A SUPPLEMENT TO

Oncology Issues

Oncology Economics & Program Management

Volume 17, No. 2 March/April 2002

ACCC

Association of Community Cancer Centers

11600 Nebel Street, Suite 201
Rockville, MD 20852
www.accc-cancer.org

Integrating Nutrition into Your Cancer Program

Publication and distribution of *Integrating Nutrition into Your Cancer Program* are made possible by an educational grant from Ross Products Division, Abbott Laboratories

Published by the Association of Community Cancer Centers

The mission of the Association of Community Cancer Centers is to promote the continuum of quality cancer care (research, prevention, screening, early detection, diagnosis, treatment, psychosocial services, rehabilitation, hospice) for patients with cancer and the community.

Integrating Nutrition Into Your Cancer Program

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Oncology Issues
Vol.17 No.2 March/April 2002

The Design and Implementation of a Model Nutritional Oncology Clinic

by Faith D. Ottery, M.D., Ph.D., F.A.C.N.,
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Four principles—early diagnosis, an improved understanding of carcinogenesis, multimodality therapy, and interdisciplinary approaches—have markedly improved oncologic outcomes during the latter half of the 20th century. In contrast, the approach to nutritional intervention in oncology during this same period has been characterized by late diagnosis, limited understanding of the pathophysiologic basis of weight loss and cachexia, single-modality therapeutic approaches, and a lack of integration. Designing and implementing successful research and clinical programs in nutritional oncology require using the four principles associated with oncologic success.

Nutritional oncology, as an integrated approach, was initially defined in the mid-1990s as the field of science and medicine that addresses the totality of interaction of nutrients and nutritional factors with cancer—spanning the spectrum of carcinogenesis and cancer prevention, adjunctive therapy, and supportive nutritional intervention.[1] During the past decade, clinicians and researchers in the field have:

- created standardized ways to assess nutritional risks and deficits and how they will affect clinical outcomes
- made extensive progress in understanding the cytokine-mediated and noncytokine-mediated catabolic stresses that contribute to progressive weight loss and malnutrition
- found ways to treat nutritional deficits using both drugs and nonpharmacologic interventions
- developed integrated algorithmic approaches to incorporate medical, nutritional, physical, and psychological interventions that work synergistically to support a patient's nutritional status, body composition, immune competence, functionality, and quality of life.[2-13]

Several organizations have developed guidelines for the nutritional care of cancer patients, including the American Dietetic Association, the Oncology Nursing Society, and the Association of Community Cancer Centers (ACCC). According to ACCC nutritional guidelines, nutrition should be discussed with all patients and their families, especially those patients who have been identified to be at nutritional risk. In addition, the clinician responsible for nutritional support should work with the patient and the patient's family to manage nutrition and hydration so they facilitate optimal health in the presence of disease and therapy. And finally, the clinician responsible for nutritional support provides dietary guidelines on reducing cancer risk through program materials and services to the community.

The practical translation of these guidelines is difficult without an integrated approach. Nutritional intervention in oncology has frequently been rather one-dimensional. Nutritional problems have been addressed in isolation: determining calorie goals with little attention to protein needs, using guidelines developed for healthy individuals, ignoring the metabolic problems created by the complex interplay of catabolic and anti-anabolic stresses (Table 1), and not appreciating the importance of inactivity on progressive muscle wasting, which adversely impacts performance status and fatigue. Nutritional problems are commonly addressed reactively rather than proactively, which has led to patients being offered interventions only when they are moderately to severely malnourished and wasted.

Nutritional assessments and interventions are often considered the exclusive domain of the dietitian or nutritionist. Many oncology clinics have no designated dietitian, even though they are working with a nutritionally high-risk population. Since the services of nutritionists are often not reimbursed by third-party payers, some institutions and practices consider nutritionists as a "cost center" and not as clinicians who can prevent complications in their patients and save the institution or practice money in the process.

Nutritional intervention in any patient is most appropriately seen as supportive. However, other factors must be considered as well, since oncology patients with poor nutrition suffer from increased treatment toxicities and respond less well to their antineoplastic therapy. Intriguing animal studies were published from the 1980s to the mid-1990s addressing the effect of diet composition, particularly protein, on therapy toxicity. The parameters that were addressed included mortality, drug clearance, tumor cell cycle kinetics, intratumoral concentration of chemotherapeutic agents, tumor response to cell cycle-specific chemotherapy, and the effects of diet on host body composition, host immunocompetence, and host marrow kinetics.[14-24] The translation of these results to clinical applications for humans has been severely limited by the lack of well-designed human clinical trials.

GOALS AND PRINCIPLES OF NUTRITIONAL ONCOLOGY

The obvious goal of nutritional intervention in cancer patients is to prevent or reverse the progressive weight loss that is seen in 80 to 90 percent of the oncology patient population at some point in their disease. However, even this simple goal is rarely achieved, and there has been no

real progress in impacting the gold standard of survival.

The three common frustrations of practitioners who use nutritional therapies to combat weight loss in cancer patients are 1) lack of consistent reversal of weight loss with intervention, 2) lack of repletion of lean tissue or muscle, and 3) lack of translation of any change in weight or nutritional parameters into improved oncology outcomes.

This relative lack of success is primarily due to a one-dimensional approach that does not integrate nutrition into a program of comprehensive cancer care. However, a definition of integrated intervention has been developed to support anabolism, or, more globally, anabolic competence. Such competence has been defined as a state that optimally supports protein synthesis and lean body mass, i.e., anabolism, as well as global aspects of muscle and organ function, immune competence, functionality, and quality of life.

This new approach is illustrated in Figure 1 and demonstrates the importance of addressing all three primary components of intervention: the nutrition of the host, the hormonal milieu of the host (including both classic hormones and cytokines), and exercise.

The most fundamental way to support anabolism is

Figure 1. Anabolic Competence

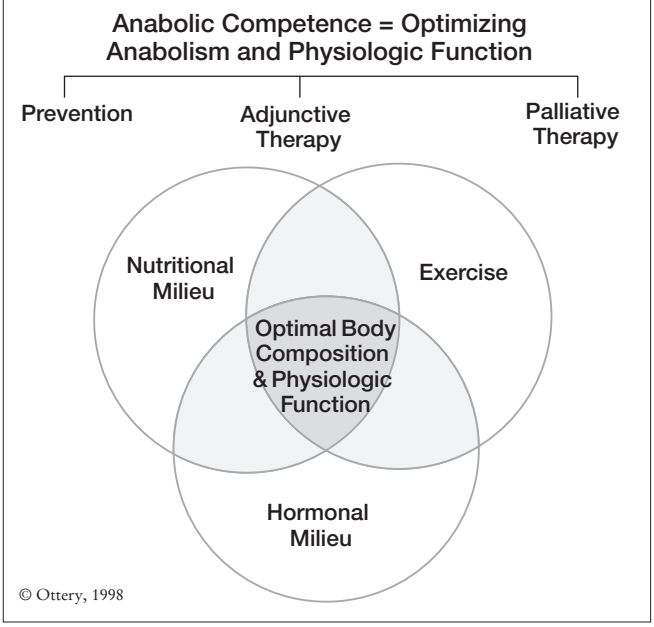


Table 1. Summary of Potential Catabolic and Anabolic Forces in the Cancer Patient

Catabolic Forces

Tumor/Host Related
Proinflammatory, cytokine-mediated catabolism
Anorexia

Therapy Related
Surgery
- Peri-operative catabolism

Chemotherapy
- Neutropenic fevers
- Infection
- Sepsis

Biologic Response Modifiers
Radiotherapy
- Inflammatory response
- Infection

} Cytokine and non-cytokine mediated metabolic changes

Mechanical impediments to adequate intake
Mechanical or physiologic impediment to absorption
Pain
Inactivity or bedrest
Increased work of ADLs associated with decreased muscle mass
Pulmonary insufficiency alone due to increased work of breathing or with complications such as atelectasis or pneumonia
Corticosteroid use – chemotherapy premedication, "inexpensive" appetite stimulant, anti-inflammatory with intracranial tumor, certain chemotherapy protocols, therapy for COPD

Anabolic Forces

Tumor/Host Related
Anticachectic cytokines

Therapy related
Surgery
- Successful tumor resection

Chemotherapy
- Successful CR

Radiotherapy
- Resolution of acute inflammatory response
- Successful CR

} Cytokine and non-cytokine mediated metabolic changes

Parenteral nutrition with insulin infusion
Enteral nutrition, oral nutrition
Resolution of impediments to intake, digestion, and absorption
Pharmacologic options
- Orexigenic agents (appetite stimulants)
  - Progestational agents, cannabinoids
- Antimetabolic/Anticatabolic Agents
  - Melatonin
  - Thalidomide
  - COX-2 inhibitors including NSAIDS
  - omega-3 fatty acids (EPA, DHA)
- Anabolic Agents
  - Anabolic androgenic steroids
  - Growth hormone

Abbreviations: CR = complete response; ADLs = activities of daily living; COPD = chronic obstructive pulmonary disease; NSAIDS = nonsteroidal anti-inflammatory drugs; COX-2 = cyclooxygenase –2; EPA = eicosapentaenoic acid; DHA = docosahexaenoic acid

to make sure the body has the right nutrients to make the amount of protein and energy it needs. However, as has been demonstrated in a number of clinical studies and animal models, providing the nutrients alone often does not ensure optimal protein synthesis and body composition.

Understanding anabolic competence and consideration of the catabolic and anabolic forces summarized in Table 1 are changing the way we design interventions to support patients through antineoplastic therapy, and are doing so in a manner that markedly increases our chances of improving oncologic outcomes. To successfully support the cancer patient through antineoplastic therapy, one must thoughtfully address each component of the anabolic competence paradigm, including:

- Providing adequate nutrients to support the estimated protein and energy goals (0.7 gm/lb ideal weight and ≥ 18 kcal/lb current weight, respectively).
- Promoting exercise, particularly progressive resistance exercise such as working with light weights or variable resistance exercise bands. Studies[25,26] have demonstrated that even one week of bed rest is associated with quantifiable changes in body mass and metabolism. Healthy volunteers who experienced seven days of complete bed rest had substantial functional, morphometric, and metabolic abnormalities, with a 1 to 4 percent decrease in the muscle volume of the back and lower extremities quantified by magnetic resonance imaging (MRI) and a 2 to 5 percent increase in fat in the lower extremities.

Decreased glucose tolerance, increased peripheral insulin resistance, and a possible decrease in skeletal muscle protein synthesis have also been reported.[25]

- Optimizing the hormonal milieu to combat both classic hormonal abnormalities and cytokine-mediated metabolic changes. Anabolism can be severely compromised by any of the following hormonal alterations: hypo- or hyperthyroidism, glucose intolerance or insulin resistance, symptomatic hypogonadism, use of exogenous corticosteroids, and the presence of a significant proinflammatory cytokine response.
- Supporting optimal muscle mass by decreasing muscle protein breakdown, increasing muscle protein synthesis, or a combination of both therapies.

SPECIFICS OF CLINIC DESIGN

A nutritional program for a cancer clinic must be designed to meet the needs of the patient population the clinic serves. In the broadest application, a nutritional oncology program should fulfill a mission of:

- patient care, education, and research
- prevention, adjunctive therapeutics, and supportive care
- consideration of special needs groups defined by age, socioeconomic status, literacy, ethnicity, or any other pertinent factor
- epitomizing the concept of interdisciplinary rather than multidisciplinary care by creating a program that integrates the services of physicians (surgeons, medical and radiation oncologists, and primary care providers), nurses, dietitians, allied health professionals (including social workers, physical therapists, occupational therapists, dentists, speech pathologists, respiratory therapists, and psycho-oncologists), and specialists in pain and symptom management, palliative care, and hospice care.

The algorithmic approach described in Figure 2 can be used to meet the most critical need of reversing significant weight loss in cancer patients. The approach is also useful for reducing the weight gain experienced by women undergoing adjuvant hormonal therapy for breast cancer. Interestingly, significant weight change in either direction may adversely impact oncologic outcomes.

In addition to addressing the issues that surround nutritional intake during cancer therapy, the clinic is often seen as a resource for information regarding the use of nutrients during therapy. Although the specifics of requirements appropriate for clinical use in this patient population have not yet been adequately researched, a large number of studies have looked at the use of vitamins, minerals, and micronutrients during therapy and are summarized by Kucek and Ottery on page 24 of this supplement. The National Center for Complementary/Alternative Medicine (NCCAM) of the National Institutes of Health is working to define the questions that need to be studied on the use of specific micronutrients during therapy. A conference on antioxidants and cancer chemotherapy and radiation therapy is tentatively scheduled for June 2002. Check the Conferences section of the NIH Office of Dietary Supplements' web site at *http://ods.od.nih.gov*.

