Preface: Cancer Cachexia, From Basic Research to Clinical Application: A Paradigmatic Translational Research Journey

This special issue includes a thorough review of the main aspects of the multifaceted cachexia syndrome and covers the most recent and stimulating approaches using experimental, translational, and clinical studies.

Cachexia may well represent the devastating flip side of the tremendous achievements of modern medicine because the incidence of cachexia is also a function of the survival of chronic illness. For a long time, cachexia has been recognized as an adverse effect of cancer. It is associated with reduced physical function, reduced tolerance to anticancer therapy, and reduced survival.[1] Although our understanding of cachexia has progressed over the past few years, a lack of definition, diagnostic criteria, and classification have prevented advances in both clinical trials and clinical practice.

A definition and classification of cachexia recently have been developed by an international panel of experts who participated to a formal consensus process. Cancer cachexia was defined as "a multifactorial syndrome defined 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."[1] Its pathophysiology is characterized by a negative protein and energy balance driven by a variable combination of reduced food intake and abnormal metabolism. The agreed diagnostic criterion for cachexia was weight loss greater than 5%, or weight loss greater than 2% in individuals already showing depletion according to current bodyweight and height (body mass index <20 kg/m^2) or skeletal muscle mass (sarcopenia). An agreement was made that the cachexia syndrome can develop progressively through various stages: precachexia to cachexia to refractory cachexia. Severity can be classified according to the degree of depletion of energy stores and body protein (body mass index) in combination with the degree of ongoing weight loss.[1]

In this special issue, 2 articles deal with inflammation, which no doubt plays a central role in cancer cachexia: the inflammatory response encompasses the abnormal production and release of proinflammatory cytokines, which mediate the most important symptoms of cachexia. The first article, by Laviano et al ("Neuroinflammation: A Contributing Factor to the Pathogenesis of Cancer Cachexia"), deals with the specific aspect of "neuroinflammation." The second article, by Argilés et al ("Counteracting Inflammation: A Promising Therapy in Cachexia"), highlights the role played by proinflammatory cytokines involved in cancer cachexia and suggests strategies based on either blocking their synthesis or action by drugs (e.g., thalidomide, anticytokine antibodies) or via nutrients as effective therapeutic approaches. The potential of multitargeted therapies in the treatment of cancer cachexia is reinforced. In their article, Johns et al ("Is Tissue Cross-Talk Important in Cancer Cachexia?") explore the possibility that adipose–muscle tissue cross-talk may be important in the potential development of the treatment and outcomes of cancer cachexia. This cross-talk occurs through adipokines and myokines, which act in an endocrine fashion to play a complex role in regulating body composition in both health and disease, but particularly in chronic diseases. To date, there has been little effort to manipulate the integrative physiology of adipose and muscle tissue for therapeutic interventions; this review suggests that an understanding of the integrative physiology that plays an important role in cachexia may provide a novel therapeutic approach for cancer cachexia. The role of ghrelin, an hormone secreted by the cells of the fundus of the stomach, in the pathophysiology of cancer cachexia has been highlighted by Fujitsuka et al ("Pathophysiology of Ghrelin and Development of Clinical Trials in Cancer Cachexia: Rikkunshito, a Traditional Japanese Herbal Medicine Releasing Ghrelin, as an Additional Novel Approach for the Treatment of Cancer Cachexia"),

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as well as the development of clinical trials with ghrelin or ghrelin-like molecules (synthetic derivatives). From the therapeutic standpoint, the clinical value of physical resistance exercise has been suggested by Maddocks et al ("Therapeutic Exercise in Cancer Cachexia") as a potentially useful tool to improve the poor physical performance often found in cachectic cancer patients. The article by Viganò et al ("The Cachexia Clinic: from Staging to Managing Nutritional and Functional Problems in Advanced Cancer Patients") is a very interesting attempt to evaluate the clinical relevance of the cancer cachexia staging (CCS) recently proposed by Fearon et al,[1] by suggesting ways to apply the CCS to the clinical practice via standardized methods in 208 advanced cancer patients from the Human Cancer Cachexia Database. The CCS was correlated with several patient-centered indicators, and the study supports the clinical relevance and applicability of CCS and represents an innovative approach to translating the cachexia definition into bedside (clinical) practice. In the article by Madeddu et al ("Multitargeted Treatment of Cancer Cachexia"), the multifactorial nature of cachexia is well explained, and the article highlights that the clinical management of cancer cachexia is a complex challenge that should address the different causes underlying this clinical event, with an integrated multimodal treatment approach targeting the different factors contributing to its pathophysiology. Apart from progestogens, the most important clinical trials carried out during the last 5 years have highlighted, for instance, that muscle strength measures and a free total physical activity monitoring system should become a standard practice in the clinical trial setting.

In the article by Lucia et al ("Cancer Cachexia: From Molecular Mechanisms to Patients' Care"), cancer cachexia is reviewed from its underlying mechanisms to the clinical approach, focusing on the diagnostic effort to recognize precachexia to prevent changes in body composition and nutritional complications secondary to cachexia. The suggestion is that "from the point of disease diagnosis, every cancer patient needs a continuous monitoring to receive effective, tailored nutritional and metabolic support." The rationale for a multimodal approach including different target combinations also is highlighted.

REFERENCE

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