Anorexia and Cachexia

June 01, 2015
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Many patients with advanced cancer undergo a wasting syndrome associated with cancer anorexia/cachexia and asthenia. In defining these terms a bit further, anorexia is associated with a marked loss of appetite and/or an aversion to food.

Overview

Many patients with advanced cancer undergo a wasting syndrome characterized by anorexia, loss of weight, asthenia, and a poor prognosis, referred to as the cancer anorexia/cachexia syndrome. In defining these terms further, anorexia describes loss of appetite and/or an aversion to food. The term “cachexia” refers to a loss of body mass, including lean body mass and fat, in the setting of a disease state, in this case cancer. In a study that assessed symptoms in cancer patients being entered into a palliative care service, anorexia/cachexia and asthenia were more common than pain or dyspnea, but typically such symptoms cluster within the top five as the most troubling and bothersome for cancer patients approaching the end of life. Patients who exhibit such signs and symptoms generally have a short survival time, respond poorly to chemotherapy agents, and suffer increased toxicity from these agents.

In addition, cancer anorexia/cachexia often is associated with weakness, fatigue, and a poor quality of life. This symptom of anorexia not only affects the patient but also frequently has a negative impact on family members, in part because the patient is no longer able to participate fully in eating as a social activity.

Diagnostic Criteria

Cancer cachexia is not difficult to identify. In North Central Cancer Treatment Group research trials involving more than 2,500 patients, simple criteria for anorexia/cachexia have been used:
• A 5-lb weight loss in the preceding 2 months and/or an estimated daily caloric intake of less than 20 calories/kg
• A desire by the patient to increase his or her appetite and gain weight
• The physician’s opinion that weight gain would be beneficial for the patient

Recently, other investigators have attempted to provide more detailed or comprehensive definitions of cachexia. For example, Fearon and others recently suggested that weight loss of greater than 2% might also serve to define cachexia in patients already showing evidence of a low body mass index or wasting of skeletal muscle. These definitions are important in stimulating further discussion of this entity and its pathophysiology.

Interestingly, recent studies also suggest that antineoplastic agents may be contributing to some of the body composition changes observed in cachexia. Artoun and others observed that cancer patients treated with sorafenib (Nexavar) manifest notable degrees of muscle wasting over time, with an 8% decrease in lean tissue at 1 year in contrast to placebo-exposed patients.

Management

Nutritional Counseling

Nutritional counseling, as provided by written materials, dietitians, physicians, and nurses, has been recommended, although its value has not been well demonstrated. Recommendations that include eating frequent, small meals (as opposed to large meals), consuming larger quantities of food in the morning than in the evening, and avoiding spicy foods are often provided to patients. Patients may eat better if they are not exposed to the aroma of cooking. Although the benefits of such nutritional counseling are clearly limited, it appears reasonable to provide them.

Recent trials have led to further interest in studying dietary counseling. Ravasco and others
observed improvements in treatment-related side effects and quality of life among colorectal cancer patients who had received dietary counseling as part of a randomized controlled trial. Similar findings from this same group were observed among head and neck cancer patients. These findings require confirmation. A meta-analysis investigating the effect of dietary counseling on clinical outcomes in cancer patients revealed a trend suggesting an improvement in quality of life. Again, the authors noted that nutritional counseling in cancer patients merits further study for purposes of truly establishing the magnitude of its efficacy.

**Appetite Stimulants**

**Corticosteroids**

Corticosteroids were the first agents to undergo placebo-controlled, double-blind evaluation for possible use in cancer cachexia. The first such trial, conducted in the 1970s by Moertel and colleagues at the Mayo Clinic, demonstrated that corticosteroids can stimulate appetite in patients with advanced, incurable cancer. Several subsequent placebo-controlled trials, using various corticosteroid preparations and doses, have confirmed these results.

Dexamethasone (3 to 8 mg/d) is a reasonable option for clinical use. Known detriments to corticosteroid use include the well-known toxicities associated with long-term administration, including myopathy, peptic ulcer disease, infection, adrenal suppression, and hyperglycemia. Many patients with advanced cancer anorexia and cachexia, however, do not survive long enough to suffer from these toxicities.

