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Cancer-Associated Weight Loss: Releasing Its Firm Grip on Negative Clinical Outcomes

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What does the future hold for treating weight loss in advanced cancer patients? The past 5 years have yielded immense disappointment in efforts to treat the cancer-associated weight loss syndrome. As reviewed by Garcia in this issue of *Current Opinions in Supportive and Palliative Care*, two large registration trials, which, in total, included over 1500 patients and cost an estimated $100 million, failed to achieve their primary dual endpoints [1–3]. Neither of these trials — one which tested the selective androgen receptor modulator, enobosarm, and the other of which tested the oral ghrelin mimetic, anamorelin — resulted in a prescribable agent, leading to the same stagnant conclusion that modest palliation with older agents such as progesterones and corticosteroids remains the only proven therapeutic approach for select weight-losing cancer patients with an incurable malignancy [4,5]. In essence, over the past four decades, the standard of care for treating cancer-associated weight loss in incurable cancer patients remains unchanged. Hence, the question posed above is not only provocative but also relevant and timely.

In this issue of the journal, investigators begin to ponder this question further. Summarizing a compendium of previously-published data, Lau and Iyengar take the novel approach of focusing on weight loss in cancer patients who are receiving radiation [6]. Only recently, Fakhry and others added yet another such study that looks at radiation in over 600 patients with oropharyngeal cancer and observed that weight loss is associated with shorter cancer progression-free survival [7]. Such studies join countless others that have reached the exact same conclusion: weight loss in cancer patients is associated with poor clinical outcomes. However, this focus on radiation-treated cancer patients is innovative; it draws attention to cancer patients who often receive aggressive multi-modality therapy, suffer high rates of severe weight loss, and yet appear to be a captive audience for a therapeutic intervention to help manage weight loss because of daily travel to the clinic to receive radiation treatments. Furthermore, relatively little has been done to rigorously study this group of patients. In their thorough paper, Lau and Iyengar have put in place the groundwork for future interventional trials for cancer-associated weight loss in patients receiving radiation [6].

Also in this issue, Dunne and others suggest that exercise merits further study to treat cancer-associated weight loss [8]. Indeed, these investigators have spearheaded exercise

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programs in cancer patients. Completing a three-arm randomized, small pilot study that recruited older patients with prostate cancer, these investigators tested a home-based walking and resistance training intervention *versus* technology-mediated walking and resistance intervention *versus* standard of care [9]. These exercise interventions generated some very early signals of promise compared to standard care – but, first and foremost, these investigators demonstrated feasibility. Importantly, this demonstration of feasibility is a salient achievement in its own right, particularly when other investigators have been hesitant to study exercise in weight-losing cancer patients and when instead they have published studies entitled, for example, "Patients with established cancer cachexia lack the motivation and self-efficacy to undertake regular structured exercise" [10]. Moreover, implementing exercise interventions in weight-losing cancer patient appears challenging: screening patients prior to their successful enrollment in an exercise-based clinical trial yields a patient accrual rate of less than 15% [11]. Despite such obstacles, exercise may yield broad-based benefit. Hypothetically, it could favorably impact fatigue [12]. Exercise also appears to provide a mechanism-based approach to the maintenance of muscle mass, as suggested by prior studies which suggest exercise reduces muscle autophagy and tamps down the inflammatory cascade that appears to drive muscle wasting [13,14]. Studying exercise might also eventually give rise to novel investigational drugs that simulate exercise, yield the putative benefits of exercise, but circumvent the presumed hesitation on the part of both patients and healthcare providers to recommend exercise interventions to weight-losing cancer patients with incurable cancer [13]. Summarizing the state-of-the-science as relevant to therapeutics for cancer-associated weight loss and providing a framework for future direction, Dunne and others make a strong argument for further studying exercise [8].

Finally, Le-Rademacher and others from our group have reviewed how rigorous study design is pivotal to answering the question above [15]. In this context, Penna and others provide a thoughtful summary of the role of vitamin D in treating cancer-associated weight loss, making the point that the evidence supporting its role for further testing is limited and further underscoring the point that the strength of a data in support of launching a large phase 3 trial is the best predictor of trial outcome [16]. In addition, Del Fabbro provide an in depth discussion of state-of-the-art practical approaches to treating cancer-associated weight loss; this discussion nicely outlines a standard of care that is not only helpful in caring for patients on a day-to-day basis but also in designing the control arm in a comparative study [17].

In summary, all the papers in the current issue of *Current Opinions in Supportive and Palliative Care* attempt to answer, "What does the future hold for treating weight loss in advanced cancer patients ?" – whether by means of identifying clinical circumstances, such as with radiation, where cancer-associated weight loss is common but not as readily recognized; whether by means of studying interventions such as exercise; whether by means of suggesting that certain interventions, such as vitamin D, should be bypassed for study in future clinical trials; or whether by means of defining a state-of-the-art control arm for a future comparative clinical trial. Taken together, these papers provide clear direction for future clinical trials with the goal of palliating weight loss in patients with advanced cancer and with the goal of enabling future therapeutics to result in the release of the firm grip this entity holds on negative clinical outcomes.

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