in linear growth rate (height) in 12 of 22 children as compared to normal controls during therapy; however, all but 2 resumed normal or accelerated growth after cessation of therapy. When evaluating weights of these children, they found one child with a sustained accelerated weight gain for 5 years and 2 others with an accelerated gain after therapy was stopped. Five years after diagnosis, all other children had weights within 1 S.D. of normal average children.

Forecast for the Future

Effects from pediatric cancer treatment modalities, specifically chemotherapy and irradiation, are not confined to malignant cell populations. Current combined-modality therapy for pediatric cancers has its major impact on rapid renewal systems, especially skin, mucous membranes, and the gastrointestinal tract epithelium. This normal tissue morbidity has a direct effect on nutritional status. The toxicities of these therapies must be considered when planning treatment programs. More than 50% of children developing cancer today will be cured and will be long-term survivors (50). Thus, we must now look carefully at the complications from our therapies versus the potential benefits of such aggressive treatment programs. If the nutritional consequences from our therapies may be effectively prevented and/or treated by attention to supportive
therapy before, during, and following such aggressive treatment, such forms of therapy are justified. A prospective randomized clinical trial of the effect of nutritional support in children undergoing radiotherapy and chemotherapy has demonstrated that nutritional intervention at the initiation of therapy is capable of preventing weight loss, during a course of therapy. In children who were malnourished at the initiation of therapy, TPN3 was effective in maintaining or improving performance status during treatment and early follow-up period. In another study of TPN in children with advanced cancer, TPN was not only shown to support weight gain but was also associated with increased serum albumin, transferrin levels, and reversal of anorexia (41). However, in children who are not overtly or marginally malnourished at the time of treatment, TPN as supportive treatment has not demonstrated a durable effect in terms of maintenance of weight.

The need having been demonstrated for nutritional support in overtly and marginally malnourished children at the initiation of therapy, there are numerous questions which still must be addressed regarding nutrition with respect to therapy of the pediatric cancer patient. Such questions include: Is there improved tolerance to radiotherapy or chemotherapy by nutritional support? Can one prevent and/or protect against normal tissue injury from present chemotherapy/radiotherapy programs by nutritional support? Answers to these questions will require carefully planned and executed prospective clinical studies to determine the risk/benefit ratio of our treatments.

References

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Discussion

Dr. Filler: I'd like to cite a few differences between adult and pediatric cancer patients. First, chronic malnutrition in children is very unusual. When children are malnourished, it usually has been on a very acute basis. Second, these children do not have degenerative diseases. They are otherwise very healthy, and ordinarily by providing nutritional support for a short period of time, even as short as a month, as Dr. Rickard showed, one can get these patients back into what we would consider a perfectly good nutritional state. Tumors in children grow rather rapidly, and mothers and fathers quickly seek medical attention. By far the greatest problem in nutrition in the children with cancer occurs during therapy, as Dr. Donaldson said, and the therapy that's given for most childhood cancers involves surgery, radiation, and chemotherapy. The surgical procedures that we perform are major, but the complications that we make are minimal, and the nutritional intake following surgery. Children tolerate surgery very well, the wound infection rate is very much lower so that septic complications are fewer, and all of this tends to make a patient, from a nutritional standpoint, much less at risk. The malnutrition that we have seen in childhood cancer is documented in our own series. There were 68 patients in this study, and out of the 68, almost 50 of those patients required total parenteral nutrition for therapy-associated complications; when the therapy could not be given because of vomiting and diarrhea, total parenteral nutrition was started. In over two-thirds of those patients, the chemotherapy and radiation were continued despite the complications that had developed, and the chemotherapy and radiation were tolerated during that period of time. So while we might not be able to show a prophylactic effect in preventing the complications, it might very well be that we should look at it in a different way, that is, when the complications develop, how much can we do by treating with nutritional means versus not treating with nutritional support. That might be a much better way to look at this problem.

Dr. Jaffe: I would like to complement some of the information that has been presented by Dr. Donaldson. As we've heard, both the tumor and therapy may be determinants of nutritional complications. The complications and the symptomatology may continue unabated with treatment despite apparent responses of the tumor, and I would like to present the results of an investigation which we conducted at the M. D. Anderson Hospital and Tumor Institute demonstrating that reduced dietary intake induced by chemotherapy was responsible for overt malnutrition. The effects appear to be more profound in preadolescent and early adolescent patients. These patients, although they received possibly more intensive treatment than the others, nonetheless did display more severe effects of the chemotherapy. In particular, these effects occurred despite apparent disappearance of disease and the beneficial responses to treatment. The patient population was as follows. All newly diagnosed patients referred to the M. D. Anderson Hospital and Tumor Institute from January 1, 1979, to March 31, 1980, were evaluated. Let us now outline the 24% who demonstrated overt malnutrition. The initial change in weight-height over the first 6 months was as follows: osteosarcomas, 75%; Ewing's sarcoma, and soft-tissue sarcoma. Patients with Hodgkin's disease, lymphoma, and leukemia did not demonstrate aberrations in nutrition. The effects appear to be more profound in patients with osteosarcoma, Ewing's sarcoma, and soft-tissue sarcoma. Patients with Hodgkin's disease, lymphoma, and leukemia did not demonstrate aberrations in nutrition, and it was determined that this was probably due to the corticosteroid administration which accompanied the chemotherapeutic regimes in these patients. Also, these patients seemed to have less nausea and vomiting accompanying the administration of chemotherapy. The average caloric intake (relative to recommended) of the initial 6 months was as follows: osteosarcomas, 75%; Ewing's sarcoma, 60%; neuroblastoma, close to 100%. Patients with soft-tissue sarcomas had close to 95% of the recommended caloric intake in contrast to those with osteosarcomas in whom profound nutritional disturbances were also detected. Now we had earlier brought up the question of the effects of different types of tumors, and I think that this is important. Possibly, some tumors do react differently than others; also the different chemotherapeutic agents may affect patients differently, and this may in fact be responsible for different nutritional aberrations observed in different groups. There was no difference in the albumin concentration in these patients despite the tremendous changes in weight that we observed and the caloric intake that the different patients experienced. We found that the average protein intake over the initial 6 months was quite satisfactory, and this was reflected in the serum albumin. The administration of aggressive chemotherapy during the first 6 months does not affect the serum albumin, and the protein intake is generally satisfactory. What was particularly interesting to me was the soft-tissue sarcoma patients. There was a tremendous weight-height loss, yet their intake was adequate. This contrasts with osteosarcoma patients for whom there was also a weight-height loss and there was a poor intake. I could account for that in the osteosarcoma group but not in the soft-tissue sarcoma patients.

Dr. DeWys: Your data suggest that patients with soft-tissue sarcomas were more likely to be hypermetabolic.

Dr. Jaffe: Right.
Effects of Therapy on Nutritional Status of the Pediatric Cancer Patient

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