To design a successful nutrition clinic, it important to remember the goals of supportive nutrition defined above. Clinicians involved in nutritional oncology research and practice have expressed concerns that as patients and patient advocacy groups have become increasingly vocal about the use of complementary and alternative medicine, nutrition is being addressed primarily or only in the context of vitamin therapy, specific dietary regimens such as macrobiotics, herbal support of immune or hepatic function, and detoxification regimens. While discussions with patients about the use of complementary therapies are important, the nutritional oncology team must understand the fundamentals of nutritional intervention and the way nutrition and cancer therapy interact and affect oncologic outcomes.[27]

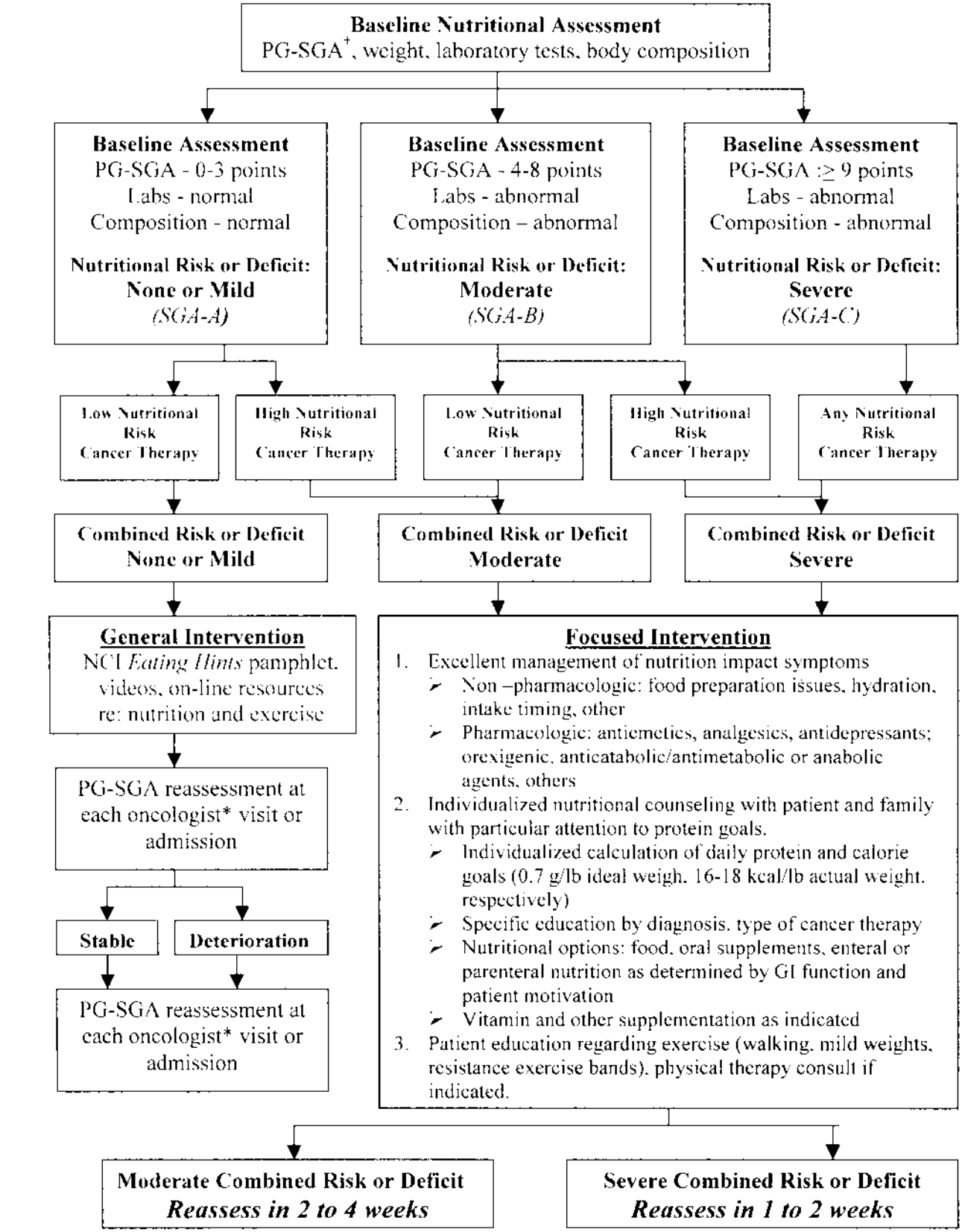
MAKING THE CLINIC WORK

While published experience with integrated nutritional oncology programs is limited, there are a number of integrated nutritional oncology pilot programs throughout the country in both academic and community-based settings. Successful programs include the following elements:

Standardized assessment tools. Using standardized tools to assess nutritional risks and deficits can help streamline the assessment process. A nutritional assessment must be easy to perform and add little or no time to the clinical process or it will not be used.

The Patient-Generated Subjective Global Assessment (PG-SGA) is a one-page form that 1) is completed primarily by the patient, 2) addresses all relevant aspects of clinical care (weight history, intake, symptoms, performance status, diagnosis, metabolic stress, and physical exam), 3) is appropriate for inpatient, outpatient, home care, and hospice settings, 4) can determine both the degree of nutritional risk and the effect of that risk on oncologic outcomes, and 5) has high sensitivity and specificity when compared with other

Figure 2. Algorithm of Optimal Nutritional Intervention



† Patient-Generated Subjective Global Assessment

*Medical oncologist: every 3 to 4 weeks, radiation oncologist: weekly

validated nutritional assessment instruments.[2-4] Resources to explain how to use the PG-SGA are available,[5-7] including ACCC's web site at *www.accc-cancer.org/publications/pgsga.pdf*.

The effect of nutritional status on quality of life can be assessed using the Functional Assessment of Anorexia/Cachexia Therapy (FAACT) questionnaire.[28] (The FAACT tool is available to view at www.accc-cancer.org/publications/faact.pdf.)

A proactive approach. Clinics must recognize the importance of proactive rather than reactive assessment and intervention. Patients should be screened as early as possible in the course of their disease and treatment.

An integrated, algorithmic approach. Algorithms that integrate the various medical disciplines into one nutritional care team should be used instead of models that receive information from each discipline and combine them in a multidisciplinary, segmented fashion (see Figure 2).

A leader with expertise in nutrition. The nutrition program should be led by a physician or other influential clinician with recognized expertise in nutrition or supportive care. This individual should believe in the importance of integrating nutritional oncology into standard oncology practice, demonstrate a respect for the collaborative expertise brought to the program by the interdisciplinary team members, and serve as an advocate for the integrated nutritional oncology program.

A full range of educational resources. Educational resources for all clinicians involved in patient care should be developed, including referring physicians and managed care and third-party payers. Teaching rounds, presentations, printed materials, research studies, and online resources should be used. Educational resources for patients and families should include printed materials (including patient education cards for each disease or condition), audiovisual aides, such as videos or CDs, in-hospital and community-based television programs, small educational groups, community-based educational programs, and listings of other noninstitutional resources.

In conclusion, a successful nutritional oncology practice and/or research program must be based on the four principles that have led to improved therapeutic outcomes in oncology during the past 50 years: early diagnosis, understanding of pathophysiology, inclusion of multimodality therapy, and interdisciplinary approaches. Adherence to these four principles offers an excellent opportunity to improve outcomes and to truly change the face of oncology.

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The Multi-Dimensional Role of the Dietitian at Your Cancer Center

by Sandra Luthringer, R.D., L.D.

A comprehensive nutritional program can benefit every area of patient care within a quality oncology program. Key to the delivery of nutritional services is the registered dietitian (R.D.), who can help the entire cancer care team.

The R.D. plays an important role in cancer prevention as well as in helping patients with cancer maintain their quality of life. The dietitian routinely screens and assesses new patients, makes post-treatment and recovery nutrition plans, and helps patients in clinical trials cope with their unique nutritional needs. In addition, dietitians help educate patients, their families, and the general public about oncology nutrition by developing informational materials and distributing them. Furthermore, dietitians work with palliative and end-of-life issues in the hospice setting.

The American Dietetic Association (ADA) reports that 65 percent of its nearly 70,000 members are employed in client or patient counseling in a health care setting.[1] The Oncology Nutrition Dietetic Practice Group (ON DPG), a subgroup of the ADA, has more than 1,100 nutrition professionals who work specifically in oncology-related fields, including prevention, treatment, research, survivorship, palliative care, and hospice.

DIRECT PATIENT CARE

Clinical studies have shown that many human cancers are influenced by diet[2,3] and that approximately one-third of the annual cancer deaths in the United States are related to dietary factors.[3]

Early detection of nutritional problems is essential for a successful therapeutic outcome, and dietary modifications and other interventions should begin early in the treatment course. When patients with cancer find that they can mitigate the side effects of their treatment through what they choose to eat, they feel as if they are actively participating in their own recovery.

Once the patient has been evaluated, the dietitian can help plan meals to correct existing nutritional deficiencies, maintain weight, and improve and maintain the patient's nutritional status throughout the treatment and recovery process. The dietitian will follow patients closely during their entire clinical course, working with the doctors, nurses, social workers, and other cancer care professionals at the treatment center.

If the disease progresses, nutritional intervention will focus more on ensuring optimal quality of life through symptom management and prevention of further complications. Maintaining energy and strength through adequate nutritional intake directly affects a patient's ability to perform the activities of daily living and to function independently for as long as possible. Dietitians are an integral part of the home health care and hospice teams as they guide patients through the end of their life.

PATIENT EDUCATION

Within the community cancer center, dietitians have many opportunities to develop educational materials for patients, their families, and the general public. Patient newsletters are a good place for dietitians to contribute articles on topics ranging from food tips and recipes to easy-to-read reviews of the scientific literature.

If your cancer center has a web site, the dietitian can write a nutrition column for it, which can be updated frequently with a "tip of the month" (or tip of the week) and might include seasonal recipes or symptom management techniques.

Speaking engagements, health fairs, newspaper articles, and radio/TV spots can help disseminate the message of nutrition for cancer prevention to the public, and the dietitian can be an asset to your public relations staff by developing many educational materials for your center.

PROFESSIONAL EDUCATION

Via lectures, in-house newsletters, or presentations, dietitians should be an integral part of the ongoing education of professional staff, keeping everyone updated on current nutritional issues and developments in the nutritional screening and assessment process. Dietitians can also be a source of information about complementary and alternative medicine (CAM) therapies, many of which have nutritional components.

In summary, the R.D. can educate, advise, and guide other oncology care team members in a mutual effort to bring the highest quality of nutritional and comprehensive care to patients with cancer and to the community. Proactively addressing nutrition can improve patient welfare in every area of a quality cancer program.

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Oncology Nutrition Standards of Care

by Dee Gabbard, R.D., C.D.,
Sandra Luthringer, R.D., L.D.
and Barbara Eldridge, R.D., L.D.

Standards of care refer to those tools that provide guidance on how optimum patient care should be delivered. Standards include practice guidelines, protocols, or clinical pathways that are used to validate or refine the delivery of care.[1]

In 1996 the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) released detailed standards of practice for nutrition that required all patients to be screened for nutritional risk within 24 hours of admission,[2] followed by nutrition assessments and interventions for those who are identified as being at risk. In 2001 JCAHO published additional standards that require ambulatory care organizations to use clinical practice guidelines to evaluate and treat patients with a specific diagnosis, condition, or symptom.[3]

THE TRIO OF NUTRITION STANDARDS

Facilities often develop their own standards of care and present them as policies and procedures. The American Dietetic Association (ADA), the National Comprehensive Cancer Network (NCCN), and the Association of Community Cancer Centers (ACCC) have developed their own standards of nutritional care specific to oncology.

The American Dietetic Association (ADA) is the nation's largest organization of food and nutrition professionals. Its members include dietitians, dietetic technicians, and students. Members work in a variety of settings including health care, business, research, and education. Within the ADA is the Oncology Nutrition Dietetic Practice Group, which has more than 1,100 members and consists of dietitians who work in all aspects of oncology nutrition.