**Progestational agents**

Several placebo-controlled, double-blind clinical trials have demonstrated that progestational agents, such as megestrol (Megace) and medroxyprogesterone, can lead to appetite stimulation and weight gain in patients with anorexia and cachexia. These trials also demonstrated that the effect of these drugs is seen in a matter of days and that they are effective antiemetics.

Although high doses of progestational agents can cause adrenal suppression because of their mild corticosteroid-type activity (a phenomenon not well understood by many clinicians), they do not appear to cause many of the side effects attributable to classic corticosteroids (such as peptic ulcer disease, myopathy, and opportunistic infections). In lieu of this adrenal suppression, however, stress doses of corticosteroids may be necessary in patients with trauma or infection or in surgical patients while on progestational agents. On the other hand, progestational agents increase the risk of thromboembolic phenomena—a side effect not seen with classic corticosteroids.

A dose-response study with megestrol demonstrated a positive correlation between appetite stimulation and increased megestrol doses, as doses ranged from 160 to 800 mg/d. Nonetheless, given that appetite stimulation has been demonstrated with megestrol acetate doses as low as 240 mg/d, much lower doses are used by many physicians, based primarily on cost considerations.

In the United States, a liquid formulation of megestrol is considerably less expensive than the tablet form and, milligram for milligram, the liquid preparation is more bioavailable. It is reasonable to start with 400 mg/d of liquid megestrol, titrating this dose upward (maximum, 800 mg/d) or downward based on clinical response or the emergence of side effects.

A randomized, prospective clinical trial comparing the utility of megestrol (800 mg/d) with that of dexamethasone (0.75 mg qid) demonstrated similar effects of these medications on patients’ appetites but different toxicity profiles. Whereas megestrol was associated with a higher incidence of thromboembolic phenomena, dexamethasone was associated with more myopathy, cushingoid body changes, and peptic ulcers.

**Other agents**

Various other drugs have been evaluated definitively for the treatment of cancer anorexia and cachexia and have demonstrated little or no benefit. These drugs include fluoxymesterone, pentoxifylline, hydrazine sulfate, dronabinol, cyproheptadine, eicosapentaenoic acid (EPA), and etanercept (Enbrel). Of note, however, the antiserotonergic drug cyproheptadine does appear to be a relatively strong appetite stimulant in patients with the carcinoid syndrome, presumably because it directly counteracts the large amounts of serotonin secreted in these patients.

EPA has been tested extensively for cancer anorexia and cachexia. Although preliminary studies had claimed improvement in appetite, body composition, and survival with EPA, these favorable findings have not been borne out in subsequent phase III trials. Three phase III trials have shown that EPA does relatively little for cancer anorexia and cachexia when tested in the setting of either EPA versus placebo or EPA versus megestrol.
A number of other drugs have been evaluated in a pilot fashion for the treatment of cancer anorexia and cachexia. They include branched-chain amino acids, thalidomide (Thalomid), metoclopramide, oxandrolone (Oxandrin), insulin, and adenosine triphosphate. Similarly, exciting data have arisen from a preliminary study of ghrelin, an endogenous ligand for the growth hormone secretagogue receptor. A study of 21 patients demonstrated the safety of this substance, allowing for the possibility of its further testing in the future. In addition, Garcia and others recently conducted a randomized, double-blind, placebo-controlled pilot study with anamorelin, an oral ghrelin mimetic, in 16 patients with cachexia and observed improvements in weight and trends to suggest greater food intake. Unfortunately, preliminary results from two phase III trials, known as ROMANA 1 and 2, show that the trials did not reach their dual primary endpoint of improved muscle mass and improved function of muscle mass. In addition, two phase III placebo-controlled studies of enobosarm, a selective androgen receptor modulator, were recently completed and reported in preliminary fashion. These preliminary data show that at a dose of 3 mg once daily, enobosarm had a favorable effect on stair climb power through day 84 of the study ($P = .0185$), although results for this endpoint were not consistent between trials. This agent also had favorable effects on lean body mass compared to placebo. Although preliminary results are promising, taken together, these two clinical trials did not meet the overall criteria for the co-primary responder endpoints of lean body mass and physical function, as outlined in the trials. The disappointing results from these large phase III studies underscore the challenge of improving outcomes for patients who are suffering from cancer-associated weight loss. A recent surge in preclinical work points to other agents that may soon undergo further testing in the clinical setting. Of greater salience, Zhou and others examined inhibition of ActRIIB, observing in tumor-bearing animal models that such an intervention completely reversed prior loss of skeletal muscle and led to a survival advantage. Such provocative findings suggest a need for further study of anti-myostatin agents in the clinical setting.

