Top Ten Tips Palliative Care Clinicians Should Know About Cachexia

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Abstract

Cachexia is a multifactorial syndrome that is common in cancer and chronic disease. It is often underdiagnosed and therefore goes un- or undertreated. Cachexia causes suffering across biopsychosocial domains and affects patients and their loved ones. In this article, a group of clinicians and researchers across cancer care, nutrition, and exercise offer tips about assessment, classification, and management of cachexia, with attention to its stage. The required multimodal management of cachexia mirrors well the interprofessional collaboration that is the mainstay of interdisciplinary palliative care and attention to screening, diagnosis, and management of cachexia are critical to maximize patients' quality of life.

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Introduction

Cachexia is an often devastating syndrome of anorexia, reduced nutritional intake, impaired function, worsened treatment response, poor quality of life, and shortened survival caused by systemic inflammation. Cachexia is commonly found in those with advanced cancer and chronic diseases like chronic obstructive pulmonary disease or congestive heart failure. Due to its complex pathophysiology, it is often underdiagnosed, and, due to its challenging management, undertreated. Cachexia's prevalence ranges from 50-80% in advanced cancer and in 20-30% of cases it can be considered as the cause of death.[1] The cachexia syndrome is often accompanied by eating-related distress and body image dissatisfaction this can affect patients and proxies as well and is a major challenge in palliative care (PC) practice.[2]

Systemic inflammation leads in an acute phase reaction to hypoanabolism and hypercatabolism. In combination with the above mentioned reduced oral intake, this ends in a vicious cycle with rapid decline. Cachexia is often described as weight loss, but is, by consensus, defined by the underlying muscle loss. [3] There is an overlap with other syndromes such as sarcopenia, frailty, and asthenia. [4] Due to the systemic nature of the syndrome, single agent treatments are typically ineffective. [5]

Corticosteroids can improve appetite and fatigue and have an anti-inflammatory effect, but cause a loss in muscle mass and therefore aggravate cachexia. Progestins can lead to improved appetite and weight gain in some studies, but no significant increase in muscle mass or quality of life has been shown. Due to progestins' potentially serious side effects such as thromboembolism and fluid retention (weight gain), they are seldom used to treat cachexia in cancer. There is some evidence that cannabinoids or olanzapine can improve appetite and there are signs NSAIDS can reduce systemic inflammation but none of these drugs were beneficial in larger cachexia trials. Trials investigating combinations of the above mentioned drugs remained negative or inconclusive.[6]

Due to its multifactorial nature, cachexia is not responsive to nutritional therapy alone and requires multimodal management. [7] This means a combination of treatment of the underlying disease, supportive measures, nutritional therapy, and exercise.

Unfortunately, the underlying disease is often not reversible in PC and, in cancer patients, cytotoxic cancer therapy can worsen cachexia due to myotoxicity or side effect such as mucositis or fatigue. Therefore, careful supportive management is essential in this situation.[8]

According to consensus, cachexia can be classified into stages: Precachexia, Cacheixa, and refractory Cachexia. Goals of treatment depend on these stages. In Pre-cachexia it is all about prevention, in Cachexia about the above described multimodal treatment and in refractory cachexia symptom control and palliation.[3] In refractory cachexia, reducing distress concerning nutrition and exercise is essential. Psychological consequences should always be kept in focus, because they contribute to suffering.

In this paper, an international group of geriatricians, PC clinicians, researchers, physiotherapist and nutritionist will present ten tips that PC clinicians should know about diagnosing, evaluating, and managing those with cachexia.

TIP 1: Screen all high-risk patients for cachexia by measuring and recording body weight on a regular basis to quickly diagnose and address the problem at an early stage.

Weight loss is the predominant marker of cachexia and reflects the muscle loss that is the hallmark of the syndrome.[3] Weight loss is a strong prognostic marker and is associated with symptoms of cachexia such as fatigue and anorexia.[9, 10]

Fortunately, body weight is quick and easy to measure. Clinicians should record the result and whether the patient wore clothes or shoes so they can compare the results from one visit to another. A downward trend in body weight should lead to communication about nutrition, appetite, and other symptoms affecting nutritional intake. Not everyone losing weight has cachexia and patients who are malnourished predominantly due to reduced supply or uptake of nutrients (e.g., malignant bowel obstruction or malabsorption) are especially important to identify because they may benefit greatly from nutritional counseling and treatment.[11] Be aware that muscle degradation in obese patients or in patients with ascites or edema may be harder to detect as body weight might not change significantly.[9]

TIP 2: Sarcopenia is a key diagnostic criterion for cancer cachexia but can be difficult to detect in the clinical setting.

