Cancer Cachexia and Its Treatment With Fish-Oil-Enriched Nutritional Supplementation

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OBJECTIVE: Cachexia is a common condition affecting those with advanced cancer. This review explores mechanisms of cachexia and possible treatments devised with these mechanisms in mind.

METHODS: Selective review of the relevant scientific literature was performed with particular emphasis on studies performed by our group over the past 10 y involving patients with advanced pancreatic cancer.

RESULTS: Cancer cachexia adversely affects patient quality of life and survival. It is characterized by a lack of a normal anabolic response to the provision of apparently adequate nutrition. It appears to result from a persistent response to illness stimulated by the cancer resulting in a proinflammatory cytokine and catabolic hormonal environment. Interventions that ignore this inflammatory milieu have had little success. More promising interventions have a broad antiinflammatory component such as nonsteroidal antiinflammatory drugs or fish oil. Preliminary studies of a combination of fish oil as an antiinflammatory agent with nutritional supplementation show promise in reversing weight loss with apparent gains in lean tissue and performance status in association with normalization of the metabolic environment in patients with advanced pancreatic cancer.

CONCLUSIONS: Cancer cachexia produces a metabolic environment that prevents the appropriate use of supplied nutrition. Antiinflammatory agents such as fish oil in combination with nutritional supplementation may reverse aspects of cachexia. *Nutrition* 2001;17:751–755. ©Elsevier Science Inc. 2001

KEY WORDS: cancer, cachexia, fish oil, eicosapentaenoic acid

INTRODUCTION

Pancreatic adenocarcinoma is a common condition with a dismal outlook. It is responsible for about 5% of cancer deaths, with a median survival of 4.1 mo.[1,2] More than 80% of cancers are unresectable at diagnosis, and even in those patients suitable for surgical resection the 5-y survival rate is less than 25%.[3] The limited effects of chemotherapy and radiotherapy leave little in the way of treatment options for the vast majority of patients with unresectable disease, thus providing a valuable model in which to study the mechanisms and mediators of decline in patients with advanced cancer to maximize supportive treatment with the potential to improve quality and perhaps length of life.

Wigmore et al. reported that 85% of patients with unresectable pancreatic cancer have unintentionally lost weight by the time of diagnosis, with a median weight loss of almost 25% close to the time of death.[4] This is a manifestation of the syndrome of cachexia, characterized by anorexia, early satiety, changes in taste perception, weight loss, weakness, anemia, and edema.[5] Cachexia is associated with a shorter survival time and reduced quality of life and is the cause of death in perhaps 20% of cancer patients.[6–10] Cachexia is not exclusive to cancer but is also seen in a variety of other inflammatory conditions.

The fundamental difference between the weight loss observed in cachexia and that seen in, e.g., starvation, is the lack of reversibility with feeding.[11,12] This seems to be due to metabolic changes in cachexia similar to those seen after surgery, trauma, or sepsis and driven by similar mediators.

MECHANISMS AND MEDIATORS OF CACHEXIA

Most patients with pancreatic cancer likely have inadequate nutrition intake, which contributes substantially to weight loss.[13,14] Patients with cancer cachexia frequently have specific problems that reduce nutrition intake, including physical obstruction of the gastrointestinal tract, nausea, constipation and debility, psychological problems such as depression, and pain and the side effects of treatment with opiates, radiotherapy, and chemotherapy. However, even if these factors are well controlled, those with cancer cachexia often describe poor appetite, early satiety, changes in taste, and classic anorexia.[5]

Cancer patients traditionally have been regarded as hypermetabolic; however, a heterogeneous picture of energy expenditure has been described, with resting energy expenditure ranging from less than 60% to more than 150% of that predicted.[15,16] A longitudinal study in a rat model of cancer cachexia suggested that the animals are initially hypermetabolic before passing through a relatively normometabolic period to a preterminal hypometabolic phase.[17] Such longitudinal studies have not been performed in humans, but this pattern would account for some of the variation in the results observed. Whereas resting energy expenditure is increased, total energy expenditure may be unchanged due to a fall in physical activity.[18] Thus, overall energy balance may be maintained by a concomitant reduction in activity, but this decreased physical activity may be a reflection of a reduced quality of life.

