The Oncologist®

Editorial

More Is Better: A Multimodality Approach to Cancer Cachexia

EGIDIO DEL FABBRO

Department of Palliative Care and Rehabilitation Medicine, The University of Texas M. D. Anderson Cancer Center, Houston, Texas, USA

Disclosures: Egidio Del Fabbro: None.

The content of this article has been reviewed by independent peer reviewers to ensure that it is balanced, objective, and free from commercial bias. No financial relationships relevant to the content of this article have been disclosed by the author or independent peer reviewers.

INTRODUCTION

Past efforts to treat cancer cachexia with nutritional or medical interventions probably failed because they were directed at appetite stimulation alone, usually with a single therapeutic agent. More recent randomized controlled trials (RCTs) using specific tumor necrosis factor α inhibitors such as etanercept [1] or infliximab [2] to reverse the underlying catabolic process have also been unsuccessful at improving weight or lean body mass (LBM). Even two-agent combinations have been largely proven to be ineffective. RCTs of dual medical therapy using megestrol with either fish oil [3] or dronabinol [4] showed no gains in weight or appetite compared with progestin monotherapy. A more effective approach might be simultaneous, multifaceted therapy targeting the different mechanisms contributing to cachexia/anorexia syndrome (CAS).

OUTCOMES

In this issue, Mantovani et al. [5] show, for the first time, that a multimodal regimen is more effective than any of its individual components. Notably, their combination of medications and nutritional supplements improved several cardinal features of CAS. LBM, spontaneous physical activity, and appetite increased while serum markers associated with an aberrant inflammatory response (interleukin-6, C-reactive protein) decreased.

Despite progress in our understanding of the mechanisms generating CAS, clinical cachexia research is beset by difficulties, including no universally accepted definition [6, 7] and variable inception points for trials. Unfortunately, cachexia is frequently detected toward the late stages of disease, making it difficult for patients to participate in extended longitudinal interventional trials. Modulating the aberrant inflammatory response and restoring endocrine homeostasis early in the disease trajectory offers the best prospect for improving LBM and function. Measuring gains in LBM usually requires $\geq$6 weeks and the study of Mantovani et al. [5] is quite remarkable for the 4-month duration of treatment. Measuring outcomes such as physical activity and nutritional status in frail and highly symptomatic patients is also challenging, and the obesity epidemic has added to the complexity of measuring body composition because adipose tissue may mask underlying muscle loss in many patients. Previous studies suggest computed tomography (CT) imaging provides a more accurate assessment of muscle mass and body composition in patients with cancer, especially those with "sarcopenic obesity." Although CT measurement of body composition is shown to have potential in predicting prognosis [8] and possibly chemotherapy toxicity [9], this study by Mantovani et al. [5] is the first clinical intervention trial in cancer cachexia using CT imaging as an outcome. The muscle gains produced by

Correspondence: Egidio Del Fabbro M.D., The University of Texas M.D. Anderson Cancer Center, 1515 Holcombe, Unit 1414, Houston, Texas 77030, USA. Telephone: 713-794-4319; Fax: 713-792-3967; e-mail: edelfabbro@mdanderson.org Received January 19, 2010; accepted for publication January 20, 2010; first published online in ***The Oncologist*** *Express* on February 4, 2010.
1083-7159/2010/$30.00/0 doi: 10.1634/theoncologist.2010-0019

the combination therapy arm were associated with improved fatigue, (a symptom proven to be notoriously resistant to pharmacotherapy) as well as improved "objective" measures such as physical activity and total energy expenditure, recorded by continuous home monitoring. Although now infrequently measured as a primary outcome in cachexia trials, the improved appetite shown in this trial may be vital to those patients whose primary goal is to enjoy meals with family members. Finally, the combination therapy arm was able to show an encouraging improvement in the Glasgow Prognostic Score and performance status, but not significantly better than with L-carnitine or thalidomide alone.

Components of Therapy

The authors suggest an additive or synergistic effect of their multimodality therapy without a higher risk for adverse events. Both thalidomide and megestrol acetate have a dose-dependent risk for thromboembolism, and progestins are associated with hypoadrenalism and hypogonadism [10]. Fortunately, despite these potential concerns, there does appear to be "negligible toxicity" in the combination therapy arm, possibly because of the low doses of thalidomide (200 mg daily) and megestrol acetate (320 mg daily). Although ineffective alone, an enriched nutritional supplement was included in the multimodal therapy. A similar strategy of supplementing nutrition has been incorporated in other multimodality approaches [11, 12], because insufficient caloric intake resulting from food aversion and other symptoms may amplify the weight loss caused by the underlying catabolism of cachexia.