Sarcopenia is an ongoing loss of skeletal muscle, which may or may not be accompanied by weight loss, and is widely prevalent across a range of cancer types and disease stages. Sarcopenia is associated with functional decline and reduced survival.[12] Defined as low skeletal muscle index, sarcopenia is a key criterion for cancer cachexia. In this context, loss of skeletal muscle is not only attributable to the aging process (as in primary sarcopenia) but arises in a complex interplay between anorexia, increased protein catabolism, systemic inflammation, and increased resting state energy expenditure. It results in a hypercatabolic state and a negative protein-energy-balance that is difficult to reverse. [3]

Early identification of sarcopenia in cancer cachexia is imperative, as, undetected and undermanaged, it can adversely affect patient care and overall prognosis. Sarcopenia can, however, be difficult to detect in the clinical setting as it is not necessarily evident upon visual inspection of the patient. Cancer patients undergo multiple evaluations with

CT scans during their treatment, providing a unique opportunity to identify patients at risk for sarcopenia as part of care planning.

Evidence supports the use of valid assessment of skeletal muscle mass at multiple vertebral levels, not only L3, as best practice in quantifying total skeletal muscle mass using CT to diagnose sarcopenia. [13] Implementation of CT evaluation of sarcopenia in the clinic follows from advances in muscle mass measurement (automatic segmentation technology) to help guide diagnosis. [12] In addition, simple screening methods, such as the rapid tool SARC-F questionnaire or muscle strength and performance testing (e.g., grip strength, sit to stand test, or gait speed), are acknowledged as diagnostic tools for sarcopenia, especially in older cancer patients and the geriatric setting, and are readily available to clinicians. [14]

TIP 3: Cachexia can occur across many diseases, cancer types, cancer stages, and clinical phenotypes and it is commonly found in GI, head and neck, and lung cancers.

Cachexia can occur due to many chronic non-malignant diseases, including heart failure, kidney disease, respiratory disease, neurological disease, AIDS, and rheumatoid arthritis. It is especially common in malignancy, affecting 50–80% of patients with advanced cancer.[15] The distribution of cachexia varies by cancer type, though different criteria to define cachexia make accurate comparison difficult.[16]

Cachexia is most common in people with pancreatic, gastric-oesophageal, head and neck, and thoracic cancers, and least common among people with prostate, breast, and hematological cancers.[17] The differences in prevalence may relate to: how often diagnosis occurs at an advanced stage; the prognosis of different cancer types; the effects of cancer type on ingestion, digestion, and absorption (affecting energy intake); and different tumors leading to altered metabolism.[17] Other characteristics associated with a higher prevalence of cachexia include more advanced disease stage, sex (men are more susceptible than women), presence of comorbid conditions, and older age. Amongst individuals with the same cancer type and stage, there is still a high degree of variation in cachexia prevalence, development, and severity.

Some cancer treatments can accelerate muscle loss and compound cachexia [18], while successful treatment of the cancer, including a positive response to palliative chemotherapy, can reduce it. Individuals may encounter new problems with food intake, while others may respond well to nutritional interventions that may reduce the energy imbalance component of cachexia. Further, some individuals appear less susceptible to cachexia due to their genetics.[19] If cachexia is not currently present, it may develop in the future. Risk is greatest for individuals with pancreatic and gastric cancer, any degree of weight loss, poor appetite, and/or comorbid respiratory disease.[20] Finally, although cachexia is highly prevalent among people near the end of life, it is not inevitable.[15] Indeed, a minority can even gain weight, muscle, and fat mass close to death.[21]

Tip 4: Cachexia is a muscle-wasting syndrome that leads to muscle atrophy and affects adipose tissue, CNS, and cardiac muscle tissue; thus, cachexia plays a leading role in the large symptom burden palliative patients experience.