Cachectic cancer patients exhibit relative glucose intolerance and insulin resistance, with an increased rate of glucose production and recycling via lactate (the Cori cycle).[19–22] These changes may become more pronounced as the disease progresses.[22] The in-

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creased glucose turnover observed in cancer may have an energy cost of up to 260 kcal/d.[21]

Whole-body protein turnover has been found to be increased in most patients with advanced cancer compared with starved normal individuals and weight-losing non-cancer patients and appears to increase further with the progression of disease.[23,24] The energy cost of this increased protein turnover has been estimated to be 100 kcal/d.[24]

Loss of skeletal-muscle protein is a prominent feature of cachexia, but skeletal-muscle protein-breakdown rates in cancer patients have not been found to be different from those in control subjects. There is, however, a reduction in the rate of muscle-protein synthesis,[25,26] which produces net protein breakdown.

The balance of liver-export proteins is altered in many cancer patients such that albumin synthesis remains unchanged and fibrinogen-synthesis rates are significantly increased.[27,28] These changes occur on a background of a decrease in the circulating concentration of albumin and an increase in the concentration of fibrinogen. These changes reflect aspects of the acute-phase protein response, a reprioritization of liver-protein synthesis often seen in trauma, inflammation, and infection.[29,30] An acute-phase protein response may be seen in a significant proportion of patients with a variety of cancers.[31–34] The proportion of patients with pancreatic cancer exhibiting acute-phase responses increases with disease progression[32,35] and its presence has been related to increased weight loss in cancer.[14,33,36] Moreover, the presence of such a response in cancer patients is strongly associated with a reduced quality of life in patients with gastrointestinal cancer [10,35] and a shortened survival in patients with renal, pancreatic, and colorectal cancers.[31,37,38] During an inflammatory response, demands for amino acids are altered. The cachectic cancer patient may have insufficient nutrition intake to provide the required amino acids, consequently, there may be a relatively increased breakdown of skeletal muscle to supply sufficient amino acids. This breakdown may be exaggerated further because there is an imbalance between the amino-acid composition of skeletal muscle and acute-phase proteins.[39] My colleagues and I showed that in cancer patients feeding stimulates the synthesis, not only of the negative acute-phase protein albumin (as seen in normal individuals) but also the positive acute-phase protein fibrinogen.[40] This may provide a mechanism whereby a proportion of supplied nutrients is diverted from anabolism in cancer cachexia.

These alterations in substrate metabolism may be designed to provide a ready supply of nutrients and proteins for host defense and tissue repair. Although beneficial in relatively short-term insults such as infection or trauma, such alterations are likely to exacerbate weight loss in the cancer-bearing patient.

It has been suggested that a tumor constitutes a new organ requiring its own sustenance and thus an increasing demand for nutrients and causing weight loss if these are not forthcoming. However, the presence and severity of cachexia often correlates poorly with the size of the tumor; it is often seen early in the course of the disease and manifestations such as alterations in appetite and nutrient metabolism cannot be explained easily by this hypothesis.[41] Thus it appears likely that the metabolic changes seen are the result of mediators produced by the tumor or by the body in response to the tumor. Candidate mediators include cytokines, neuroendocrine hormones and tumor specific products.

Several proinflammatory cytokines, including tumor necrosis factor (TNF), interleukin-1 (IL-1), interleukin-6 (IL-6), interferon-γ, and ciliary neurotrophic factor, have been implicated in cachexia.

