Survival: the relevant primary outcome for nutrition therapy in cancer patients

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INTRODUCTION

Nutrition intervention has been much studied in the setting of nonsurgical oncology. There has been no generally agreed standard in the primary and secondary outcomes of nutrition intervention. Recently published clinical nutrition research, as well as current trials posted on www.clinicaltrials.gov reflects a salad of endpoints. There is a culture of the use of traditional nutritional endpoints as the primary outcome; many trials also have multiple secondary endpoints. These outcomes are diverse and reflect different facets of our conception of nutritional status. Several studies ongoing in 2012 or published in the last 18 months have as primary endpoint variables such as body weight, lean body mass, caloric intake, blood values (i.e., (pre)albumin, inflammatory markers), bioelectrical impedance analysis-derived phase angle, quality of life, and symptoms (e.g., mucositis). The clinical benefit of some of these outcomes to patients with cancer can be questioned. Patients, healthcare providers, and regulatory agencies may equally well demand what direct benefit may ensue from the gain of 1.5 kg of muscle, for example, and it is currently difficult to respond to that question.

Compared with the foregoing indices of nutritional status, it is somewhat less common for the primary outcome of a study of nutrition therapy to be the same as in studies of cancer treatment. Oncologists focus on either outcomes of the cancer (i.e., progression-free survival, overall survival, recurrence) or the incidence of complications or toxicities of antineoplastic therapy, or both. There is much evidence that malnourished cancer patients have reduced survival; however, the corollary hypothesis related to this finding, that reversal of nutritional deficits should extend survival, remains unproven.

Several recent findings point to the possibility that improved survival may indeed be a benefit of interventions designed to reverse or prevent nutritional deficits and this has fuelled the development of a small number of clinical investigations with survival as the primary outcome. This development has been in two thematic areas.

Prevention of the erosion of the lean body mass, specifically skeletal muscle through inhibition of the action of myostatin

Myostatin, also known as growth and differentiation factor (GDF)-8, is a member of the transforming growth factor-β family. Its normal action is to limit muscle mass. Inhibitors of myostatin signaling or mutations in the gene encoding this protein result in dramatic increases in muscle mass whereas overexpression of myostatin results in cachexia-like wasting. There is striking evidence that blocking myostatin improves survival of animals with cancer in experimental systems. Zhou et al. [1] and Benny Klimek et al. [2] examined the effect of blocking the myostatin pathway in mice bearing cachexia-inducing tumors. These authors blocked this signaling pathway by interfering with its target, the activin type II receptors. This treatment was effective in preserving skeletal muscle mass and grip strength so resulting in larger muscles with increased functional capacity; cardiac muscle mass was also maintained. Zhou et al. showed increased survival of mice bearing the colon-26 tumor even though the intervention had no effect on tumor growth. These studies have provided clear evidence that blocking muscle wasting per se can have significant beneficial effects on survival, but there is a large step between these animal models and establishment of such clinical benefit in patients with cancer.

Extensive efforts have been directed at developing agents capable of modulating myostatin signaling for applications in clinical settings. One of these is LY2495655, a proprietary agent listed on the...
National Cancer Institute Drug Registry as an anti-myostatin monoclonal antibody. This antibody binds to and neutralizes myostatin protein and is the subject of an ongoing trial. This phase II study (NCT01505530) is a multicenter, randomized, double-blind, placebo-controlled trial in participants with locally advanced/inoperable or metastatic pancreatic cancer and will investigate two different doses of LY2495655 in combination with chemotherapy. The primary outcome measure in this study is overall survival, with secondary endpoints including muscle mass and physical performance. This is a welcome large step forward in assessing the potential clinical benefit of antimyostatin therapy.

**Nutrition therapy with long chain n-3 polyunsaturated fatty acids eicosapentaenoic acid and docosahexaenoic acid**

Nutrition therapy with fish oils, or purified docosahexaenoic acid (DHA) or eicosapentaenoic acid (EPA) has been the subject of many studies in experimental animals. Clinical research is relatively less developed, however, two recent studies probed for a potential relationship between n-3 polyunsaturated fatty acids and cancer outcomes. Murphy et al. [3] assessed the potential interest of fish oil supplementation on the response rate to first-line chemotherapy in patients with nonsmall cell lung cancer. They evaluated whether the combination of fish oil and chemotherapy (carboplatin with vinorelbine or gemcitabine) provided a benefit over standard of care (nonrandomized study design) on response rate and clinical benefit from chemotherapy. Response rate was defined as the sum of complete response and partial response, and clinical benefit was defined as the sum of complete response, partial response, and stable disease divided by the number of patients. The fish oil group had significantly higher response rate (60.0 vs. 25.8%) and greater clinical benefit (80.0 vs. 41.9%) compared with standard of care. These findings hearken back to a similar study by Bougnoux et al. [4], who gave metastatic breast cancer patients DHA in an open label Phase II study. Patients stratified into subgroups by level of DHA incorporation into plasma phospholipid, and the subgroup with high DHA incorporation had strikingly longer time to tumor progression (8.7 vs. 3.5 months, \( P = 0.02 \)) and overall survival (34 vs. 18 months; \( P = 0.007 \)) than the group with low incorporation.

While cancer therapies have been approved on the basis of clinical benefits of the same magnitude as that shown in the studies by Murphy et al. and Bougnoux et al., the lack of randomized study designs is a considerable impediment to the evaluation of the potential clinical benefit of n-3 supplementation. It is thus with considerable interest that we note the development of a new trial by Bougnoux et al. which is stratified and powered to detect differences in progression-free survival. The study is a phase III, randomized, multicentre, two-arm double-blind trial to evaluate the usefulness in terms of efficacy of a dietary supplementation with DHA during chemotherapy in patients with metastatic breast cancer (DHALYA study). Progression-free survival defined as the time from the date of randomization to the earliest of the date of first radiologic disease progression will be the primary outcome of this study.

**CONCLUSION**

The recent initiation of trials to test for survival as an outcome of therapy to maintain lean body mass or maintain long chain n-3 polyunsaturated fatty acid levels in patients with cancer, is an exciting development, for which the results are eagerly anticipated. These investigations are randomized, stratified and powered to detect differences in survival, and will begin to provide conclusive evidence as to whether or not these interventions provide meaningful benefit.

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**Conflicts of interest**

There are no conflicts of interest.

**REFERENCES**