The ADA provides Standards of Professional Practice for all dietetic professionals in all settings.[4] Guides for practice specific to the oncology population are available in the ADA document *Medical Nutrition Therapy Across the Continuum of Care*, second edition. This publication consists of medical/nutrition therapy protocols that were developed by consulting nutrition experts, oncology clinicians, and the available research. Screening, assessment, interventions, and outcome measures for those in treatment or recovery are provided.

These protocols were consensus-based in the past, but are currently being revised to reflect evidence-based practices. Government agencies, professional associations, and health systems increasingly need to use evidence-based practices since the goals of quality patient care and cost effectiveness are becoming inextricably combined in medical treatment.[5]

The ADA protocols are thorough and include suggested length of visits, step-by-step interventions, and expected outcomes. They do not, however, address palliative care. As the term "guideline" infers, these protocols are flexible since reimbursement and support for services, for example, vary among institutions. Furthermore, ADA is upgrading these protocols to reflect current research, making them evidence-based. This upgrade will improve clinical outcomes, economic outcomes, and patients' quality of life.

The National Comprehensive Cancer Network (NCCN) is a not-for-profit corporation composed of 19 of the leading cancer centers in the United States. The NCCN has three key programs to improve cancer services: practice guidelines, an outcomes database derived from information from NCCN members, and information services.[6]

An interdisciplinary panel has drafted nutrition care guidelines, which should be released in spring 2002. These standards of care will focus on weight loss as a risk factor and will include both medical management and nutritional interventions for symptoms such as mucositis and poor oral intake.

The *Association of Community Cancer Centers* (*ACCC*) promotes quality cancer care in the community hospital and office practice setting. ACCC members represent more than 680 medical centers, hospitals, cancer clinics, and private practices across the U.S.[7]

In March 2000 ACCC issued standards to assist cancer programs in designing and/or maintaining a comprehensive interdisciplinary program that meets the needs of patients and families. ACCC cannot accredit or credential such programs,[8] but its standards provide a model for cancer centers.

ACCC's nutrition support standards have three parts:

- *Standard I* states that a nutritionist should be available to work with patients and their families, especially those identified at risk for having nutritional problems or special needs. The nutritionist should have education and experience in the specialized nutritional needs of patients with cancer and in minimizing the risk of cancer through dietary counseling. Staffing of nutritionists should be adequate to meet the needs of cancer patients

Table 1. Common Toxicity Criteria (CTC)

Toxicity Grade	Definition
Grade 0	< 5%
Grade 1 (Mild)	5–9.9%
Grade 2 (Moderate)	10–19.9%
Grade 3 (Severe)	≥ 20%
Grade 4 (Life-Threatening)	No Criteria Defined
Grade 5 (Death)	

Source: National Institutes of Health. Available at http://ctep.cancer.gov.

and their families. The nutritionist provides education to medical and nursing staff to ensure appropriate assessment and referral of patients.

- *Standard II* states that the nutritionist in conjunction with the patient, family, and oncology team manages nutrition and hydration.

- *Standard III* states that the nutritionist provides dietary guidelines on reducing cancer risk through program materials and services to the community.

These standards clearly define nutritional care across the continuum of cancer prevention, medical care, survival, and palliation and recognize the role of family and caregivers. Though brief and concise, they incorporate JCAHO standards and can be useful for programs seeking to establish a more comprehensive approach or trying to improve their nutritional services.

EVALUATING WEIGHT LOSS

Achieving and maintaining appropriate weight for height should be an integral part of the overall goals for nutrition therapy.[9] The weight lost during cancer therapy is more often muscle tissue (lean body mass) and not fat stores. Since weight loss can contribute to fatigue and delay and lengthen recovery,[10] the maintenance of lean tissue and body cell mass during treatment and recovery should be encouraged, even if individuals are overweight. If weight loss is desired, it is best initiated after treatment, under the guidance of health care professionals.[11]

Both the Common Toxicity Criteria (CTC) and the Scored Patient Generated-Subjective Global Assessment (PG-SGA) evaluate weight loss and the patient's risk of malnutrition. The National Cancer Institute (NCI) requires that cancer patients be closely monitored for the occurrence of treatment-related adverse events and late-occurring adverse events (adverse events occurring more than 90 days after treatment).[12]

The CTC defines commonly experienced adverse events using a scale from 0 to 5. Adverse events graded 1, 2, or 3 (mild, moderate, or severe) generally cause patients to experience pain and discomfort and can require the use of supportive therapies such as medication, blood products, IV fluids, delays in treatment, and even hospitalization. Grade 4 adverse events are typically described as life threatening or disabling and require hospitalization and often withdrawal from treatment. Grade 5 adverse events result in death. Weight loss is included in the Constitutional Symptoms section of the CTC list of side effects, and Table 1 describes the weight changes seen in cancer patients and ranks them from 0 to 5 on the CTC scale.[12]

The Scored PG-SGA, a screening and assessment tool, which was adapted from the original Subjective Global Assessment developed by Detsky, also includes criteria with which to evaluate weight loss in cancer patients.[13-15] The Scored PG-SGA weight loss criteria are described in Table 2.[16]

Both the CTC and the PG-SGA have sections that address the significance of weight loss, but the PG-SGA criteria include a time-frame parameter and so are likely to be a more accurate reflection of the patient's degree of malnutrition. The following examples highlight the differences between these tools. To learn more about the PG-SGA tool, visit *www.accc-cancer.org/publications/pgsga.pdf.*

> Facilities often develop their own standards of care and present them as policies and procedures. The American Dietetic Association (ADA), the National Comprehensive Cancer Network (NCCN), and the Association of Community Cancer Centers (ACCC) have developed their own standards of nutritional care specific to oncology.

Example 1. A 66-year-old man weighing 110 pounds presents to the oncology unit with a 1.5 pack-per-day smoking habit over 45 years and a weight loss of 14 pounds over a one-month period (11 percent weight loss). He says that he now has a very poor appetite, decreased taste, difficulty with swallowing, little energy, and has a past history of chronic alcohol abuse. He is subsequently diagnosed with head and neck cancer and begins a course of chemotherapy and concomitant radiation therapy, followed by a possible neck dissection.

Example 2. A 45-year-old woman weighing 230 pounds is diagnosed with ovarian cancer. When she comes to the clinic, she is post-surgery and is undergo-

Table 2. PG-SGA – Scoring Weight Loss

Weight Loss in 1 Month	Points*	Weight Loss in 6 Months
10% or greater	4	20% or greater
5 to 9.9%	3	10 to 19.9%
3 to 4.9%	2	6 to 9.9%
2 to 2.9%	1	2 to 5.9%
0 to 1.9%	0	0 to 1.9%

*Scoring is defined as none, mild, moderate, severe, and life-threatening.

Source: The Clinical Guide to Oncology Nutrition. American Dietetic Association 2000

ing chemotherapy. She reported nausea, fatigue, and loss of appetite during chemotherapy and lost 34 pounds
(15 percent weight loss) over her six-month course of treatment.

Both individuals have experienced a loss of body weight. The CTC grades both weight losses as "2" or "moderate" weight loss, and time frame is not considered. When the Scored PG-SGA is used, the weight losses are evaluated quite differently. The man in Example 1 receives four risk points for an 11 percent weight loss that occurred over only one month. After his full work-up (patient history, disease, metabolic stress, and nutrition-related physical examination) using the PG-SGA by the health care team, he most likely will be considered Stage C or severely malnourished. Since the woman in Example 2 sustained her 34-pound weight loss over six months, she is given three risk points for weight loss. After her work-up she will most likely be considered Stage B, moderately malnourished or suspected malnutrition, despite her obesity.

While the CTC and the Scored PG-SGA both evaluate weight loss and the patient's risk of malnutrition, cancer care professionals should be aware that very different values can be obtained. In addition, cancer care professionals need to consider how the weight loss has occurred and the impact of symptoms, treatment modalities, and treatment-related side effects on nutrition status when determining the appropriate nutritional intervention.

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Nutritional Screening and Assessment: An Overview

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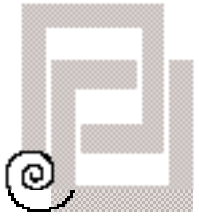

While scientific discoveries continue to advance our understanding of the cancer process and many therapeutic advances have been made, the management of nutrition in cancer care remains a major challenge. More than 50 percent of cancer patients have already lost weight at the time of diagnosis[1-3] and in some types of cancer, weight loss occurs before any other symptoms manifest.[2]

Weight loss and pronounced nutritional depletion are often considered to be symptoms of advanced malignancy, caused by the metabolic needs of the tumor taking precedence over the needs of the host.[2] Although the incidence of weight loss varies widely by tumor type, survival is shorter in patients who experience weight loss.[4] Weight loss and poor nutritional status can also exacerbate the toxicities associated with cancer treatment (which interferes with the patient's ability to respond to therapy)[1] and reduce immunocompetence (which increases the patient's risk of infection).[1,5] Understanding the role that nutrition plays in the management of cancer and ensuring that oncology patients receive adequate nutrition are essential components of quality cancer care.

SCREENING FOR NUTRITIONAL ALTERATIONS

All patients undergoing treatment for cancer should have their baseline nutritional status documented to determine whether they are at risk for developing nutritional problems. A study by Ottery and colleagues at the Fox Chase Cancer Center in Philadelphia, Pa., clearly demonstrates the benefits of identifying nutritional risks and/or deficits early in the treatment process.[6] These benefits include 1) the prevention of further nutritional deterioration, 2) the prevention of malnutrition-induced complications that increase health care costs as well as morbidity, and 3) the maintenance of or improvement in the patient's quality of life.

The Ottery study focused on 186 cancer patients referred to the nutrition clinic at Fox Chase for the treatment of weight losses that averaged 16.8 percent. Each patient's nutritional status was evaluated using an early version of the Patient Generated-Subjective Global Assessment (PG-SGA) tool. (To learn more about the current PG-SGA tool, visit *www.accc-cancer.org/publications/pgsga.pdf*.) The initial 60 percent of the questions in this screening tool are completed by the patient and assess weight, food intake, symptoms that impact nutrition, and activity level. The clinician is responsible for completing the remaining questions, which cover all relevant diagnoses, the evaluation of metabolic stressors, and the physical exam.

After the initial screening, aggressive symptom management strategies were employed and individualized counseling and/or oral nutrition plans were begun. Ottery and colleagues[6] were able to help 50 percent of their patients stop losing weight and improve their visceral protein status (transferrin or albumin). Those patients who had a life expectancy of greater than six weeks had an 80 percent success rate. This experience demonstrates that the success of any nutritional intervention depends more on the strength of the initial screening and the comprehensiveness of the intervention program than the specific disease process or oncologic therapy being used.[2]

As a result of the Ottery study and others, the Oncology Dietetic Practice Group (ONDPG) of the American Dietetic Association now uses the scored PG-SGA as the standard of nutritional assessment for oncology patients.[6] Results of the screening will help clinicians categorize a patient's nutritional status, identify the presence or absence of nutrition impact symptoms, and identify those patients who have experienced a weight loss of more than 5 percent in one month or 10 percent over six months.[2]

The Joint Commission on Accreditation of Healthcare Organizations (JCAHO) now requires that all hospitalized patients be screened for nutritional risk as soon as possible. A plan for nutritional therapy must be developed for all patients with current or potential nutritional deficits. A referral to a nutritionist is recommended if patients have lost 5 percent of their bodyweight in the past month, their albumin is less than 3.2, their present weight is less than 90 percent of their ideal body weight, or they are receiving therapy that has a known risk of nutritional toxicity.[6]

ASSESSING NUTRITIONAL STATUS

Preventing or correcting nutrient depletion can minimize or eliminate malnutrition-related morbidity and mortality.[3] With this fact in mind, each nutrition assessment has three goals:

- to identify patients who have, or are at risk of developing, protein/energy malnutrition or deficiencies of specific nutrients
- to quantify a patient's risk of developing malnutrition-related medical complications, and
- to monitor the adequacy of nutritional therapy.[3]

The interaction between illness and nutritional status is complex, so an accurate nutritional assessment must include the patient's history, physical examination, and laboratory studies. The most frequently used assessment parameter of nutritional status is body weight. Although practical, body weight and anthropometric measurements in oncology patients are confounded by such factors as age, dehydration, edema, physical activity, and ascites.[3]