Administration of many of these cytokines leads to anorexia, weight loss, an acute-phase protein response, protein and fat breakdown, rises in levels of cortisol and glucagon and falls in insulin levels, insulin resistance, anemia, fever, and elevated energy expenditure in animals.[42–47] Some tumor cell lines will produce cytokines in culture.[48] However, elevated circulating concentrations of proinflammatory cytokines are detected rarely in cancer patients, even those losing weight,[49] although elevated circulating concentrations of IL-6 have been associated with weight loss and the acute-phase protein response in some cancer patients.[36,50] Antibodies to TNF and IL-6 have produced only limited effects on the cachectic process[51,52] and different models of cachexia seem to rely on different cytokines. Production of TNF and IL-6 by isolated peripheral blood mononuclear cells have been shown to be elevated in weight-losing pancreatic-cancer patients, suggesting that local rather than systemic production of these cytokines is more important.[32] We recently showed that a genetic polymorphism of the IL-1β gene associated with increased IL-1β production also was associated with the presence of an acute-phase protein response and shortened survival.[53]

Thus, different proinflammatory cytokines seem to play major roles in many aspects of cachexia. However, individual cytokines do not appear to work alone, so a complex network of cytokines in combination with other factors may be responsible.

Infusion of hormones such as cortisol, glucagon, and adrenaline into humans will produce features of cachexia such as protein loss, an acute-phase protein response, increased energy expenditure, and glucose intolerance.[54,55] Changes in hormone levels and target-organ sensitivity have been described in animals and humans with cachexia. In humans with cancer, elevated levels of cortisol and glucagon have been observed.[56,57]

Additional potential mediators for cachexia have been described. A 24-kDa glycoprotein proteolysis-inducing factor (PIF) has been isolated from the urine of weight-losing cancer patients but not those losing weight due to other causes.[58] This produces protein breakdown in experimental animals and appears distinct from known cytokines.[59] A mouse tumor-derived lipid-mobilizing factor[60] has been identified in the urine of weight-losing cancer patients.[61] The failure of proinflammatory cytokines such as IL-6 to reliably induce cachexia in animal models has led to the suggestion that tumor-derived factors such as proteolysis-inducing factor (PIF) act as cofactors with host- or tumor-derived cytokines to produce a cachectic state.[62]

Our understanding of the role of inflammatory mediators in cachexia has opened up a new opportunity to manipulate the inflammatory response and so influence the development of cachexia. Such attempts to modulate the metabolic response to cancer have the potential to improve quality and length of life and should form a part of the integrated care of patients with advanced cancer.

TREATMENT OF CANCER CACHEXIA

The best way to treat cancer cachexia is to cure the cancer. Unfortunately, this remains a rare achievement. The next obvious option is to increase nutrition intake by enteral or parenteral means.

Two substantial randomized trials have examined the effect of enteral feeding in patients with advanced cancer undergoing chemotherapy.[63,64] Both studies included patients with a variety of cancer types who were randomized to receive or not receive nutrition counseling (to raise their energy and protein intake). Both trials showed significant increases in nutrition intake in the intervention groups. However, the increases did not improve weight, anthropometric measures, response rate, survival, or quality of life.

Parenteral nutrition is difficult to supply over long periods and has its own complications. A number of trials of parenteral nutrition were performed in cancer patients in the 1980s and, in general, showed no benefit in terms of nutritional measures and an increase in infective complications. This led the American College of Physicians to publish a position paper in 1989[65] that concluded that in cancer patients "parenteral nutritional support was associated with net harm, and no conditions could be defined in which such treatment appeared to be of benefit." Since then, a number of further large trials of parenteral nutrition in cancer, particularly in

the perioperative setting, have been performed but little objective benefit has been demonstrated.

The disappointing results of conventional nutrition supplementation in cancer patients has led to the suggestion that there is a block to weight gain in this group[12] perhaps related to the metabolic changes described above. This has led to attempts to manipulate the metabolic milieu with a variety of pharmacologic agents from knowledge of the mediators thought to be involved in cachexia.

Steroids and progestational agents are among the most widely used agents in patients with cancer cachexia and were developed without reference to the biology of cachexia. Both appear to improve appetite[66–70]; however, any effect on weight appears to be due to an accumulation of water.[71,72] Concerns over adverse effects probably should limit the use of these agents to the preterminal phases of a patient's illness.

