Cancer and Nutrition—The Importance of Preventing Weight Loss Throughout the Treatment Continuum

a report by
James T D'Olimpio, MD

Director of Supportive/Palliative Oncology and the Cancer Pain and Symptom Control Service, North Shore University Hospital

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James T D'Olimpio, MD, is the Director of Supportive/Palliative Oncology and the Cancer Pain and Symptom Control Service at North Shore University Hospital in Manhasset, New York. He is also an Assistant Professor of Medicine at the New York University School of Medicine. His research focuses on symptom control, palliative care, and cancer cachexia. Dr D'Olimpio is the author of multiple professional and technical papers and his findings have appeared in numerous exclusive journals. Dr D'Olimpio is a member of several professional organizations, including the American Society of Clinical Oncology, the American Academy of Hospice and Palliative Medicine and the Multinational Association for Supportive Care in Cancer (MASCC).

Introduction

Patients facing a cancer diagnosis are presented with many challenges throughout the course of their disease process. This includes making a series of shared decisions with their physician and cancer care team that will influence response to therapy and eventual outcomes.

Much of the success or failure of treatment is dependent on the underlying health, including nutritional health of the patient, irrespective of age. The existence of comorbid conditions can greatly impact on compliance with surgery, chemotherapy and radiation programs, which are becoming increasingly complex and frequently combined in sequence, whether the intent is cure, a prolonged expected remission, or clinically meaningful palliation of symptoms and/or disease progression. Indeed, the very notion of cancer becoming a more manageable chronic disease state, nearly incomprehensible a generation ago, is becoming more and more of a reality with the development of a new generation of targeted therapies.

One element of this targeted approach concerns the area of nutritional oncology, a field now maturing as an important component of supportive care of the cancer patient from diagnosis through primary treatment and palliation. Loss of appetite, fat and lean body mass (LBM) are critical occurrences that negatively impact compliance with therapy and performance status, and can influence quality of life and even survival in many cases.

This article will focus on a common and challenging problem for the cancer clinician in the approach to assessing, managing and selecting a targeted therapeutic nutritional program to replenish, stabilize and build meaningful LBM, which is considered the most important element and therapeutic goal for the cancer patient at risk of losing weight.

The Scope of the Problem

It is estimated that up to 80% of patients with solid tumors will experience weight loss at some point in their disease process.[1] Certain cancers, such as pancreatic, gastric, head and neck, and lung cancer (among others), especially in advanced stages, are almost invariably associated with some degree of appetite loss and muscle wasting also known as anorexia/cachexia syndrome. Patients with high-grade lymphoma associated with B symptoms also are at similar risk.[2]

The pathophysiologic derangements that occur in these situations are multifactorial and can be related to both the unique biologic aspects of each neoplastic system encountered and its treatment considerations, i.e. surgery, chemotherapy, radiation, or combinations of both. The resultant spectrum of clinical problems can be highly significant; severe weight loss is directly or indirectly responsible for almost half of all deaths in advanced cancer.[3]

In addition, less optimal compliance with therapy, increased hospital lengths of stay, poor wound healing, and the higher frequency of infection, particularly pneumonia, are additional clinical consequences that ultimately lead to poor performance status and overall quality of life, and decreased survival.[4] Indeed, when one considers a relatively simple metric of organ health, such as LBM (in essence, protein stores), when approximately 40% is lost, mortality approaches 100%. Even at 20% loss, mortality approaches 40%[5] (see *Figure 1*).

The Nature of the Problem

Reduced to the most essential of concepts, malignant tumors produce constitutive products that are toxic to normal physiologic nutritional mechanisms.[5] The toxic elements involved relate to the production and release of various pro-inflammatory cytokines, which act to amplify the biochemical signals leading to sustained inflammation and upregulation of the nuclear factor kappa B (NFκB) pathway. It is a highly selective targeting process that is believed to result not from downregulation of all proteins, but through mechanisms that effect a unique cachectic response to

the most important structural proteins, such as myosin.[6] Additional signal modulation that can affect appetite, hunger and satiety also are impacted by these cytokines, and symptom clusters that are the clinical manifestation of these aberrant pathways result (see below).