Laboratory values. Nutritional status can be assessed by measuring blood levels of transport proteins, such as albumin, pre-albumin, and transferrin.[7] These proteins are known as negative acute-phase proteins and are the main facilitators of protein synthesis under normal circumstances.[7] When a catabolic process occurs, protein synthesis shifts from negative acute-phase reactants (i.e., albumin or transferrin) to positive acute-phase reactants (i.e., C-reactive protein or fibrinogen).[8] The acute-phase response is thought to be strongly influenced by pro-inflammatory cytokines such as interleukin-1 (IL-1), tumor necrosis factor (TNF), interleukin-6 (IL-6) and interferon gamma, which have been implicated in the pathogenesis of cancer cachexia. Since these cytokines are difficult to measure by blood tests alone, transferrin, albumin, and pre-albumin are frequently monitored. These proteins have different synthesis rates, however, and their blood levels reflect changes in nutrition very differently.[7] For instance, the mid-range half-life of transferrin reflects global nutritional status more accurately than the long half-life of albumin or the short half-life of pre-albumin.[6]

> Historically, oncologists have addressed nutritional deficits in patients with cancer only during end-stage disease…

The single most sensitive baseline indicator of protein/calorie malnutrition is the creatinine height index.[9] Creatinine is the breakdown product of creatine, a liver-synthesized energy molecule stored in skeletal muscle.[10] Creatinine height levels reflect the amount of lean muscle tissue in the body,[11] which is equivalent to the amount of usable protein in the body. A creatinine height index of 80 percent or less may indicate depletion of lean body mass.[11] Unlike weight, the creatinine height index is not affected by fluid retention and may be a more accurate measure of somatic protein depletion.[12]

COLLABORATIVE ASPECTS OF NUTRITIONAL THERAPY

A survey of 64 oncology patients at the Cleveland Clinic found that the major provider of nutritional information was the nurse (57 percent) followed by the dietitian (22 percent) and the physician (19 percent). JCAHO recommends that the nurse, dietitian, and physician work collaboratively to address nutritional deficits in cancer patients.[13]

The dietitian can perform nutritional screening, identify high-risk patients, determine protein and energy needs, serve as a resource for dietary issues, and translate dietary prescriptions into food and/or tube feeding options.

Helping patients consume adequate amounts of needed foods has been a part of the nurse's task since Florence Nightingale emphasized the need to give patients frequent small portions of foods that are nourishing and easy to swallow and digest.[14] The nurse can also help the patient eat and manage the symptoms that interfere with eating adequately, monitor nutrition administration devices such as catheters and feeding tubes, and work with the nutritionist and physician to ensure that the patient's nutritional needs are met.

Historically, oncologists have addressed nutritional deficits in patients with cancer only during end-stage disease, and then have been surprised when their nutritional interventions did not successfully reverse the patient's deterioration.[2] If nutritional issues are dealt with early in the patient's clinical course, many problems can be prevented and the possibility for a good outcome improves.

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Quality of Life and Nutrition in the Patient With Cancer

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Most oncologists and clinicians agree that maintaining adequate nutrition throughout the treatment process is crucial if patients with cancer are to achieve a good outcome. What most practitioners have not adequately recognized is how much impact nutritional status has on an individual's quality of life.

Maintaining quality of life is important for patients with cancer. Many clinical trials now measure quality of life (QOL) as part of their reportable outcomes instead of focusing exclusively on survival and the observable antitumor effects of the new therapy.

Nutritional status plays a critical role in maintaining a positive QOL from both a physical and emotional point of view.[1] Physically, nutrient depletion adversely affects morbidity and mortality, length of hospital stay, wound healing, response to chemotherapy, immune function, and the patient's ability to tolerate treatment.[2,3] Fear, anxiety, grief, and depression can diminish appetite and food intake. Patients who are not eating adequately may also lack the enjoyable, nurturing experiences of social interactions with family and friends, which can further depress appetite.

Many aspects of cancer and cancer treatment can significantly influence food intake, including anorexia and cachexia,[4] fatigue, taste and smell aversions, difficulty in chewing and swallowing, and insufficient energy to purchase or prepare food. Often these problems are exacerbated in patients age 60 and older because of the normal effects of aging on oropharyngeal swallowing (lost reserve and flexibility)[5] and reduced taste sensation.[6] Finally, pain, either from the disease or as a result of treatment, may limit the individual's tolerance and desire for food.[2]

Nutrition and QOL studies for oncology patients are limited and have generally focused on more aggressive issues of nutritional care such as enteral and total parenteral nutrition, but recently more research has been conducted on nutritional issues and QOL, particularly among head and neck cancer patients.

List and colleagues evaluated performance and QOL in 64 advanced-stage head and neck cancer patients for a period of 12 months during treatment.[7] The most frequent symptoms reported were dry mouth, difficulty tasting food, and dislike of the soft food diet. The authors concluded that the continuing inability to eat a full range of foods warranted further attention and monitoring.

In another study, Campbell and colleagues evaluated a cohort of three-year survivors of head and neck cancer for persistent QOL concerns and long-term treatment effects.[8] The results showed that advanced-stage cancer was correlated with lower QOL scores in chewing
ability and eating in public.

ASSESSMENT TOOLS

Since nutritional QOL is important, there needs to be a way to adequately evaluate it. Objective measures such as calorie intake, weight gain or loss, and albumin levels, although important, will not reflect the overall nutritional QOL. Similar objective changes in weight or calorie intake may lead to a significant disruption in the daily activities of one patient, and have only a minimal impact on another. The disparity can stem from differences in physical self-esteem, emotional and functional well-being, and other less well-defined concerns. In light of these difficulties, two evaluation tools for measuring nutritional status and nutritional quality of life have been developed.

FAACT. A questionnaire entitled the Functional Assessment of Anorexia Cachexia Therapy (FAACT) Subscale has been developed to measure nutritional quality of life.[9] The questionnaire was initially validated as an 18-item addition to the Functional Assessment of Cancer Therapy-General (FACT-G) questionnaire.[9,10] The FACT-G, which is the core of the FACT measurement system, consists of subscales to assess physical well-being (7 items), social and family well-being (6 items), emotional well-being (6 items), and functional well-being (7 items). The FACT-G yields a total score as well as individual subscale scores.

The 18-item anorexia/cachexia subscale was amended to the FACT-G to create the FAACT. A clinical trial conducted from 1994-1997 evaluated the feasibility of shortening the anorexia/cachexia subscale. In this trial a combined empirical and conceptual approach led to the reduction of the anorexia/cachexia subscale from 18 to 12 items. The shortened anorexia/cachexia subscale was found to provide unique, important information not captured by a generic chronic illness questionnaire.[11] The current FAACT is comprised of 27 general (FACT-G) questions and 12 questions specific to anorexia/cachexia. To view the FACCT tool, visit ACCC's web site at *www.accc-cancer.org/publications/faact.pdf*.

The FAACT assessment system is a marked advance in the ability to measure nutritional QOL scores. It has

been validated in a prospective clinical trial and found to be reliable.[11] The test allows researchers to measure the impact of interventions on QOL and nutritional well-being, but should not be used as a screening tool for clinical intervention.

PG-SGA. The Patient-Generated Subjective Global Assessment (PG-SGA) is a validated nutrition screening instrument appropriate for use in all outpatient settings, including the oncology office, clinic, home care, and hospice. This tool provides a global assessment of the patient's nutritional status based on nutrition-related history and physical symptoms, and can be used to evaluate nutritional quality of life.

The initial portion of the PG-SGA is completed by the patient and includes questions concerning weight, food intake, nutritional impact symptoms, and activity.

Good nutritional care is multidisciplinary…

These questions identify individuals who are potentially at risk for malnutrition or the QOL effects of malnutrition. The rest of the assessment is performed by an appropriate health care provider, usually a nurse or nutrition professional, and includes a physical exam and the evaluation of lab results. This section of the test addresses the patient's disease and how it affects nutritional requirements, as well as metabolic demands and physical indicators.

Patient status using the PG-SGA is categorized in two ways, a global assessment and a patient score. Global assessment is based on the definition of the original validated SGA by Detsky and colleagues.[12] The patient score is a "snap-shot" of where the patient is on the day of the assessment and identifies potential intervention targets such as nutrition impact symptoms and metabolic stress. Intervention pathways are defined by the score (*see www.accc-cancer.org/publications.pgsga.pdf*). It is important to remember that there is not necessarily a direct correlation with a high score (e.g. many untreated symptoms) and global assessment of malnutrition. However, without intervention, progressive malnutrition will inevitably result with inceasingly compromised quality of life.

NUTRITIONAL INTERVENTION AND QUALITY OF LIFE

Nutritional care plans depend on the stage of the patient's disease, the probable length of treatment, and the patient's prognosis. In advanced cancers, the primary goal is improved comfort.[13] In less severe cases, nutritional intervention can be an essential component of antitumor therapy. Appropriate and timely nutritional care can help maintain body weight and protein status, reduce fatigue, improve tolerance to treatment, minimize surgical complications, and enhance well-being. Nutritional plans and other lifestyle changes are also part of preventive care strategies for recovered cancer patients.

Good nutritional care is multidisciplinary and requires the collaboration of nurses, nutritional specialists, speech-language pathologists who are also swallowing specialists,[14] social workers, pharmacists, and physicians.

The ability to improve the nutritional QOL should be a major objective of integrated cancer care. The FAACT questionnaire provides a practical, validated nutritional QOL measuring tool, and the PG-SGA can identify patients in need of nutritional intervention. If the need for intervention is detected, the entire cancer care team should work together to devise a nutritional plan that will both maintain the patient's nutritional status and improve the patient's quality of life.

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Nutrition Impact Symptoms in the Oncology Patient

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Nutrition impact symptoms are those symptoms that impede oral intake.[1] They include nausea, vomiting, diarrhea, stomatitis, mucositis, dysphasia, constipation, anorexia, sensory changes (including alterations in taste and smell), and pain. The etiology of these symptoms is often multifactoral, which makes their management complex. A proactive approach to symptom control with anticipatory interventions and aggressive management is the most effective way to maintain nutritional status.[1]

Nausea and Vomiting. Patients with cancer develop nausea and vomiting as a side effect of therapy or as part of the disease itself.[2] Understanding the pathophysiology of symptoms, the efficacy and limitations of pharmacologic interventions, and the use of nonpharmacologic techniques is essential to ensure adequate nutritional intake.[3] Nausea and vomiting occur after stimulation of the vomiting center in the medullary lateral reticular formation.[4] The vomiting center is rich in neurotransmitter receptors (such as dopamine, serotonin, acetylcholine, and histamine) that are sensitive to chemical toxins in the brain and cerebrospinal fluid.[5] Pharmacologic management of nausea and vomiting is aimed at blocking these neurotransmitters so the vomiting center cannot be stimulated. A number of nonpharmacological approaches (such as relaxation, meditation, and visualization) have also been effective when used in conjunction with pharmacologic agents.

Stomatitis. Stomatitis, or oral mucositis, is described as an acute inflammation or ulceration of the oral or oropharyngeal mucosal membranes. It occurs as the result of multiple stressors, which again include both the disease and its treatment.[6] Stomatitis is one of the most common side effects of cancer therapy, occurring in approximately 40 percent of patients at some time during the course of their treatment.[7] There is substantial variation in the management of this symptom, and patients often receive an array of "magic mouthwashes" to hydrate the mucosa and remove oral debris and microorganisms. Until the effectiveness of these mouthwashes is empirically established,[8] the use of salt and soda mouthwash (one teaspoon of baking soda and one teaspoon of salt in one quart of water) is recommended.

Diarrhea. Many of the factors that cause diarrhea in the general medical setting can also be observed in patients with cancer. However, diarrhea in someone who is receiving chemotherapy can result in a number of complications, including life-threatening septicemia, malnutrition, electrolyte disturbances, and eventual death.

Patients should be encouraged to eat a bland diet of bananas, rice, and applesauce and increase their fluid intake to six to eight glasses of decaffeinated beverages a day. They should avoid caffeine, alcohol, lactose-containing products, and roughage. A number of antidiarrheal medications (such as opiate derivatives, absorbents, and adsorbents) can control cancer-related diarrhea that cannot be managed by dietary manipulation,[9] and should be prescribed to treat the specific underlying pathophysiology involved.

Constipation. Constipation in patients with cancer can be caused by decreased intestinal motility, metabolic changes, inadequate fluid intake, decreased physical activity, opioid medications, tumor obstruction, and certain chemotherapeutic drugs. When patients become constipated, they often complain of fullness, bloating, and, on occasion, nausea and vomiting. All these symptoms influence appetite, which affects nutritional status. Managing constipation starts with determining its cause, followed by patient education and acute and prophylactic interventions. Patients should be encouraged to increase their fluid intake to six to eight glasses of liquid a day, increase exercise and the dietary intake of roughage, and take stool softeners, laxatives, or prokinetic agents as prescribed.