Though an antitumor effect by some of the agents (especially thalidomide) cannot be excluded completely, modulation of the proinflammatory response and acute-phase reactants appears to be the likely mechanism of action. Although there may be debate about the relative importance of the various interventions in this multimodality model for cancer cachexia, the rationale for the therapeutic composition is clearly based on prior successful monotherapy studies (e.g., L-carnitine and thalidomide). At the same time, it should be recognized that there is likely to be some heterogeneity in cancer cachexia patients, and a one-size-fits-all approach is not suitable. Ideally, treatment should be modified to target the pathophysiology affecting individual patients, because the contribution of the different mechanisms of cachexia may vary. For example, not all patients have an elevated resting energy expenditure (some may be hypo- or eumetabolic), and for patients with cancer cachexia, poor appetite is a common, but not universal, symptom. In future studies a low-cost comprehensive approach could be extended to include treatment of nutritional impact symptoms [13], testosterone replacement, and resistance training. Gastrointestinal symptoms [14] (such as dysgeusia, early satiety, constipation, and nausea) and hypogonadism are frequently encountered in patients with advanced cancer and could be exacerbating muscle wasting and fatigue.

In conclusion**,** the multimodal therapy by Mantovani and colleagues [5] improves two conditions (cachexia and fatigue [15]) that are traditionally seen as being resistant to pharmacologic interventions and an inevitable consequence of advanced cancer. The study also indicates that multimodality therapies for cachexia need not have significant side effects and should ideally be introduced against a background of "best supportive care" that includes optimal symptom management and physician–patient communication. A greater awareness of CAS by clinicians and the development of reliable inexpensive biomarkers [16] would facilitate earlier intervention and individualized multimodal therapeutic regimens composed of pharmacological interventions, nutrition, counseling, and exercise. The findings by Mantovani et al. [5] in this issue strongly suggest that such clinical trials are justified.

References

1 Jatoi A, Dakhil SR, Nguyen PL et al. A placebo-controlled double blind trial of etanercept for the cancer anorexia/weight loss syndrome: Results from N00C1 from the North Central Cancer Treatment Group. Cancer 2007;110:1396–1403.

2 Wiedenmann B, Malfertheiner P, Friess H et al. A multicenter, phase II study of infliximab plus gemcitabine in pancreatic cancer cachexia. J Support Oncol 2008;6:18–25.

3 Jatoi A, Rowland K, Loprinzi CL et al. An eicosapentaenoic acid supplement versus megestrol acetate versus both for patients with cancer-associated wasting: A North Central Cancer Treatment Group and National Cancer Institute of Canada collaborative effort. J Clin Oncol 2004;22: 2469–2476.

4 Jatoi A, Windschitl HE, Loprinzi CL et al. Dronabinol versus megestrol acetate versus combination therapy for cancer-associated anorexia: A North Central Cancer Treatment Group study. J Clin Oncol 2002;20:567–573.

5 Mantovani G, Macciò A, Madeddu C at al. Randomized phase III clinical trial of five different arms of treatment in 332 patients with cancer cachexia. ***The Oncologist*** 2010;15:200–211.

6 Evans WJ, Morley JE, Argilés J et al. Cachexia: A new definition. Clin Nutr 2008;27:793–799.

7 Bozzetti F, Mariani L. Defining and classifying cancer cachexia: A proposal by the SCRINIO Working Group. JPEN J Parenter Enteral Nutr 2009; 33:361–367.

8 Tan BH, Birdsell LA, Martin L et al. Sarcopenia in an overweight or obese patient is an adverse prognostic factor in pancreatic cancer. Clin Cancer Res 2009;15):6973–6979.

9 Prado CM, Baracos VE, McCargar LJ et al. Sarcopenia as a determinant of chemotherapy toxicity and time to tumor progression in metastatic breast cancer patients receiving capecitabine treatment. Clin Cancer Res 2009;15: 2920–2926.

10 Dev R, Del Fabbro E, Bruera E. Association between megestrol acetate treatment and symptomatic adrenal insufficiency with hypogonadism in male patients with cancer. Cancer 2007;110:1173–1177.

11 Lundholm K, Körner U, Gunnebo L et al. Insulin treatment in cancer cachexia: Effects on survival, metabolism, and physical functioning. Clin Cancer Res 2007;13:2699–2706.

12 Cerchietti LC, Navigante AH, Peluffo GD et al. Effects of celecoxib, medroxyprogesterone, and dietary intervention on systemic syndromes in patients with advanced lung adenocarcinoma: A pilot study. J Pain Symptom Manage 2004;27:85–95.

13 Del Fabbro E, Dalal S, Delgado M et al. Secondary versus primary cachexia in patients with advanced cancer. J Clin Oncol 2007;25(suppl 18):9128.

14 Yavuzsen T, Walsh D, Davis MP et al. Components of the anorexia-cachexia syndrome: Gastrointestinal symptom correlates of cancer anorexia. Support Care Cancer 2009;17:1531–1541.

15 Minton O, Richardson A, Sharpe M et al. A systematic review and meta-analysis of the pharmacological treatment of cancer-related fatigue. J Natl Cancer Inst 2008;100:1155–1166.

16 Tan BH, Deans DA, Skipworth RJ et al. Biomarkers for cancer cachexia: Is there also a genetic component to cachexia? Support Care Cancer 2008;16: 229–234.