Other agents being studied at the present time include thalidomide and melotonin, β2-adrenoceptor agonists, growth hormone, and insulin and related proteins.

With an appreciation of the role of the inflammatory state and eicosanoids in cachexia, non-steroidal antiinflammatory drugs have been investigated in cancer patients. A randomized trial of patients with different cancers receiving indomethacin produced a stabilization of performance status and a near doubling of survival in the indomethacin group.[73] Ibuprofen has been shown to reduce levels of acute phase proteins, interleukin-6 and cortisol and to normalize whole-body protein kinetics to some extent in cachectic colorectal cancer patients.[74,75] Ibuprofen will also reduce levels of acute phase proteins and resting energy expenditure in those with pancreatic cancer.[76]

A new approach to the management of cachexia has been to combine the appetite-stimulating properties of a progestational agent with the antiinflammatory properties of the non-steroidal antiinflammatory drugs by using megestrol acetate and ibuprofen together. Early trials have suggested that this combination stabilizes quality of life and weight in patients with advanced gastrointestinal cancer.[77,78]

FISH-OIL–BASED INTERVENTIONS IN CANCER CACHEXIA

General interest has focused on the properties of ω-3 fatty acids. These are an essential component of the diet and are involved in the synthesis of eicosanoids (prostaglandins, leukotrienes, and thromboxanes) and in membrane, receptor, and enzyme functions. Their usual source in the diet is oily fish. Interest in fish oils, notably eicosapentaenoic acid (EPA), was initially in the cardiovascular field, where their consumption was associated with a reduced tendency to platelet aggregation, reduced blood viscosity, and an improvement in lipid profile.[79] A reduction in mortality after myocardial infarction has been demonstrated with consumption of two fish meals a week.[80] These effects might be mediated by an alteration in the balance of eicosanoids to less inflammatory and aggregatory compounds than those produced from ω-6 fatty acids, the other class of essential fatty acids in the human diet. Suspicions of low rates of cancer in populations with high intakes of ω-3 fatty acids have led to animal studies suggesting a slowing of tumor growth rate with the provision of ω-3 fatty acids, although clinical studies are lacking.[81–83]

Fish oil and EPA appear to affect a number of potential mediators of cachexia. The administration of fish oil reduces production of cytokines such as IL-6, TNF, and IL-1 in healthy subjects.[84–86] Our group[87] demonstrated a reduction in the production of IL-6 and TNF in patients with pancreatic cancer receiving 6 g/d of EPA.[87] The provision of ω-3 fatty acids will reduce the concentration of the positive acute-phase protein fibrinogen in those with cardiovascular disease.[88] Wigmore et al. reported reduced concentrations of C-reactive protein in pancreatic-cancer patients receiving EPA.[87,89] EPA also might reduce the end organ effects of PIF in experimental studies.[90] These effects on mediators of cachexia have led to the study of the effects of fish oil and EPA on the cachectic process in cancer patients.

In a clinical study, a group of 18 weight-losing patients with advanced pancreatic cancer was been given oral fish-oil preparations providing approximately 2.2 g of EPA and 1.4 g of the related docosahexanoic acid daily. Before treatment all patients were losing weight at a median rate of 2.9 kg/mo. After 3 mo of supplementation, patients' weights stabilized, with less than half of the patients continuing to lose weight. There was no change in the percentage of total body water during the study, suggesting that patients were not simply retaining fluid.[89]

Subsequently, 27 patients with unresectable pancreatic cancer were given 6 g/d of 95% pure EPA orally after a 4-wk dose-escalation period. Patients lost a median of 2.0 kg/mo at baseline. After 4 wk patients' weights stabilized and remained so for at least 3 mo. There was no change in the percentage of total body water over the course of the study, confirming that the achievement of weight stability was not due to changes in hydration. Side effects were seen in five subjects with nausea or steatorrhea, and many reported fishy burps.[91]