Taste changes. Taste changes are common in patients with cancer and include changes in the perception of bitter and sweet foods and a metallic or distorted taste. These changes have been associated with chemotherapy, radiation therapy, nonchemotherapy drugs, surgery, environmental factors, direct tumor invasion, and deficiencies in zinc, copper, nickel, vitamin A, and niacin.[10-13] Taste changes have been reported in 36 to 71 percent of patients receiving chemotherapy and have a variable onset and duration.[12]

Strategies for patients with taste changes include the avoidance of tart foods, the consumption of cold foods, increasing food seasoning, meticulous oral hygiene, and chewing sugarless gum.[13] If patients complain of a

metallic taste, then using plastic utensils and preparing food in glass or plastic containers should be encouraged.

Because food plays a major role in social activities, the loss of taste can lead to a lack of interest and loss of pleasure in social contact[10,14] and a subsequent decrease in the overall quality of life.[12]

Pain. Pain can also influence a patient's ability to eat. Pain may have a psychological component, be the result of direct tumor invasion, or be the consequence of treatment. Appropriate pain medications should be used, including topical anesthetics, anti-inflammatory agents, and opioid analgesics.

Anorexia. Anorexia is defined as a loss of appetite that results in a decrease in oral intake.[10] It may be the result of a tumor or host- and treatment-related variables.[15] A number of studies have suggested that the amount of tryptophan (a precursor of serotonin) in the brain plays a role in cancer anorexia by increasing the serotoninergic activity of the ventromedullar hypothalamus.[16]

Cachexia, or the progressive loss of lean tissue and body fat,[17] is the result of major metabolic and biochemical abnormalities such as increased glucose synthesis, insulin resistance, decreased glucose tolerance and turnover, increased glucogenesis, increased Cori-cycle activity, increased fat and protein metabolism, increased metabolic rate, and hormonal abnormalities produced by a combination of tumor by-products and the host's cytokine release.[17] It is not a simple matter of an increase in energy consumption by the tumor and starvation by the patient as previously thought.

> …multidisciplinary care that combines a nutritional assessment, symptom management, and pharmacological and non-pharmacological interventions is necessary…

Meeting the nutritional needs of patients with cancer is challenging and may require the use of a pharmacologic agent to stimulate appetite. A number of agents have been investigated with varying levels of success. For more details, see Table 1 and "Pharmacologic Intervention for Cancer-related Weight Loss" by Jamie H. Von Roenn, M.D., on page 18 of this supplement.

Since the weight loss associated with cancer cachexia cannot be remedied by increasing food consumption alone,[19] a number of interventions must be incorporated into the plan of care.[20] Because survival is shorter for those who develop cachexia, addressing this symptom is a critical issue.[16]

In summary, multidisciplinary care that combines a nutritional assessment, symptom management, and pharmacologic and nonpharmacologic interventions is necessary to improve the quality of care, the patient's quality of life, and produce the best possible disease outcome for those who have cancer.

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Table 1. Pharmacological Agents Used to Treat Anorexia/Cachexia

Pharmacological Agents	Dosing	Outcome	Side Effects
Megestrol actetate (Megace®)	40 mg/day titrated to 1,600 mg/day	Weight gain consisting mostly of fat, increased sense of well-being	Thromboembolic phenomena, breakthrough bleeding, peripheral edema, hyperglycemia, hypertension, alopecia, and Cushing's syndrome
Medroxyprogesterone acetate	300 to 4,000 mg/day	Increased appetite	Same as Megestrol *Rare to stop drug because of adverse effects
Dronabinol (Marinol®)	2.5 mg one hour after meals	Increased appetite, increased food intake	Somnolence, mental confusion, and cognitive status disturbances
Corticosteroids Dexamethasone Methylprednisolone Prednisolone	 0.75 to 1.5 mg po q.i.d. 125 mg IV 5 mg po t.i.d.	Pain control, antiemetic, short-term effect on symptoms (appetite, food intake, well-being, and performance)	Diabetes, immunosuppression, osteoporosis, increased muscle weakness, increased protein requirements
Cyproheptadine	8 mg t.i.d.	Failed to prevent weight loss	Increased dizziness and sedation, decreased nausea and vomiting
Metoclopramide	10 mg AC & HS	Improved gastric motility, decreased early satiety, improved appetite	Diarrhea
Thalidomide	200 to 400 mg/day	Significant body weight gain in HIV	Mild sedative effects
Melatonin	20 mg/day in the evening	Improved performance status, antidepressant effect, decreased weight loss	No toxicities related to melatonin were observed
Eicosapentaenoic Acid (EPA)	1 to 6 gm po/day	Small body weight gain of 0.3 kg/month, less fatigue, slowed weight loss	Further studies on cachexia in advanced cancer need to be done to establish EPA's efficacy in that setting.

Pharmacologic Interventions for Cancer-related Weight Loss

by Jamie H. Von Roenn, M.D.

Involuntary weight loss and its end-stage manifestation, the anorexia-cachexia syndrome, are frequent complications of cancer[1] and have a negative impact on both survival and quality of life.[1-4] How much weight is lost varies according to both the extent and the primary site of the patient's disease. For example, anorexia-cachexia occurs in approximately 30 percent of patients with non-Hodgkin's lymphoma, but more than 85 percent of patients with gastric cancer.[1] Even small degrees of weight loss (less than 5 percent) have an impact on survival, with the greatest effect seen in those patients with good performance status.[1] Autopsy studies demonstrate that cachexia, as a cause of cancer-related mortality, is the only significant abnormality in up to 22 percent of cancer deaths.[5]

The mechanisms behind cancer-related weight loss are complex and vary with each type of malignancy. Complicated interactions among decreased energy intake, altered energy expenditure, malabsorption, and hormonal/cytokine and metabolic abnormalities seem to be the principal drivers.

Pharmacologic treatment for cancer-related weight loss falls into four main categories: 1) drugs to treat symptoms that interfere with adequate nutrition, 2) appetite stimulants, 3) drugs that affect metabolic or specific humeral and inflammatory responses, and 4) anabolic agents. In addition, prokinetic drugs have been useful in the treatment of early satiety and anorexia.

All of these drugs produce different results, and the patient's total situation must be carefully evaluated before a drug is prescribed. Whether the patient has recently gained weight cannot be the primary criterion for deciding if nutritional deficits are present because weight gain can be caused by fluid retention or an increased amount of fatty tissue (neither of which is produced by good nutrition) rather than an increase in lean muscle mass. Some patients have low levels of serum proteins; drugs must be chosen for them with care to make sure that their protein reserves are built up rather than further depleted.

TREATING SYMPTOMS THAT INTERFERE WITH NUTRITION

Symptom control is the first step in preventing the involuntary weight loss that occurs in up to 85 percent of people with advanced cancer.[6] Most of the symptoms that cause anorexia and malnutrition in cancer patients (i.e., nausea and vomiting, early satiety, impaired taste, mucositis) are easily reversible. No one has formally studied the impact of aggressive symptom control on oral intake, but eliminating these gastrointestinal and neurological problems clearly increases the amount that people can eat and improves most patients' quality of life.

Unfortunately, the treatment of symptoms alone is often not enough to maintain or replenish weight and/or total body protein mass. The following medications have been useful in correcting some of the underlying metabolic difficulties that are caused by malignant disease processes and the therapies that treat them.

APPETITE STIMULANTS

A variety of substances (including corticosteroids, progestational agents such as megestrol acetate, cannabinoids, and certain antihistamines) improve appetite, but only a few of them promote weight gain as well. Even fewer promote the addition of lean muscle mass instead of fatty tissue, and all of them have side effects which must be carefully considered before they are administered to patients.

Corticosteroids. Randomized, double-blind studies have proven that glucocorticoids are effective appetite stimulants in patients with advanced cancer.[7-11] Unfortunately, this appetite improvement is short-lived (four to eight weeks) and fails to translate into weight gain.

Glucocorticoid therapy can also produce significant toxicities, which increase as treatment time increases. The prolonged use of steroids results in progressive muscle wasting, electrolyte imbalances, and fluid retention, and the neuropsychiatric complications of steroids may be severe. Affective disorders are uncommon (less than 5 percent), while mild mental disturbances are frequent (up to 50 percent of patients).[12] The most severe abnormalities are organic mood disorders and delirium, which generally occur within the first two weeks of treatment and resolve with dose reduction. There are currently no standard dosing schedules for glucocorticoids. Patients with very advanced cancer and limited survival (less than three months) may benefit from corticosteroids to relieve their anorexia, and bedridden patients are excellent candidates for this therapy since muscle wasting is not of particular concern.

Corticosteroids may be a particularly good treatment choice for patients who require co-analgesia with an anti-inflammatory agent (e.g., the patient with painful bone metastases). Dexamethasone is often recommended in this setting because of its limited mineralocorticoid

activity and relatively low cost. A reasonable dose and schedule to consider is dexamethasone 4 mg orally with the morning meal. Dosing after noon should be avoided because of the potential for insomnia.

The results of a recent comparative trial of dexamethasone, megestrol acetate, and fluoxymesterone (an anabolic agent) in patients with advanced cancer and weight loss showed that megestrol acetate and dexamethasone produced similar increases in appetite and weight gain, and both were more effective than treatment with fluoxymesterone.[13] Study subjects were randomized to receive megestrol acetate 800 mg/day, dexamethasone 0.75 four times a day, or fluoxymesterone 10 mg twice a day. Median time on study was about two months, and all three drugs were fairly well tolerated for this relatively brief period of time.

Progestational agents. Megestrol acetate is a synthetic, orally available progestational agent widely used to treat advanced, hormonally responsive breast cancer and other tumors. Conventional doses (160 mg/day) will stimulate appetite and weight gain, regardless of the hormone sensitivity of the tumor.[14] A phase I/II study of high-dose megestrol acetate (Megace®) (480 to 1,600 mg/day) in women with advanced breast cancer reported appetite stimulation and a weight gain of 2 kg or greater in 81 percent of the subjects.[15] Other studies have reported similar results.[16-20]

The weight gain that occurs secondary to megestrol acetate is made up primarily of fat mass, not body fluid.[20] Although no significant toxicities have been reported, there have been important endocrinologic consequences. Megestrol acetate has glucocorticoid effects, which can depress the pituitary and adrenal glands and make diabetes mellitus worse.[21-23] In men, decreases in testosterone are routinely identified after one week of therapy.[24] Even though high-dose studies showed no significant differences in the incidence of thromboembolic phenomena from those seen at the regular dosage, concerns remain about the risk of thromboembolic events in patients receiving megestrol acetate, particularly patients with metastatic adenocarcinoma.

It is difficult to recommend an "ideal" dose of megestrol acetate. Megestrol acetate oral suspension, milligram for milligram, is 10 percent more bioavailable than the tablet formulation.[25] An intermediate dose of 400 mg/day, titrated up or down based on response, is an appropriate starting point. It is important to note, however, that nearly 75 percent of patients reach their maximum weight change by six weeks after the start of therapy.[26]

Dronabinol. Dronabinol, the primary orexigenic component of marijuana, stimulates appetite in patients with AIDS and cancer-related anorexia, according to a number of phase II studies. In one six-week, dose-ranging study, 30 patients with advanced cancer received 2.5 mg of dronabinol daily, 2.5 mg twice daily, or 5 mg once a day.[27] Mood and appetite improved in those patients receiving the 5 mg daily dose. Weight loss continued in all treatment groups, although the rate of weight loss decreased.

Appetite stimulation by cannabinoids is highly variable and does not clearly translate into weight gain. Toxicities may be significant and include dizziness, euphoria, somnolence, and decreased concentration. Children and elderly patients appear most sensitive to these effects. Nelson demonstrated reasonably good tolerance of dronabinol 2.5 mg three times a day, and suggested this as a reasonable starting dose.[28] Elderly patients should probably start at 2.5 mg once a day with escalation as tolerated.

Cyproheptadine hydrochloride. Cyproheptadine is an antihistamine, antiserotonergic agent approved in the United States for the treatment of allergic disorders. In geriatric patients, adults with essential anorexia, and adolescents with anorexia nervosa, cyproheptadine has been reported to improve appetite and stimulate weight gain. Researchers think that cyproheptadine might decrease the cerebral production of tryptophan and serotonin, which can decrease the appetite. A randomized, double-blind, placebo-controlled trial performed by the North Central Oncology Group enrolled 295 patients with advanced cancer.[29] Patients were randomized to receive either placebo or 8 mg of oral cyproheptadine three times daily. Though well tolerated overall, cyproheptadine only produced a minimal, non-significant increase in appetite without an increase in body weight.