**Enteral or Parenteral Nutrition**

Despite the demonstrated efficacy of corticosteroids and progestational agents in patients with cancer anorexia and cachexia, these drugs do not have a major long-term impact on the vast majority of such patients. Consequently, other treatment approaches, such as enteral or parenteral nutritional methods, have been studied extensively. Several randomized trials failed to demonstrate that these nutritional approaches improve either quantity or quality of life. As a result, experts generally agree that the routine use of parenteral or enteral nutrition cannot be justified in patients with advanced cancer anorexia and cachexia. There are, however, relatively rare circumstances in which parenteral nutrition may play a role in patients with advanced cancer. Such circumstances have been documented by case reports and small case series and have included patients with gastrointestinal insufficiency due to surgery, radiation therapy, or abdominal carcinomatosis (without impending failure of other organs). The decision to initiate parenteral nutrition under these circumstances typically requires a multidisciplinary approach with extensive discussions between healthcare providers and family members.

With respect to enteral nutrition, Baldwin and others conducted a systematic review and meta-analysis encompassing 13 studies that altogether included 1,414 cancer patients, all of whom either appeared malnourished or at risk for becoming so. The purpose of this effort was to better understand the role of enteral nutrition among cancer patients who appeared malnourished. Enteral nutrition interventions were associated with improvements in weight and energy intake (mean difference in weight = 1.86 kg; 95% confidence interval [CI], 0.25–3.47; $P = .02$; and mean difference in energy intake = 432 kcal/d; 95% CI, 172–693; $P = .001$), and they also seemed to have a positive effect on quality of life (emotional functioning, dyspnea, loss of appetite, and global quality of life). However, no impact on survival was noted (relative risk = 1.06; 95% CI, 0.92–1.22; $P = .43$; $I^2 = 0%$; $P$ (heterogeneity) = .56). Perhaps one of the main messages to emerge from this study is the large heterogeneity among studies and, hence, the need to undertake more rigorous research in this area. This latter point, coupled with a lack of survival advantage, suggests that enteral nutrition support should continue to be used with caution in selected cancer patients.

**Prophylactic Therapy**

Given the positive impact of corticosteroids and progestational agents on cancer anorexia and cachexia and the fact that many patients with advanced cancer die with, and/or of, inanition, the potential prophylactic use of these agents was evaluated. A double-blind trial was conducted in
which patients with newly diagnosed, extensive-stage small-cell lung cancer were randomized to receive megestrol or placebo along with standard chemoradiation therapy. This trial was unable to demonstrate any beneficial effect of megestrol on treatment response, quality of life, or survival. Thus, patients should not be prophylactically treated routinely for cancer anorexia and cachexia outside of a clinical trial. Rather, such treatment should be reserved for patients in whom anorexia and cachexia are patient-determined, symptomatic clinical problems.

**Nutrition as It Relates to End-of-Life Care**

Anorexia and cachexia are problematic for many oncology patients as they approach the final stage of life. Family members share in this distress. Questions commonly arise about giving enteral or parenteral nutrition or “forcing” patients to consume more calories in the belief that they would feel better, get stronger, and live longer. Appropriate education, with a compassionate explanation that more calories do not always appear to provide clinical benefit, can help patients as they struggle with loss of appetite and weight at the end of life.

**Suggested Reading**


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