A controlled trial of a fish-oil preparation providing about 3 g of EPA per day in a mixed group of 60 cancer patients suggested a prolonged survival in patients receiving fish oil. The effect on weight loss was not reported.[92]

Thus, the ongoing weight loss in cachexia is likely due to the metabolic alterations seen in this syndrome, which prevent the appropriate use of supplied nutrients. Fish oil and EPA appear to affect some of the mediators of these metabolic changes and have a beneficial effect on cachexia with stabilization in weight in previously weight-losing pancreatic-cancer patients. Therefore, my colleagues and I felt it would be appropriate to test the effects of a combination of fish oil to downregulate the cachectic process and additional nutrients to provide substrate for potential anabolism. An experimental nutrition supplement enriched with fish oil was available for trial use (Ross Products Division, Abbott Laboratories, Columbus OH, USA), so we performed a number of interrelated studies in cachectic patients with advanced pancreatic cancer.

The fish-oil–enriched nutrition supplement providing 2 g of EPA and 600 kcal daily was given to 20 patients with advanced pancreatic cancer who were losing weight at a median rate of 2.9 kg/mo. Patients had not received chemotherapy and treatment was delayed until at least 4 wk after any surgical intervention or biliary stenting. Patients tolerated the supplement well. Three patients had minor problems with steatorrhea that were easily controlled with pancreatic-enzyme supplements. Consumption was confirmed by a significant increase in the percentage of EPA and docosahexanoic acid in patients' plasma phospholipids. After 3 wk patients had gained a median of 1 kg ($P = 0.024$) and after 7 wk a median of 2.5 kg ($P = 0.028$). Body-composition analysis using bioimpedence suggested no change in fat mass (supported by a stable leptin concentration) but a significant gain in lean body mass ($P < 0.01$). Negative nitrogen balance was reversed from a median of -0.8 g/d to $+1.9$ kg/d. The Karnofsky Performance Score, which reflects the functional ability of patients, improved significantly with consumption of the supplement. Functional aspects of quality of life improved or were stabilized in most patients in whom aspects were measured. Appetite improved significantly with an increase in nutrition intake of around 400 kcal/d, suggesting that the supplement was not simply replacing normal food intake.[93] Examination of the potential mediators of cachexia showed a significant decrease in the production of IL-6 in patients and insulin concentrations rose. The proportion of patients excreting PIF also fell significantly. Concentrations of acute-phase proteins stabilized; in untreated patients, concentrations of positive acute-phase proteins continued to rise and negative acute-phase proteins

to fall.[94] The metabolic response to feeding also was normalized in patients receiving the fish-oil–enriched nutrition supplement, with a relative fall in resting energy expenditure.[95]

Taken together these results suggest a profound modulation of the cachectic process. The fish-oil component of the supplement may have affected cachectic mediators, allowing a degree of normalization of the metabolic state. This may have allowed the additional nutrients supplied to have an anabolic effect. The gain in lean tissue mass with resultant improvement in functional ability observed with the consumption of the fish-oil–enriched supplement is in marked contrast to the relative weight stability produced by fish oil or EPA alone and the lack of effect of nutrition supplementation alone. The findings of these studies await confirmation in larger controlled studies. Such a study recruiting nearly 200 patients has recently closed and results are eagerly awaited.

The treatment of cachexia is only one aspect of the care of the patient with advanced cancer and is, on its own, not going to cure anyone of cancer. However, the potential to restore a degree of lean tissue with apparent functional benefits has the potential to improve the lot of this unfortunate group of patients.

CONCLUSIONS

Although progress has been made in understanding the physiologic changes in advanced cancer that give rise to cachexia, it remains a significant cause of morbidity and mortality in malignant disease. The metabolic alterations that occur in these patients might prevent the effective use of additional calories supplied, resulting in ongoing wasting. Broadly speaking, antiinflammatory agents such as fish oil have the potential to normalize these metabolic alterations and may allow the supply of additional nutrition to produce anabolism and the potential for improved quality of life in patients with advanced cancer.

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