METABOLIC AGENTS AND CYTOKINE BLOCKERS

Changes in the patient's metabolism caused by an increased number of cytokines in the bloodstream may be a cause of the weight loss (cachexia) seen in cancer.[30] Although a number of cytokines (tumor necrosis factor [TNF], interleukin-1 [IL-1], interleukin-6 [IL-6], and interferon gamma) are suspected of a role in cancer cachexia, it has been difficult to show an association between the serum levels of these proteins and weight loss. The administration of a variety of cytokines leads to anorexia, weight loss, an acute-phase protein response, and increased muscle and fat breakdown; but this cachectic process is only minimally affected by the administration of antibodies to TNF or IL-6. This supports the belief that multiple cytokines must be present to produce cancer weight loss. Drugs that inhibit prostaglandin synthesis diminish the cachectic effects of TNF and IL-1 in animals, which suggests that prostaglandins may also be partially responsible for this condition.[31,32]

Hydrazine sulfate. Hydrazine sulfate is a metabolic inhibitor that has been tested as both an antitumor agent and a potential therapy for cancer-related weight loss. Hydrazine sulfate inhibits the production of phosphoenolpyruvic kinase, and laboratory data suggest that this agent interferes with the cell-killing activity of TNF.[33] Multiple non-randomized trials in the 1970s and early 1980s produced conflicting results regarding the utility of this drug; but in the 1990s three large, placebo-controlled trials testing the ability of hydrazine sulfate to stop cancer-related weight loss failed to demonstrate either increased appetite or weight gain when the drug was given.[34-36]

Pentoxifyline. Pentoxifyline, a methylxanthine derivative, slowed the production of TNF and suppressed protein breakdown in rats with cancer who were losing weight.[37,38] In a double-blind, placebo-controlled, randomized trial, 70 patients with cancer-related weight loss received either placebo or pentoxifyline, 400 mg orally

three times daily.[38] Pentoxifyline failed to improve patient-reported appetite, food intake, or weight.

Thalidomide. Thalidomide selectively inhibits the production of TNF-alpha by speeding up the breakdown of the RNA that helps produce this substance.[39] An open-label study of thalidomide, 100 mg daily, in 37 patients with cachexia and metastatic cancer reported improvements in appetite and sense of well-being.[40] All 27 patients who were able to complete their food intake diaries reported that they ate significantly more after taking thalidomide. A randomized, placebo-controlled evaluation of thalidomide in patients with cancer cachexia has not been done, but such a trial in patients with AIDS-related wasting showed that thalidomide could play a role in reducing weight loss in that setting.[41]

Melatonin. Melatonin, a pineal hormone with multiple biologic effects, reduces TNF production.[42] Lissoni and colleagues[43] randomized 100 patients with advanced solid tumors to receive either best supportive care or supportive care plus melatonin, 20 mg orally each night. Serum TNF levels were measured at baseline and monthly. Weight loss greater than 10 percent was seen in a significantly higher number of patients treated with supportive care alone than in those treated concurrently with melatonin ($p < 0.01$). No difference in oral intake was noted. Mean serum concentrations of TNF increased in the control arm and significantly decreased ($p < 0.05$) in patients treated with melatonin, suggesting that melatonin could have a role as an anticytokine therapy.

> The medical management of cancer-related weight loss requires a careful evaluation of both the symptoms that cause patients to eat less and the medications to treat these symptoms.

Eicosapentaenoic acid. Eicosapentaenoic acid (EPA), an essential polyunsaturated fatty acid of the n-3 class, is under evaluation as an anticytokine agent.[44] EPA reduces the inflammatory responses that investigators think may contribute to cancer-related weight loss. In a phase II study, 26 patients with pancreatic cancer and weight loss were given 1 gm of EPA per day, which was slowly increased over a four-week period to 6 gm per day.[45] Patients were evaluated at baseline, 4, 8, and 12 weeks for body weight, body composition, acute-phase protein response, performance status, and toxicity. The supplement was well tolerated and, in general, EPA supplementation was associated with weight stabilization. Before EPA was administered, all patients were actively losing weight at a rate of 2 kg per month. After four weeks of EPA supplementation, patients had a median weight gain of 0.5 kg, which remained stable over the 12-week study period. Additional trials are underway.

NSAIDS. Non-steroidal anti-inflammatory drugs (NSAIDS) have inhibited prostaglandin synthesis in animal models, which slowed both tumor progression and weight loss. However, the ability of these agents to inhibit weight loss in humans has not yet been established.

ANABOLIC AGENTS

Anabolic agents have the potential to improve body composition by maintaining, and ideally replenishing, lean body mass. However, the usefulness of anabolic agents in the treatment of cancer-associated cachexia has not been adequately evaluated. While a number of agents (growth hormone, oxandrolone, nandrolone) are either approved or currently being evaluated for the treatment of AIDS-associated weight loss, little data are available regarding their use in the weight loss caused by cancer.

Oxandrolone is a synthetic anabolic steroid currently approved to enhance weight gain following extensive surgery, severe infections, or trauma, and in some patients who fail to gain or maintain normal weight. Compared to testosterone, oxandrolone has relatively little androgenic effect and greater anabolic activity. The drug can be given orally with rapid absorption and minimal hepatic metabolism.

In a community-based, randomized, double-blind, placebo-controlled study of 63 patients with AIDS-related wasting, patients were treated with placebo, 5 mg, or 15 mg of oxandrolone for four months.[46] The group receiving oxandrolone had a sustained increase in weight throughout the study to a mean increase of 3.9 pounds at week 14, compared with a decrease of 1.5 pounds in the placebo group. In addition, the oxandrolone treatment group had a statistically significant improvement in overall physical activity and a reported improvement in both appetite and strength.

Other placebo-controlled and open-label studies of oxandrolone in weight-losing cancer patients are underway but have not yet been reported. The results of these trials will define the usefulness of this agent in the treatment of cancer-related cachexia.

PROKINETIC DRUGS

Decreased gastric emptying can contribute to early satiety and/or a feeling of fullness. These symptoms can be exacerbated in oncology patients by the decreased intestinal motility associated with opioid analgesics.

Prokinetic drugs are a number of structurally unrelated compounds that share the same pharmacological activity of stimulating gastrointestinal motility. The motor functions of the gastrointestinal tract are expressions of a balance between inhibitory mechanisms in smooth muscle cells, mainly regulated by dopamine, and stimulatory events mainly regulated by the release of acetylcholine.

Metoclopramide (Reglan®), a prokinetic agent, increases the action of the intestines and has been used with some success in the treatment of early satiety and anorexia.

SUMMARY

The medical management of cancer-related weight loss requires a careful evaluation of both the symptoms that

cause patients to eat less and the medications to treat these symptoms. If there are no specific, easily reversible phenomena (i.e., nausea, early satiety, mucositis) that can be treated, then drugs specific for the treatment of cachexia should be considered.

An intervention for a particular patient should be chosen based on the patient's treatment goals and prognosis. For patients with very limited survival whose primary goal is to increase the enjoyment of eating, megestrol acetate or corticosteroids may be helpful. For the majority of patients, however, treatment needs to improve not only oral intake but also weight and overall functioning. To achieve this, an approach that combines an orexigenic agent with exercise and/or an anabolic medication may be ideal. Further study will be necessary to define new agents as well as beneficial combination therapies.

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Dietary Supplements During Cancer Treatment

by Omer Kucuk, M.D., F.A.C.N., and Faith D. Ottery, M.D., Ph.D., F.A.C.N.

Many patients with cancer have nutritional deficiencies when they enter treatment due to poor diet and lifestyle factors or the metabolic effects of the cancer itself. These deficiencies can worsen during radiation therapy or chemotherapy because of the adverse effects these treatments have on the gastrointestinal tract and other organs. In addition, treatment-induced deficiencies of micronutrients (such as zinc; selenium; vitamins C, E, and A; and the carotenoids alpha-carotene, beta-carotene, cryptoxanthin, lutein, and lycopene), which have critical cellular functions, can cause significant morbidity and mortality and intensify the adverse side effects of chemotherapy and radiation.

Patients undergoing chemotherapy or radiation therapy who receive micronutrient supplementation usually do not develop these nutritional deficiencies and have less severe side effects from their treatment. Nutritional supplementation may also improve immune function, treatment outcome, and the patient's quality of life.

Because many micronutrients and phytochemicals are antioxidants, there is concern about whether they will inhibit the antitumor effect of radiation and chemotherapy. These compounds could theoretically have a tumor-protective effect, but there has been almost no clinical investigation of the problem, and very little data are available. Since dietary supplement and phytochemical use is common among cancer patients, there is a great need for clinical studies investigating the potential risks and benefits of using these compounds during chemotherapy and radiation therapy

Epidemiological studies show an inverse relationship between cancer risk and the dietary intake of antioxidant micronutrients;[1] but placebo-controlled randomized clinical trials with these compounds have produced conflicting results. These conflicting results could be due to the fact that nutrients that are part of a healthy diet react synergistically with other nutrients that are ingested at the same time, and this synergy produces a number of positive effects that might not occur when a pharmacological dose of a single compound is taken during a clinical study. Dietary micronutrients are consumed in small quantities over a long period of time, whereas clinical trials typically administer a large quantity of a single micronutrient over a short period of time.

Many cancer patients have low antioxidant micronutrient levels at presentation. One reason for these nutritional deficiencies is the fact that cancer is a disease of aging and micronutrient deficiencies are common among older individuals. Monget and colleagues[2] found that the serum concentrations of most micronutrients were inversely associated with age and most elderly nursing home residents had low serum levels of vitamin C, zinc, and selenium.

Micronutrient deficiency may also be present in non-geriatric cancer patients. Donma and colleagues[3] found reduced hair zinc levels in children with active cancer compared to healthy children and children with cancers in remission. Melichar and colleagues[4] found an increased level of zinc excretion in the urine of cancer patients, which could be due to poor renal tubular

function. It may be that chemotherapeutic agents with renal tubular toxicity worsen the zinc deficiency in these patients.

MICRONUTRIENTS AND TOBACCO/ALCOHOL CONSUMPTION

Tobacco consumption is also a major risk factor for many human cancers and tobacco use has consistently been associated with increased oxidative stress and decreased serum antioxidant micronutrient levels.

Pamuk and colleagues[5] reported on the relationship between current cigarette smoking and the serum concentrations of vitamins C, E, and A plus five carotenoids in 91 low-income, African-American women. Among smokers, serum concentrations of alpha-carotene, beta-carotene, cryptoxanthin, and lycopene averaged only 71 to 79 percent of the concentrations among non-smokers. Mean serum concentrations of vitamins C and E and lutein/zeaxanthin were only slightly lower among smokers than non-smokers. Among current smokers, mean serum concentrations of all five carotenoids decreased with increases in the amount smoked.

Ross and colleagues[6] determined the concentrations of carotenoids, ascorbic acid, alpha-tocopherol, and gamma-tocopherol in the plasma of 50 male smokers and 50 age-matched men who had never smoked. Significantly less alpha-carotene, beta-carotene, cryptoxanthin, and ascorbic acid were found in the smokers' plasma than in the plasma of the men who had never smoked.

Pakrashi and Chatterjee[7] measured the prostatic excretion of zinc in the ejaculates of 29 tobacco smokers, 25 tobacco chewers, and 30 nonusers of tobacco and found reduced levels of zinc in tobacco smokers compared to tobacco chewers and men who had never used tobacco.

Faruque and colleagues[8] observed a lower dietary intake of vitamin C, carotenoids, and zinc and lower plasma level of vitamin C in 44 male students who smoked compared to 44 male nonsmoking students.

Alcohol consumption has also been associated with increased oxidative stress and decreased micronutrient levels and alcohol and tobacco in combination may result in even more severe micronutrient deficiencies than either one used alone.

Tsubono and colleagues[9] examined the association between smoking, alcohol, and plasma levels of beta-carotene, alpha-carotene, lutein, lycopene, and zeaxanthin in 634 healthy men between the ages of 40 and 49. After controlling for age, serum cholesterol, serum triglycerides, body-mass index, green and yellow vegetables, and fruits, there was a significant inverse association between smoking and alcohol consumption and the plasma levels of beta-carotene and alpha-carotene. Only smoking reduced the level of lutein, and neither smoking nor alcohol significantly reduced the level of lycopene or zeaxanthin.