Recently, the discovery of proteolysis-inducing factor (PIF), a low molecular weight glycoprotein seen at especially high levels in the urine of patients with certain solid tumors such as pancreatic, lung cancer, and others, has led to an increased understanding of the mechanism of loss of LBM seen in these patients.[7] When produced in cancerous conditions, PIF is associated with degradation of skeletal muscle and LBM by amplifying intracellular signals involved in inflammation and proteasome degradation, which leads to lysis of amino acid sequences of myosin, essentially disintegrating structural integrity as a result, with free amino acids now burdening the delicate balance that comprises LBM. Taken together, the mechanisms of cytokine and PIF release are potent mediators of metabolic problems for tumor systems (see *Figure 2*).

Preservation of LBM is critical; composed of approximately 70% water, 20% protein, and 10% minerals, it includes skeletal muscle, bone, skin, collagen, vital organs, antibodies, and various enzymes important for maintaining homeostasis, as well as the extracellular matrix (ECM) that supports the tissue foundation of the body. It is not intended as an energy source but, during the anorexia–cachexia syndrome, inappropriate cancer-related energy utilization is tapped into; sometimes because all carbohydrate stores (very modest even in health) and fat stores (the usual source of stored energy) have already been exhausted, either due to treatment/mechanical-related issues of enteral health, or lack of intake for psychological reasons, such as depression or anxiety.

Loss of sufficient substrate to maintain a robust or even functional immune system is a frequent occurrence and additional factors that can impact on bone marrow function and hematologic parameters, such as anemia, also coexist.[8]

Clinical Issues—Risk Factors and Assessment

So how are these issues all sorted out to make sufficient clinical sense that can lead to a targeted nutritional intervention? The first goal is to assess which clinical problem predominates (see *Figure 3*). Tumor type can be important: patients who are losing weight despite correction of mechanical factors or treatment-related problems such as nausea, vomiting, mucositis, or bowel dysmotility/obstruction should be suspected as having a predominant metabolic/biologic abnormality or

