Message from the Editor-in-Chief

Cancer cachexia: definitions, outcomes, and treatments

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The January issue of *Annals of Palliative Medicine* is a focused issue dedicated to the incredibly important syndrome of cancer cachexia. This issue is guest edited by Mellar Davis, MD, the Director of Palliative Services at Geisinger Health System in Danville, Pennsylvania and Eduardo Bruera, MD, the FT McGraw Chair in the Treatment of Cancer and Chair of the Department of Palliative, Rehabilitation and Integrative Medicine at MD Anderson Cancer Center in Houston, Texas.

Cancer cachexia has been defined by an international consensus group as "a multifactorial syndrome characterized by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment. Its pathophysiology is characterized by negative protein and energy balance driven by a variable combination of reduced food intake and abnormal metabolism" (1).

The tumor itself can induce cachexia through an upregulation of inflammatory cytokines, electrolyte abnormalities, or physical obstruction or impairment in bowel function. Patient-related factors can contribute to cachexia, including pain, fatigue, and depression. The therapies that are intended to treat the malignancy, including cytotoxic chemotherapies, immunotherapies, and radiation therapy, can also contribute to cachexia by causing changes in taste or smell, decreased salivary function, nausea, and fatigue.

Cancer cachexia is underreported and undertreated but is actually quite common, with as many as 80% of cancer patients suffering from cachexia during the course of their illness (2-4). Malignancies that are especially aggressive and that can affect swallowing or appetite are particularly associated with cause cachexia, including upper gastrointestinal, head and neck, and lung cancers (4,5). As cancer cachexia is characterized by a loss of skeletal muscle (1), patients with cachexia often have significant functional impairment and compromised quality of life. These effects can, in turn, limit patient tolerance to anti-cancer therapies. Furthermore, cancer patients with cachexia have more frequent treatment-related toxicities and have worse overall survival compared with cancer patients without cachexia (4,6-8).

In the first review article of the focused issue, Baracos and colleagues set the stage for remainder of the issue by defining cancer cachexia according to quantitative measures of skeletal muscle mass loss (9). They detail how the etiology of cancer-associated muscle wasting is multifactorial, and that alterations in muscle protein synthesis, autophagy and ubiquitin-mediated proteolysis are major drivers of muscle loss.

Shalini Dalal next discussed lipid metabolism in cancer cachexia. He reports on the significance of adipose tissue lipid metabolism alterations in the development and progression of cancer cachexia. The thorough review addresses the biological and molecular underpinning of cancer cachexia and provides logic to the choice of targets and treatments discussed throughout the remainder of this focused issue.

Rony Dev reviews the diagnostic criteria for measuring cachexia across quality of life and anorexia endpoints. Dev also discusses measures of caloric intake, nutritional impact and symptoms, weight and body composition, and laboratory biomarkers of cancer cachexia. He describes measurements using malnutrition screening tools, energy balance calculations, and body composition assessments. He calls for providers to assess all cancer patients for risk for malnutrition at presentation and periodically thereafter

throughout their disease course regardless of a history of weight loss.

Next, Kasvis *et al.* discuss health-related quality of life across cancer noncachexia, pre-cachexia, cachexia, refractory cachexia stages. In a large cohort of patients completing health-related quality of life assessment questionnaires, refractory cachexia patients self-reported significantly poorer wellbeing. They also demonstrated that cannabinoid treatment has the ability to improve assessment scores for lack of appetite.

Jeffrey Crawford then outlines the criteria for response to cachexia treatment. This is of vital importance since a barrier to the development and approval of effective interventions has likely been, in part, a lack of agreement on the proper endpoints in cancer cachexia trials. Perhaps the most controversial criteria centers on assessing physical function, as improvements in lean body mass do not always correlate with improvements in muscle function or importantly physical function. Crawford advocates for patient reported outcomes to best assess for improvements in physical function in future trials.

In the next article of this focused issue of *Annals of Palliative Medicine*, Childs and Jatoi review palliative therapies for cancer-associated anorexia. They focus their report on non-invasive nutritional support, invasive and parenteral nutritional support, and appetite stimulants. As commonly used treatment approaches, such as nutrition education, support and exercise, are often of limited efficacy in improving quality of life and overall survival, the authors call for healthcare providers to be vigilant about diagnosing this syndrome and for investigators to conduct additional clinical trials evaluating novel approaches for stimulating appetite in patients with advanced cancers who are losing weight.

Egidio Del Fabbro then evaluates combination therapies in cachexia. As cancer cachexia is a multifactorial syndrome, he reviews the difficulties of treating cachexia when directing single-agent therapy at a single domain of the syndrome, such as anorexia or muscle wasting. He advocates for early intervention and combining pharmacological and non-pharmacological therapies that can simultaneously modulate multiple major mechanisms causing cachexia.

Next, Prado and Qian assess anti-cytokines in the treatment of cancer cachexia. In addition to fatigue and functional limitations, cachexia can lead to anemias, electrolyte and albumin deficiencies, and elevations in inflammatory markers (10). As such, anti-cytokine agents might be particularly attractive in attempting to combat cancer cachexia. The authors review the rationale and data for the use of anti-cytokine agents used in prior phase I and phase II trials to treat cancer cachexia, including TNF-alpha, IL-1 alpha, IL-6. They then detail the promising results achieved to date with thalidomide and MABp1, a natural IgG1k human monoclonal antibody targeting IL-1 alpha. These agents are of particular interest since they target multiple cancer cachexia-related cytokines and pathways, and they can also exert anti-tumor effects. The authors conclude with recommendations for future cachexia clinical trials.

The issue next addresses important symptomatic implications of cancer cachexia: nausea and early satiety. While chemotherapy (11,12) and radiation therapy (13,14) has been well associated with anorexia and treatment-induced nausea, muscle wasting and energy imbalances from cancer cachexia also commonly lead to nausea and early satiety. Malik and Yennurajalingam review the utility of prokinectics and of ghrelin-receptor agonists in improving chronic nausea and early satiety associated with cancer cachexia. Prokinectic agents can improve nausea and early satiety related to cachexia (15,16). Ghrelin, a natural ligand of the growth hormone secretagogue receptor, can stimulate appetite, modulate pro-inflammatory cytokine synthesis, promote growth of adipose tissue, and influence regulation of skeletal muscle mass (17,18).

In the last article of this focused issue of *Annals of Palliative Medicine*, Davis and Panikkar discuss methods to diagnose, causes of, outcomes associated with, and treatments for sarcopenia, which is a quantified loss of muscle and associated loss of function (19). This can lead to reduced physical function, poor quality of life, poorer results with systemic therapy, and correspondingly poorer survival outcomes. As with more general cancer cachexia, the authors advocate for a multimodal and multiple drug approaches to treat sarcopenia, although data to date on such combination therapies for sarcopenia are limited.

Finally, in a Meeting Report, Johnstone and colleagues provide a Report from the Fifth Annual Meeting of the Society for Palliative Radiation Oncology, and international group of radiation oncologists committed to delivering high quality, evidence-based palliative radiotherapy (20). Accomplishes to date and future goals of the society were discussed and chronicled in the report.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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