Brady and colleagues[10] conducted a population-based study of 400 individuals and found an association between smoking and alcohol consumption and lower serum levels of alpha-carotene, beta-carotene, beta-cryptoxanthin, and lutein/zeaxanthin. Lower levels of serum lycopene were associated with older age.

Lecomte and colleagues[11] measured plasma carotenoid levels in 118 healthy men consuming low or moderate amounts of alcohol and 95 alcoholics. Beta-carotene, alpha-carotene, lutein/zeaxanthin, lycopene, and beta-cryptoxanthin levels were significantly lower in alcoholics, but 21 days after alcohol consumption was stopped, plasma levels of all the carotenoids increased.

Leo and colleagues[12] did not find a significant difference in the levels of carotenoids, retinol, and alpha-tocopherol found in the oropharyngeal mucosa of 11 chronic alcoholics with oropharyngeal cancer and 11 control subjects.

NUTRITIONAL STATUS AND MORBIDITY

Nutritional status is known to profoundly impact treatment morbidity, efficacy, and the eventual outcome of cancer patients.[13-20] For example, approximately 30 to 40 percent of patients with advanced-stage head and neck cancer have severe malnutrition, and an additional 20 to 30 percent have moderate malnutrition at the time of presentation.[13,17] These patients frequently present with significant weight loss and chronic protein-calorie malnutrition, which may be exacerbated if tumor-induced dysphagia further reduces oral intake.[13,17] Head and neck cancer patients with poor nutritional status are at increased risk for postoperative wound breakdown and infections, fistula formation, and flap loss.[13,17]

Olmedilla and colleagues[21] found that the plasma levels of carotenoids, retinol, and vitamin E were significantly lower in patients who had undergone a laryngectomy for laryngeal cancer than in healthy control subjects. After commercial enteral formula feeding, carotenoid levels further decreased and retinol and tocopherol levels increased, but all micronutrient levels remained lower than the corresponding levels in control subjects.[21]

Postoperative alterations of the upper aerodigestive tract may further compromise intake, increase metabolic demands, and compound nutritional deficiency.[15,18] Since there are no known zinc stores in the human body, zinc deficiency develops quickly with malnutrition in these patients.[22] Another potential contributor to zinc deficiency in head and neck cancer patients is alcohol use, which is common among patients who present with this disease. Alcohol intake is known to result in zinc deficiency.

Zinc deficiency causes a profound reduction in the activity of the thymic hormone thymulin. Prasad and colleagues[23] found decreased production of interleukin-2 and interferon-gamma by TH1 cells, reduced NK cell activity, and decreased recruitment of T cell precursors in zinc-deficient subjects.

Mocchegiani observed a significant increase or stabilization in the body weight of AIDS patients who received zinc supplements in addition to AZT. Zinc supplementation was also associated with an increase in CD4 cells and plasma thymulin and a decrease in the frequency of opportunistic infections.[24]

Abdulla and colleagues[25] observed that plasma zinc was decreased and the copper/zinc ratio was significantly increased in patients with squamous cell carcinoma of the head and neck compared to healthy controls. The patients with a marked decrease in their plasma zinc

level died within 12 months. The authors suggested that plasma zinc and the copper/zinc ratio may be of value in predicting the prognosis of patients with head and neck cancer, but Garofalo and colleagues[26] found that these tests were not able to predict the prognosis of patients with squamous cell carcinoma of the head and neck.

THE NUTRITIONAL CONSEQUENCES OF RADIATION AND CHEMOTHERAPY

Both radiation therapy and chemotherapy have been associated with increased oxidative stress, which may further deplete tissue levels of antioxidant micronutrients, particularly in smokers and in the presence of inadequate dietary intake.

Faber and colleagues[27] measured lipid peroxidation, plasma glutathione and glutathione peroxidase activity, and plasma micronutrient levels in patients with cancer before and after doxorubicin-containing chemotherapy. The concentration level of lipid peroxidation products (measured as thiobarbituric acid reactant materials) in the plasma of cancer patients was higher than in controls, and the level increased still more after chemotherapy. These results indicate that the subjects had increased oxidative stress at presentation, which was further aggravated by doxorubicin treatment. Cancer patients had lower levels of glutathione, glutathione peroxidase, selenium, and zinc, but these were not further modified by chemotherapy.

Torii and colleagues[28] reported that doxorubicin treatment caused cardiomyopathy, increased lipid peroxidation, and lower alpha-tocopherol levels in the myocardium of spontaneously hypertensive rats.

The radiation of malignancies in the head and neck area results in a marked reduction in saliva flow and alterations in saliva composition within the first week of therapy, and impairs saliva flow throughout the duration of therapy. The decreased secretion of saliva may lead to symptoms such as oral pain and burning sensations, the loss of taste and appetite, and an increased incidence of oral disease. These symptoms can affect eating and increase the risk of inadequate nutritional intake.

Backstrom and colleagues[29] investigated the average nutritional intake of 24 patients treated for malignancies in the head and neck region who had dry mouth symptoms that had persisted for at least four months after the completion of radiation therapy. The average caloric intake was 1,925 calories in the irradiated patients with dry mouth symptoms and 2,219 calories in age- and sex-matched controls. The average intakes of vitamin A, beta-carotene, vitamin E, vitamin B6, folic acid, iron, and zinc were significantly lower in the irradiated patients than in controls.

EFFECTS OF MICRONUTRIENTS ON RADIATION AND CHEMOTHERAPY TOXICITY

Micronutrient use, including vitamin E, zinc, and selenium, has been shown to prevent or decrease treatment-induced toxicities.

Vitamin E. Many of the toxicities associated with chemotherapy and radiation therapy may be prevented with vitamin E supplementation. The protection afforded by vitamin E could be due to either its antioxidant effect[30] or its immunomodulatory effects.[31-34] Vitamin E has effectively prevented chemotherapy-induced oral mucositis[35,36] and may decrease doxorubicin cardiotoxicity without compromising the antitumor activity of the drugs.[37]

Vitamin E selectively protects murine erythroid progenitor cells from chemotherapy toxicity[38] and prevents the severe toxicity caused by tumor necrosis factor.[39] It also has a selective antitumor effect against murine leukemia cells while protecting the murine bone marrow against the toxicity of doxorubicin.[40]

Srinivasan and Weiss[41] showed that alpha-tocopherol could protect mice against lethal radiation and enhance the effect of another radioprotective agent, WR-3689. Nattakom and colleagues[42] observed complete resolution of the clinical and biochemical signs of severe hepatic dysfunction when they used vitamin E and glutamine to treat a 44-year-old woman who developed significant veno-occlusive disease after bone marrow transplantation.

In addition to its cardioprotective effect, alpha-tocopherol pretreatment prevented the development of doxorubicin-induced focal glomerulosclerosis and renal failure in an animal model.[43] Topical application of vitamin E was also very effective in promoting the healing of skin wounds caused by doxorubicin-induced skin necrosis.[44] In animals given an oral or topical vitamin E preparation prior to treatment with doxorubicin, dermal incision wounds healed much faster compared to control animals, suggesting that vitamin E may play an important role in postoperative wound healing, especially in doxorubicin-impaired wounds.[45]

An oral preparation of Vitamin E was given concurrently with intravenous chemotherapy with cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) in rats, and protected their intestinal membranes against chemotherapy-induced toxicity.[46] CMF-induced decreases in intestinal basolateral membrane levels of ATPases, alkaline phosphatase, 5'-nucleotidase and sulfhydryl groups, and increases in malondialdehyde levels were also restored to normal by the co-administration of vitamin E.

Vascular endothelial damage induced by intravenous cisplatin administration was prevented by vitamin E treatment in rats.[47] In the cisplatin plus vitamin E group, cisplatin-induced morphological changes in the endothelium were reversed and superoxide dismutase and Na/K-ATPase levels returned to normal.

Zinc. In a review article,[48] Sorenson said that copper, iron, manganese, and zinc complexes will protect lethally irradiated animals against radiation-induced immunosuppression, cell damage, and death. Srivastava and colleagues[49] have observed decreased platinum-induced nephrotoxicity and gastrointestinal toxicity in animals given a zinc-chelate of histidine before chemotherapy treatment.

Radiation therapy to the head and neck region frequently results in xerostomia and lack of taste. Abnormalities of taste have also been related to a deficiency of zinc in humans by several investigators.[50,51] Decreased taste acuity (hypogeusia) has been observed in zinc-deficient subjects with liver disease, malabsorption syndrome, and chronic uremia, and after burns and

the administration of penicillamine. Chronically debilitated patients (such as cancer patients) also develop hypogeusia. Mahajan and colleagues[51] conducted a double-blind study that revealed that zinc could improve taste acuity in subjects with chronic uremia.

Another neurosensory disorder, decreased dark adaptation, has also been connected to a deficiency of zinc.[52] Warth and colleagues discovered that giving zinc to zinc-deficient sickle cell anemia patients with decreased dark adaptation will correct this abnormality.[52] Decreased dark adaptation has recently been identified as the dose-limiting toxicity for fenretinide (4-hydroxyphenylretinamide), a cancer chemopreventive retinoid compound currently under intensive clinical investigation. Clinical trials could be conducted with zinc and fenretinide to determine if the combination of the two substances can decrease fenretinide toxicity and enhance its chemopreventive activity at the same time.

Antioxidant micronutrients can prevent the gastrointestinal toxicities of radiation and chemotherapy, doxorubicin-induced cardiotoxicity, and cisplatin-induced nephrotoxicity.

PREVENTION OF TOXICITY

Antioxidant micronutrients can prevent the gastrointestinal toxicities of radiation and chemotherapy, doxorubicin-induced cardiotoxicity, and cisplatin-induced nephrotoxicity.

Oral and gastrointestinal toxicity. Antioxidant micronutrients prevent the gastrointestinal toxicities of radiation and chemotherapy. Mills reported that beta carotene decreases the oral mucositis that is induced by chemotherapy and radiation therapy,[53] and Klimberg and colleagues[54] observed a protective effect of glutamine on the small bowel mucosa of rats receiving abdominal radiation. Carroll and colleagues[55] found that a variety of antioxidant compounds and micronutrients (including ribose-cystein, amifostine, glutamine, vitamin E, and magnesium chloride/ATP) prevented radiation-induced small bowel and large bowel injury in rats.

Cardiotoxicity. Various micronutrients and micronutrient compounds have been used to prevent doxorubicin-induced cardiotoxicity. In an animal model, benzylideneascorbate protected against doxorubicin-induced cardiotoxicity but ascorbate, 6-palmitoylascorbate, and cysteamine were ineffective.[56] In vitro studies showed that benzylideneascorbate was a very effective antioxidant, scavenging both superoxide anions and hydroxyl radicals and preventing the auto-oxidation of linoleic acid.[56] Glutathione at biological concentrations decreased doxorubicin-dependent hepatic microsomal lipid peroxidation in rats, whereas acetylcystein had no effect.[57] This inhibition appears to be enzyme dependent and requires tocopherol. A similar mechanism has been observed in the microsomal membranes of the rat heart.[57]

Geetha has reported the effects of doxorubicin on rat heart mitochondria[58,59] and lysozymes.[60] Doxorubicin caused swelling, lipid peroxidation, and thiol depletion in vitro in rat mitochondria, and this effect was preventable by pretreating the animals with alpha-tocopherol.[58] In vivo chronic doxorubicin treatment decreased the activity of NADH-dehydrogenase, cytochrome-C-oxidase, and Na/K-ATPase in rat heart mitochondria, and this effect was prevented by the concurrent oral administration of alpha-tocopherol.[59] The in vivo effects of chronic doxorubicin treatment on rat heart lysosomes included a decrease in the activities of acid phosphatase, beta-D-glucuronidase, cathepsin D, and beta-D-galactosidase with a concomitant increase in microsomal lipid peroxide. These effects were also prevented when oral tocopherol was administered concurrently with doxorubicin.[60]

Hida and colleagues[61] showed that the stimulation of microsomal lipid peroxidation could be prevented in vitro by zinc, superoxide dismutase, alpha-tocopherol, and desferrioxamine; but glutathione, catalase, and selenium were not effective in preventing lipid peroxidation.

