Treatment of cancer cachexia

The incidence of cachexia is of crucial importance for survival in chronic diseases, including cancer. Modern medicine has to deal with this important interdisciplinary problem, worldwide. Cancer is now better treated by novel therapies. New therapeutic strategies represent an advantage over the previous standards of care, but patients continue to face the nutritional and metabolic consequences of the illness process itself and the effects related to the therapies.

This book focuses on cachexia as a clinical syndrome that accompanies different types of cancer. There is not yet an unified definition of cancer cachexia. It may be considered the result of a complex cascade of events including chronic inflammation, free radical generation, chronic hyperactivation of immune and endocrine systems with consequent dysregulation of appetite, hormone resistance syndromes, increased catabolism and impaired anabolism. During recent years research has particularly focused on the role of inflammation and on the dysregulation of most of the catabolic and anabolic pathways. The results of such intensive research should lead in the near future to the development of new treatments for cancer cachexia.

The main signs and symptoms of cachexia are represented by weight loss, muscle and adipose tissue wasting, inflammation, asthenia and loss of appetite. They are often under-recognized in clinical practice.

This book aims to increase awareness of cancer-related metabolic and nutritional impairments, as well as knowledge of the pathophysiological mechanisms of cachexia leading to muscle and fat tissue wasting. The clinical consequences of cachexia are now receiving more attention from health-related professionals as a consequence of the enormous efforts of scientific societies, individual researchers, patient associations, and pharmaceutical industries. Cancer cachexia is an extremely complex syndrome and an important clinical event, particularly because of its implications in terms of increased morbidity, mortality, socio-economic issues and its negative impact on the quality of life.

In summary, cachexia can be analyzed from different perspectives, including those of morphologists, epidemiologists, biochemists, biologists, physiologists, and clinicians. The primary purpose of this work is to spread knowledge of cancer cachexia among health care professionals, and in particular, nutritionists, internists, oncologists and dietitians.

We hope that this book will help to more clearly understand the clinical impact of cancer cachexia, highlighting the importance of the early diagnosis and treatment of this severe and disabling clinical condition.

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Cachexia is a complex and multifactorial syndrome featuring the loss of skeletal muscle mass (with or without loss of fat mass), impairing the quality of life (QoL), and increasing morbidity and mortality in patients affected by chronic diseases. The term “cachexia”, derived from the Greek words kakōs (bad) and hexis (condition or appearance), is associated with a progressive wasting syndrome leading to death. Cachexia originates from the complex interplay between a tumor, host metabolism, and proinflammatory cytokines; it is not fully reversible by conventional nutrition support and it should be differentiated from starvation, age-related loss of muscle mass, primary depression, malabsorption, and hyperthyroidism.1, 2 Among cancer patients, cachexia accounts for up to 20% to 30% of patient deaths and it is estimated that two million people die annually across the world, solely because of the consequences of cancer-related cachexia.1, 2 Cancer cachexia has a higher prevalence in gastrointestinal, lung, and head-neck tumors than in other kinds of neoplasia such as breast, hematologic, and endocrine tumors.3 Until recently, cancer cachexia was considered a terminal cancer event substantially refractory to available treatments and uniquely amenable to palliative support. Currently, a better understanding of its pathogenesis suggests that cachexia should be considered an early phenomenon. Indeed, significant biochemical and molecular changes occur in cancer patients before any evidence of body weight loss, thus suggesting the use of early, appropriate, tailored interventions aimed at preventing, reversing, or delaying the metabolic perturbations that ultimately lead to cachexia. A panel of experts has suggested a multimodal intervention performed by a synergistic approach implemented by oncologists and nutritionists and represented by the so called “parallel pathway”.2 This intervention consists of an early assessment combined with an intensive nutritional and functional follow-up, proceeding in parallel to the oncological follow-up. The scientific community has been focusing on spreading the message that cancer cachexia is not related to the last period of cancer disease, but that it may instead be present from the early phases, even without obvious clinical manifestations: the early detection of cancer cachexia along with a periodic follow-up of nutritional status changes may be an efficacious intervention to treat this devastating condition and even to prevent it.2 This strategy appears decisive in order to guarantee the patient’s best performance during anticancer treatments, thus avoiding administration of scheduled dose reduction or even premature treatment suspension.

Although the pathway is clearly defined, daily practice describes a different scenario: many patients are evaluated too late, when a high percentage of body weight has already been lost and the refractory stage of cancer cachexia has already occurred, rendering available interventions ineffective.

In this light, some authors have recently proposed a classification system and practical diagnostic criteria in order to promote the early detection of cancer cachexia, thus allowing prompt efficacious intervention.2, 4 Considering cancer cachexia as a continuum, experts have identified three stages of clinical...
TREATMENT OF CANCER CACHEXIA

**Table 1-I – The main clinical determinants characterizing cancer cachexia staging according to the definition.**

<table>
<thead>
<tr>
<th></th>
<th>Pre-cachexia</th>
<th>Cachexia</th>
<th>Refractory cachexia</th>
</tr>
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<tbody>
<tr>
<td>Weight loss</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Low BMI</td>
<td></td>
<td>X</td>
<td></td>
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<tr>
<td>Inflammation</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anorexia</td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>Sarcopenia</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Anticancer therapy unresponsiveness</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Low PS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Life expectancy &lt;3 Mo</td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

Abbreviations: BMI = Body mass index; PS = Performance status; Mo = Months.

relevance: pre-cachexia, cachexia, and refractory cachexia, distinguishable from each other by different clinical determinants (Tab. 1-I).