Figure 1: Skeletal Muscle Degradation

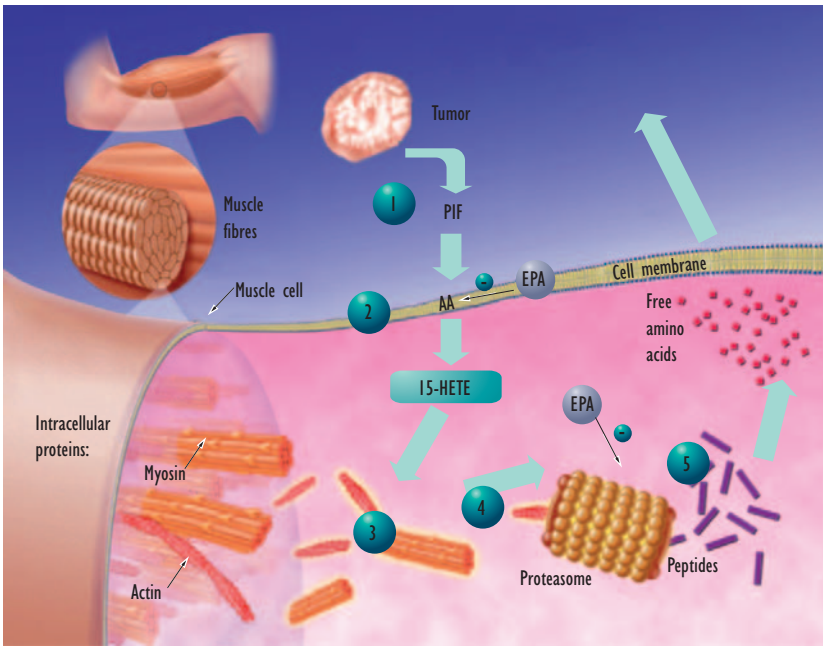


Figure 2

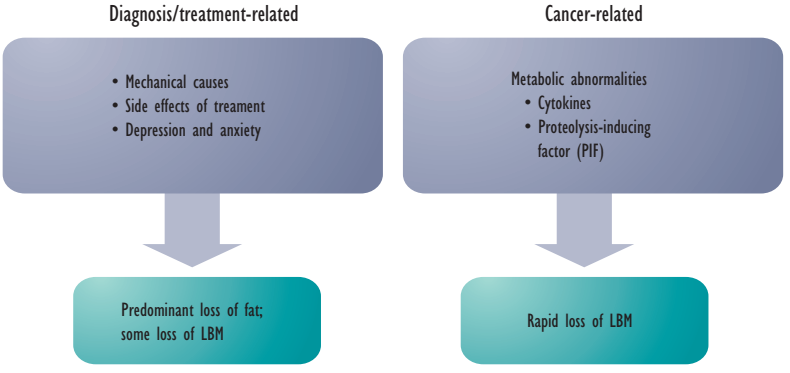
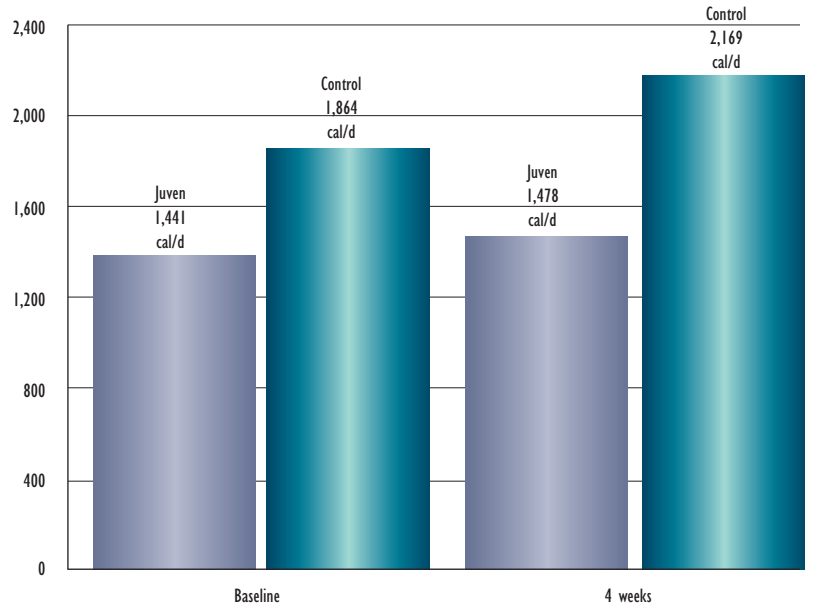


Table 1: Loss of LBM is Devastating[5]

Loss of total LBM	*Complications*	*Associated mortality*
10%	*Decreased immunity, increased infections*	*10%*
20%	*Decreased healing, weakness, infection*	*30%*
30%	*Too weak to sit, pressure ulcers, pneumonia, no healing*	*50%*
40%	*Death, usually from pneumonia*	*100%*

Figure 3: Mean Calorie Intake at Baseline and at Four Weeks



multiplicity of abnormalities that lead to excessively depleted or catabolized LBM. Clinically, a symptom cluster defines these issues and can be considered comprised of appetite loss, weight loss, weakness, early satiety, fatigue and diminished performance status. Laboratory abnormalities having valid sensitivity include an elevated C-reactive protein and decreased pre-albumin levels.[9]

Nutritional Solutions

Once the predominant clinical spectrum is assessed, the nutritional intervention can be planned. If the target is preserving LBM, which implies a metabolic issue, the administration of specific amino acid supplements that become especially depleted has been clinically studied in cancer patients. These include a combination of the synthetic leucine metabolite beta hydroxy-methyl butyrate (HMB), arginine and glutamine, known under the proprietory name Juven (Ross Products Division).

HMB is a particularly interesting metabolite; evidence exists that it can attenuate proteasome-induced proteolysis in cancer-induced muscle loss as a single agent.[10] Arginine and glutamine have additional salutary effects in stimulating wound healing and immune function and enhancing/protecting intestinal integrity, respectively.[11–14]

In a positive clinical cancer study examining this product, which was a prospective, randomized, double-blind placebo-controlled trial,[15] 49 advanced cancer patients were enrolled and completed the study over a 24-week evaluation period. Eligible patients who developed a 5% or greater weight loss not related to treatment or mechanical causes were randomized to receive either Juven or an isocaloric placebo. LBM was measured with bioelectric impedance and air displacement plysmography (Bodpod). Results revealed a statistically significant improvement in LBM compared with placebo. In addition, patients needed to take in fewer calories to achieve the superior result (see *Figure 4*). This trial provided the first evidence that a nutritional intervention could be utilized in cancer patients that could target LBM without drug therapy or complex enteral or parenteral formulation. HMB/Juven has also been examined and found to be useful in cachectic patients with HIV disease and in patients undergoing wound care and burn treatment.[16]

The formulation is composed of 1.5g of HMB, 7g of arginine, and 7g of glutamine. This formula represents a synergistic combination: HMB was originally developed to prevent muscle degradation during weight training; arginine and glutamine are conditionally essential amino acids important for sustaining muscle and gut physiology, respectively, as well as providing an important substrate for a variety of components of LBM as noted above.[17]

Intact renal and hepatic function are necessary to avoid accumulation of nitrogenous by-products (hyperammonemia and electrolyte imbalance.