Miura and colleagues[62] reported that doxorubicin inactivated the erythrocyte membrane enzymes Na/K-ATPase and Ca-ATPase during lipid peroxidation in vitro, and this effect was prevented by the administration of trolox (a water-soluble form of vitamin E) and butylated hydroxytoluene.

Nephrotoxicity. Cisplatin is a drug that is active against many cancers. Its dose is limited by severe nephrotoxicity and neurotoxicity, both of which can result in significant morbidity. Pre- and post-treatment hydration and mannitol-induced diuresis lowers the concentration of cisplatin in the kidneys and reduces its nephrotoxicity.

An alternative approach is the use of chemoprotectors. Selenium has been reported to reduce cisplatin-induced nephrotoxicity[63,64] in addition to its known chemopreventive properties,[65] and sodium selenite protects rodents against cisplatin nephrotoxicity without reducing the drug's antitumor activity.[64]

Vermeulen and colleagues[67] also concluded that sodium selenite protected rodents against cisplatin-induced nephrotoxicity without influencing the systemic availability of cisplatin. Reactions between cisplatin and the nucleophilic metabolites of selenite may be responsible for these protective effects.[66]

Sadzuka and colleagues[68,69] demonstrated that cisplatin-induced nephrotoxicity was closely associated with an increase in lipid peroxidation and a decrease in the activity of enzymes that protect against lipid peroxidation. Pretreatment with alpha-tocopherol and glutathione significantly decreased the amount of lipid

peroxides produced in the kidney by the administration of cisplatin.[70]

Sugihara and colleagues[71,72] found that alpha-tocopherol prevented the lipid peroxidation and nephrotoxicity induced by cisplatin in rodents, and Bogin and colleagues[73] reported that pretreatment with a combination of cysteine and alpha-tocopherol is protective against the nephrotoxicity and biochemical changes induced by the administration of cisplatin in rats.

MICRONUTRIENTS AND THE ANTITUMOR VS TUMORIGENIC EFFECTS OF RADIATION AND CHEMOTHERAPY

The mechanism of action of radiation therapy and some chemotherapeutic agents involves the generation of toxic oxygen free radicals. Supplementing patients with antioxidant micronutrients during therapy may potentially interfere with the antitumor effects of the treatment. Fortunately, many of the antioxidants have been found to prevent treatment toxicity without reducing the efficacy of radiation or chemotherapy, and certain micronutrients have antitumor effects of their own, including inhibiting cancer cell proliferation and inducing malignant cells to differentiate and divide properly.

Vitamin E inhibits growth and causes morphological changes in several tumor cell lines in tissue culture.[74,75] Animal studies and clinical trials have demonstrated the chemopreventive[76,77] and antineoplastic activities[78,79] of vitamin E, and a number of experimental studies suggest that vitamin E can enhance the growth inhibitory effect of various cancer treatment modalities such as radiation, chemotherapy, and hyperthermia.[74] At some doses, vitamin E enhanced the tumor killing properties of irradiation.[80]

Prasad and colleagues[81] observed the growth inhibitory effects of vitamin C alone, vitamin E alone, and combinations of vitamin C, vitamin E, beta-carotene, and 13-cis-retinoic acid on SK-30 melanoma cells in vitro. They also found that ascorbic acid, alone or in combination with beta-carotene, vitamin E, and 13-cis-retinoic acid, enhanced the growth-inhibitory effect of cisplatin, dacarbazine, tamoxifen, and interferon-alpha 2b.

Certain micronutrients have chemopreventive properties and may play a role in the prevention of radiation- and chemotherapy-induced cancers.

Krishnaswamy and colleagues[82] produced a 57 percent complete remission rate for oral preneoplastic lesions in 150 subjects by administering a multivitamin capsule containing vitamin A, riboflavin, zinc, and selenium twice weekly for one year.

Satoh and colleagues[83] reported that increasing the level of pulmonary metallothionein by giving animals zinc or bismuth compounds could prevent the development of lung cancer in mice that received repeated injections of cisplatin and melphalan. Zinc aspartate administration potentiated the radioprotective effect of diltiazem in mice given lethal doses of radiation;[84] and the combination of zinc aspartate with amifostine, an antioxidant compound, conferred protection against the lethal effects of radiation and the development of radiation-induced lymphomas in mice.[85]

The oral administration of vitamins A and E in conjunction with FEMTX (fluorouracil, epirubicin, methotrexate) chemotherapy in patients with unresectable or metastatic gastric cancer did not appear to reduce the antitumor activity of the chemotherapeutic agents.[86] Glutathione administration protected rodents against both the renal and lethal toxicity of cisplatin, but did not interfere with the drug's antitumor activity.[87] Small clinical studies similarly found that glutathione had a protective effect against the renal toxicity of cisplatin[88,89] with no reduction in its antitumor activity.[89]

Di Re and colleagues[90] confirmed these results in a larger series of 40 patients with ovarian cancer who were treated with high-dose cisplatin and cyclophosphamide plus pre-and post-treatment glutathione. The glutathione had a significant protective effect against renal toxicity with no effect on antitumor activity.

Oral glutamine supplementation enhances the sensitivity of the tumor cells to methotrexate chemotherapy while protecting normal cells from methotrexate's adverse effects.

Rouse and colleagues[91] hypothesized that intravenous glutamine would protect liver cells from oxidant injury by increasing their intracellular glutathione content, and thought that supplemental oral glutamine would increase the therapeutic index of methotrexate by improving host tolerance through changes in glutathione metabolism. Giving rats with implanted fibrosarcomas being treated with methotrexate a glutamine-rich diet decreased tumor glutathione and increased the antitumor effect of methotrexate, while maintaining or increasing host glutathione stores.[92] Significantly decreased glutathione levels in tumor cells correlated with their susceptibility to methotrexate and tumor shrinkage in animals that received the combination of glutamine and methotrexate.

Unfortunately, zinc has been shown to interfere with the antitumor activity of cisplatin by increasing metallothionein synthesis, which in turn increases the amount of cisplatin that the body can eliminate.[93] C3H mice inoculated with bladder tumors (MBT-2) were given cisplatin and zinc sulfate, and reductions in both renal toxicity and the antitumor activity of cisplatin were observed.[93]

COMBINING NUTRITIONAL AND PHARMACEUTICAL COMPOUNDS TO PREVENT TOXICITY

Certain pharmaceutical compounds have been used for the prevention and treatment of the toxicities caused by chemotherapy and radiation therapy. Thiosulfate, calcium channel blockers, bismuth, glycine, cimetidine, and probenecid[63] have been used to prevent the nephrotoxicity of cisplatin.

Floersheim[84] reported that mice were protected against lethal dose of radiation by diltiazem and other calcium channel blockers such as nifedipine and nimodipine, and that synergistic effects occurred when diltiazem was combined with zinc aspartate, dimethyl sulfoxide, and nifedipine. In another study, Floersheim and colleagues[85] found that small doses of zinc aspartate and amifostine also protected mice against lethal radiation.

George and colleagues[94] have shown that pretreat-

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Antioxidant Use During Radiation or Chemotherapy: A Summary

by Kathleen Mayer, M.S., R.D., and Maree Ferguson, Ph.D., R.D.

Use of antioxidants during cancer therapy is widely discussed, and at times debated, by clinicians, researchers, and patients. Many patients with cancer are using alternative nutritional methods alone or as a complement to standard therapies to treat their disease. Controversy exists in the literature regarding whether the use of antioxidants, such as vitamins A, C, E, beta-carotene, and selenium, inhibits or enhances the antitumor effects of radiation and chemotherapy.[1] Discussion centers around general use during therapy, dosing (meeting requirements versus pharmacologic doses), and timing of antioxidant use (prior, during, and after the specific antineoplastic intervention). An extensive review is available in the supplement but the general issues are summarized here.

Radiation and certain types of chemotherapy agents promote oxidation and free-radical production as part of their tumoricidal effect. Some researchers have suggested that pharmacologic doses of antioxidants may protect the tumor, thereby decreasing the effectiveness of the cancer therapy.[2] The impact of antioxidants on the effectiveness of cancer therapies depends on the type and dosage of the antioxidant and the therapeutic agent involved, as well as the tumor type.[3] However, the evidence that antioxidants actually decrease the antitumor effects of cancer therapies is limited.[3,4] Much of the available information is speculative or anecdotal.[1]

Other researchers have indicated that antioxidants actually enhance radiation and chemotherapy by increasing tumor response to therapy and decreasing toxicities.[5,6] These researchers have indicated that antioxidant administration, in both animal and human studies, did not reduce the efficacy of radiation or chemotherapy. Because the antioxidants protect healthy cells against free radical damage, there were actually fewer adverse events when antioxidants were provided.[7] The specifics of dose and timing are important variables in study design and clinical intervention. Several studies have found that antioxidants can prevent some of the negative side effects resulting from treatment with antineoplastic agents.[5] Antioxidant nutrients have been shown to prevent chemotherapy-induced oral mucositis and gastrointestinal toxicity, cisplatin-induced nephrotoxicity, and doxorubicin-induced cardiotoxicity without inhibiting the antitumor effects of these agents.[8] Certain antioxidants, such as vitamin E, may also prevent chemotherapy toxicities due to immunomodulating properties.[8] One study even demonstrated prolonged survival among patients who received antioxidants in combination with radiation and chemotherapy.[9] No studies have examined the long-term effects of using antioxidants in combination with radiation and chemotherapy in humans.[2,4]

The following information should be considered with respect to taking antioxidants during radiation or chemotherapy:

- Patients with cancer, especially those undergoing therapy, have reduced food intake. Many of these patients do not meet the recommended daily intake for many nutrients. Studies have shown that patients with cancer have lower levels of plasma antioxidants than patients without cancer.[8] Therefore, patients with cancer may be deficient in several important nutrients, and vitamin and mineral requirements must be considered.
- No recommended minimum or maximum levels of antioxidants exist for patients with cancer during radiation and chemotherapy.
- Antioxidant dosing used in animal and clinical research studies are much higher (pharmacologic doses) than the levels found in foods or oral medical nutritional supplements.
- Critical questions in the area are under investigation.

A comprehensive review of this topic can be obtained by referring to the designated articles referenced.[2,3,4,6,8,10]

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ment with a combination of 5-hydroxy-L-tryptophan (5-HTP) and 2-aminoethyl isothiuronium bromide hydrobromide (AET) prior to total body irradiation protected mice against radiation-induced oligospermia and infertility.

Somani and colleagues[95] observed that mice given cisplatin had increases in their creatinine levels and decreases in the amount of glutathione in their kidneys. Both of these effects were prevented by giving the rats diethylthiocarbamate at the same time that cisplatin was administered.

The phosphorothioate amifostine has recently been approved for the prevention of cisplatin toxicity in humans. Its ability to prevent radiation toxicity and the toxicities of other chemotherapeutic agents is under investigation.

Phosphorothioates have toxicities of their own that limit their use, and it has been proposed that combining other agents with phosphorothioates may improve their efficacy and/or lower their toxicity.[96] Since zinc aspartate and the combination of zinc aspartate with amifostine protect normal tissue from radiation better than tumor tissue,[97-99] further clinical studies should test low-dose amifostine and zinc combinations to see if they can prevent radiation toxicity so high-dose amifostine, with its associated side effects, can be avoided.

Hamers and colleagues[100] found that pretreatment with reduced glutathione protected rats against cisplatin-induced neuropathy without interfering with the drug's antitumor activity. Metallothionein induction by bismuth subnitrate has been reported to prevent cisplatin and doxorubicin toxicity,[101] although Sadzuka and colleagues found no protective effect by bismuth subnitrate in their experiments.[70]

Storm and colleagues[102] found that mice were protected from the toxic cellular effects of radiation when they were fed a diet containing 2 percent squalene prior to and after receiving a lethal dose of whole body radiation. Irradiated mice fed squalene had significantly higher white cell and lymphocyte counts, better jejunal histology, and longer survival times than the control group.

CONCLUSIONS

Micronutrient supplementation may prevent the adverse effects of cancer chemotherapy and radiation therapy without interfering with their antitumor capabilities, resulting in an improved quality of life for cancer patients. Certain dietary supplements may enhance the antitumor effect of radiation and chemotherapy while protecting normal tissues from their adverse effects. However, caution should be exercised at this time regarding the concurrent use of antioxidant dietary supplements with chemotherapy and radiation because of the lack of data from well-designed randomized clinical trials about the effect of antioxidants on the potency of anticancer therapies. There is a great need for clinical trials that investigate the potential risks and benefits of supplementation with micronutrients and phytochemicals during cancer therapy.

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