- **Pre-cachexia** is defined by unintentional weight loss of ≤5% of usual body weight during the last six months, chronic or recurrent systemic inflammatory response (e.g., elevated serum levels of C-reactive protein), and anorexia or anorexia-related symptoms.
- Patients are classified as having cachexia when they have more than 5% loss of stable body weight over the past 6 months, a body-mass index (BMI) less than 20 kg/m² and ongoing weight loss of more than 2%, or sarcopenia and ongoing weight loss of more than 2%.
- In refractory cachexia, the cachexia can be clinically refractory as a result of very advanced cancer (pre-terminal) or the presence of rapidly progressive cancer unresponsive to anticancer therapy. This stage is characterized by a low performance status and a life expectancy of less than three months and is associated with active catabolism, or the presence of factors that render the active management of weight loss no longer possible or appropriate.

**CLINICAL FEATURES OF CANCER CACHEXIA**

Patients with cancer might present with malnutrition (secondary to anorexia and starvation), cachexia, or both. Cachexia should also be differentiated from starvation, age-related loss of muscle mass, primary depression, malabsorption and hyperthyroidism, and should instead be considered a metabolic derangement, originating from the complex interplay between chronic disease, host metabolism and the imbalance between pro-inflammatory and anti-inflammatory cytokines. This interaction also implies an abnormal production of neuropeptides and hormones, at least in part responsible for anorexia, insulin resistance, and increased lipolysis and lipid oxidation, increased protein turnover. Although cachexia is not fully reversible by conventional nutrition support, reduced nutrient availability (because of reduced intake, impaired absorption or increased losses, or a combination of these) may be a significant component and play a role in the pathogenesis of cachexia. Indeed, it is noteworthy that while not all malnourished patients are cachectic, all cachectic patients are invariably malnourished.

The most clinically relevant phenotypic features of cachexia are represented by anorexia, weight loss, inflammation, body composition derangement and sarcopenia. Chemosensory alterations in cancer and during cancer therapy are well documented, with alterations in taste and smell often contributing to the development of food aversion and reduced hedonic response. The disruption of central and peripheral signaling for
regulation of eating behavior in cancer patients may lead to anorexia, defined as the loss of desire to eat, consisting of appetite loss, early satiety and/or altered food behavior finally determining a reduced energy intake. Anorexia accounts for up to 55% of patients at the point of the cancer diagnosis and this is even higher in terminally ill cancer patients, leading some authors to use the term “cancer anorexia-cachexia syndrome” (CACS) to describe this clinical condition.

Body weight loss has largely represented the cornerstone of cachexia diagnosis and staging. It can vary significantly according to cancer location and stage and is directly related to a worse clinical outcome and prognosis. However, body weight is influenced by a number of physiological and pathological changes (such as water retention, fat store replenishment, intracellular and extracellular water distribution alterations) and may in certain clinical conditions have low diagnostic accuracy. Therefore, although body weight loss was in the past the main diagnostic determinant, recent definition and classification has highlighted the preeminent role of body composition derangements in identifying cachectic patients.

Weight-losing patients suffered a loss of both fat and lean body mass. The loss of lean body mass, most notably skeletal muscle, is more dramatic in cancer patients and represents an independent predictor of morbidity and mortality. A systematic literary review has revealed that there is a limited correlation between muscle mass and muscle function: muscle strength in lung cancer patients seemed to be affected regardless of loss of muscle mass. In patients with pre-cachexia, exercise capacity was significantly reduced, despite maintenance of muscle mass, and resistance exercise training increased all parameters of muscle strength and physical performance, with no difference to muscle mass.

Low muscle mass associated with low muscle function (i.e. strength and performance) are features of the clinical condition called sarcopenia, which is a key diagnostic criterion for the definition of cancer cachexia, as mentioned above. In various populations with cancer, sarcopenia is associated with poorer performance status (PS), reduced overall survival and an increased risk of chemotherapy toxicities. The common pathway for muscle degradation involves ubiquitin-proteasome. Upstream activation is performed primarily through the NF-κB and STAT3 pathways, making them targets for potential interventions. Cytokines are important not only to establish tumor-host interaction and deregulate inflammatory response to tumor burden, but also as mediators of muscle wasting by directly targeting muscle tissue. In this regard, cachexia appears to be a genetically regulated response, dependent on a specific subset of genes, which control a highly regulated process of muscle protein degradation. In clinical practice, several easily identifiable factors have been studied in an attempt to quantify the degree of inflammation and use that data to predict outcomes or guide treatment. The most commonly used inflammatory markers are represented by the elevated neutrophil: lymphocyte ratio (NLR), the C-reactive protein and the modified Glasgow Prognostic Score, which have been associated with impaired clinical outcomes.

Inflammation and sarcopenia may be concurrently present in overweight/obese cancer patients: sarcopenic obesity appeared to be an additional prognostic risk factor leading to lower pathological complete response rate and shorter progression-free survival to anticancer therapies. In cancer patients affected by sarcopenic obesity, and the loss of...
lean body mass is notably related to poor survival, irrespective of age, sex, and functional status. Thus, even in obese cancer patients, in which low-grade weight loss or stable body weight may be registered, the detection of body composition alterations and/or functional impairment should always be a guide to a more accurate assessment for the diagnosis of sarcopenia and/or cachexia that may significantly impair clinical outcome.

REFERENCES