Patients who should consider using Juven under medical supervision are those with a diagnosis of cancer or HIV disease undergoing treatment or losing weight for any associated reason. Patients with wound healing issues and those with other causes of LBM loss can also be considered. Intact renal and hepatic function are necessary to avoid accumulation of nitrogenous by-

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Lean Body Mass (LBM) Gain With JUVEN[1]

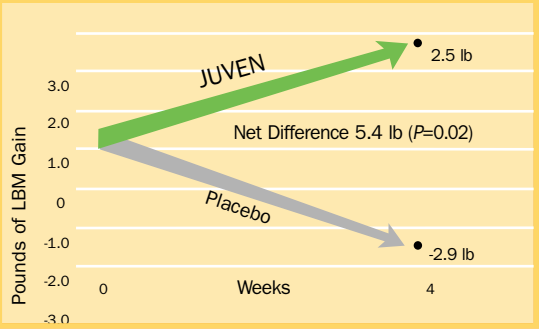

Chart developed from information in May PE et al: *Am J Surg* 2002;183:471-479.

In this double-blind study, patients (N=49) with advanced solid tumors (stage IV) and >5% weight loss were randomized to receive JUVEN BID or a nitrogen content–matched nutrient mixture BID.

- JUVEN patients gained more LBM despite taking in fewer calories and less protein*[1]
  - 32% fewer calories/day than the control group (1487 Cal/day vs 2169 Cal/day)
  - 34% fewer grams of protein/day than the control group (62 g/day vs 94.5 g/day)
- JUVEN patients continued to gain LBM throughout the 24-week study†[1]

JUVEN combines HMB‡ with other important LBM-building nutrients

Only JUVEN has a patented blend of ingredients that uniquely work to prevent concurrent wasting while building LBM, effectively targeting the two key contributors to weight loss.

- **HMB** reverses muscle breakdown[2] and builds lean body mass[3]
- **Arginine** improves nitrogen balance and promotes wound healing[4,5]
- **Glutamine** supports gut integrity[6] and preserves muscle glutamine

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- Two packets a day, administered orally or as a modular tube feeding
- Dissolves easily in water or juice
- Well tolerated

*Reported in dietary intake questionnaire after first 4 weeks. † Data analyzed by ITT repeated measures ANOVA and adjusted using baseline observation as a covariant. The quadratic contrast of treatment on time was significantly different over the 24 weeks ($P=0.02$). ‡ ß-hydroxy-ß-methylbutyrate. 1. May PE et al: *Am J Surg* 2002;183:471-479. 2. Knitter AE: *J Appl Physiol* 2000;89:1340-1344. 3. Nissen S: *J Appl Physiol* 1996;81:2095-2104 4. Barbul A: *Surgery* 1990;108:331-337. 5. Kirk et al: *Surgery* 1993;114:155-160. 6. Souba WW: *JPEN* 1985;9:608-617.

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products (hyperammonemia and electrolyte imbalance (potassium and phosphorus)).

Summary

Patients facing the challenges of maintaining meaningful weight during periods of severe stress when undergoing treatment for cancer, HIV and aspects of wound healing, should have a comprehensive program of risk assessment and targeted therapeutic intervention that addresses the specific needs unique to this group; preservation of LBM is a critical and integral part of this process. In addition, the use of a specifically formulated medical food supplement as part of an aggressive nutritional program, along with primary disease treatment, correction of reversible pathophysiologic mechanisms, aggressive pain and symptom management, and effective communication strategies in an inter-disciplinary setting, will maximize the desired outcomes for ever-evolving treatment strategies. ■

It is estimated that up to 80% of patients with solid tumors will experience weight loss at some point in their disease process.

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