Cachexia is based on poorly understood metabolic alterations and systemic changes in both cancer and chronic illnesses that precede a later weight loss. At a systemic level, cancer cachexia is associated with insulin resistance, hyperlipidemia, and inflammation.[22] Tumor-derived catabolic factors such as those in the TGF β-family are responsible of both myofibrillar protein breakdown and contractile dysfunction. In addition, pro-inflammatory cytokines originating from the tumor/immune system crosstalk, such as IL-6, IFNγ and members of the TNF-family, induce catabolism. In addition, emerging data suggest that mitochondrial dysfunction add to skeletal muscle atrophy and altered adipose tissue metabolism.[23, 24]

The central nervous system is now thought to have the overall control of the pathogenesis of cachexia by recognizing cytokines as signals of sickness, including fatigue and anorexia, thereby modulating food intake. As an example, by signaling in the hypothalamus, IL-1β results in both anorexia and catabolic effects on muscle tissue and adipose tissue.[25] Furthermore cancer cachexia can lead to cancer-related impairment of function and autonomic regulation of the heart.[26] However, our understanding of cancer-induced cardiac cachexia is still very limited.

Less well described is the role of cytokines in cachexia of chronic illness, and mechanistic data are scarce. Nonetheless, elevated serum levels of TNF, IL-6 and IFNγ can be found in patients with heart failure, chronic kidney disease, chronic obstructive pulmonary disease, and rheumatoid arthritis.[27] Altogether, we must understand cachexia as a systemic syndrome with impacts on multiple organs and is responsible for large parts of the symptom burden of palliative patients' experience. It calls for a stronger focus on mechanistic and translational research - and it underlines the importance of a multidisciplinary and patient-centered approach to care.

Tip 5: Assess the functional and inflammatory status of the host using the Eastern Cooperative Oncology Group - Performance Status (ECOG-PS) and the modified Glasgow Prognostic Score (MGPS).

The central pillars of cachexia are inflammation and function and both need to be assessed. Functional status is best assessed using the Eastern Cooperative Oncology Group – Performance Status (ECOG-PS). Inflammatory status is best assessed using the modified Glasgow Prognostic Score (mGPS combining C reactive protein [CRP] and albumin) – the most examined inflammation score. Independently these predict survival and quality of life but, combined in the ECOG-PS/mGPS framework, they are synergistic in predicting survival and quality of life.[28, 29]

Across multiple trials, it has been shown that the inflammatory status (CRP) of the patient influences response to systemic anti-cancer therapy.[30] Cachexia therefore could be regarded as an inflammatory rather than a nutritional syndrome.[31]
As the systemic inflammatory response is central to the definition of cachexia, response to treatment, strong relationship with lean mass and function, staging the inflammatory status of the host is key. Combining ECOG-PS with the mGPS results in a highly validated framework for use in all patients with cancer, particularly when cachexia is likely.

TIP 6: When cachexia is noted, treat the underlying cause and any reversible symptoms simultaneously.

Cancer cachexia is a condition with multifaceted pathophysiology requiring a multimodal and multidisciplinary approach for its management.[32] Such an approach

should consider physical and psychological causes and consequences of cachexia, addressing underlying causes and reversible symptoms. This includes pain and symptom control, nutrition support, exercise, anti-catabolic and anti-inflammatory treatment, anemia therapy, and psychological and social support provided in the context of optimal oncological management.[7]

The success of this complex multimodal approach is achieved by a cohesive and patient-centered interdisciplinary team treating patients with or at risk for cancer cachexia. A critical review of the literature on interventions for cachexia in different conditions supported the benefits of multimodal approaches noting improvements in body composition, nutrition, metabolic and functional biomarkers.[33] The authors also noted the need for larger, well-controlled trials of longer duration. The latter is of notable importance as wasting occurs at an accelerated pace compared to a much slower restoration process, similarly to an analogy of a wildfire followed by reforestation: early and continued interventions are needed.[34] Several trials are underway, many focusing on muscle anabolic response to multimodal interventions in patients with pre-cachexia or cachexia. In this context, nutrition intervention is being explored with revigorated interest in the framework of multimodal cachexia care to halt malnutrition and muscle loss. [8, 35, 36]

TIP 7: in some cancer groups with high cachexia prevalence, such as pancreatic cancer, consider a proactive approach and start treatment before overt signs of cachexia develop.

For some cancer diagnoses, the development of malnutrition or cancer cachexia is so frequent that withholding interventions until the patient starts losing weight and muscle seems unreasonable.[37 38] High risk patients could thus potentially benefit from starting interventions early in order to mitigate future deficits. Accordingly, guidelines now suggest that the goal of cachexia intervention is to maintain or gain muscle mass.[39]

The evidence base for recommending individual preventive treatments is still small, but the biological basis to immediately attend to symptoms and conditions that lead to reduced nutritional intake is solid. Consequently, a strong focus on treating conditions such as nausea, stomatitis, and pain and ensuring that patients have sufficient nutritional intake is important. Similarly, is there a strong rationale for exercise, both

considering its potential to decrease the cancer- and treatment-induced abnormalities in muscle metabolism and to avoid the inactivity-induced sarcopenia that cancer patients are prone to develop.[40] Interventions and the intensity of the treatment need to be individualized so as not to induce eating and exercise related distress.

TIP 8: Patients at risk of or diagnosed with cachexia should be guided and supported to maintain and increase daily physical activity and be offered adequate amounts of substrates and energy, if necessary, by artificial nutrition.

Patients with active cancer, especially when undergoing anti-cancer treatment, are at high risk of developing malnutrition and unintentionally losing body mass. [11, 41] In many cases, as a response to the tumor, systemic inflammation will be activated simultaneously, representing inflammatory malnutrition, i.e. cachexia.[41] While the degree of inflammation may vary, the associated metabolic derangements induce anorexia, fatigue, insulin resistance, and general catabolism. These derangements will lead to decreased food intake and ongoing loss of muscle mass, endangering quality of life, tolerance of anticancer therapies, and ultimately shortening survival.[41]

To avoid underdiagnosing malnutrition, repeated malnutrition screening should be mandatory for all cancer patients. Validated screening tools are brief and may be applied without an expertise in nutrition. Patients found to be at risk by screening should be assessed in more detail by a nutrition expert. Assessment aims at diagnosing treatable deficits and quantifying nutritional status to allow monitoring the effects of planned nutritional support.[8]

Treatment of malnutrition and cachexia should be initiated as early as possible, because body mass lost is usually difficult to regain. To maintain adequate food intake and muscle mass, patients require multi-professional support including 1) professional guidance and individualized motivation to regularly perform physical exercises, comprising 3 to 4 sessions per week of endurance training and 2 sessions targeting muscle strength;[8] 2) repeated professional dietary counseling plus access to oral nutritional supplements and, if necessary, tube or intravenous feeding to ensure provision of adequate amounts of energy and nutrients, particularly protein and micronutrients. International guidelines recommend the following targets per day per

kg of body weight: energy: 25-30 kcal; protein: 1.2-1.5 g; micronutrients: recommended daily allowances. [2, 42, 43]

TIP 9: Cancer cachexia-related distress has negative impact on quality of life; to mitigate distress, work with interdisciplinary team members to educate patients and their family members on the possible causes of eating problems and weight loss in cancer and factors within their control.

Distress is common in patients with cachexia and their family members. Distress can be caused by involuntary weight loss, eating difficulties, and other symptoms of cachexia disrupting everyday life.[2, 41] Factors that affect quality of life for people with cachexia include: knowledge of cachexia, weight loss and physical decline, food and eating, emotional response, coping approach, personal identity, sense of control, and interpersonal relationships.[44]

Education around cachexia, along with psychosocial support to aid adjustment and coping, can mitigate distress.[45] Patients need education provided by the interdisciplinary team if they are to understand and successfully self-manage cachexia-related problems.[46] Patients and family members may associate weight loss and physical decline with dying and thus find these difficult topics for discussion. Asking about food and fluid intake and how it has changed over time can facilitate talk about weight- and eating-related concerns, opening-up opportunity to offer advice. Advice from a respected clinician is likely be remembered. It can intertwine advice on ways to improve nutritional intake with support for emotional coping.

Education about the causes of cachexia is important for enabling insight into what is and isn't in personal control. Sharing information as a professional with expertise (credible source), normalizing using stories, and involving family so that they can encourage appropriate goal setting and problem solving, are evidence-based behavioral change techniques that interdisciplinary team members can use to support self-management of cachexia-related problems.

TIP 10: In refractory cachexia, the focus is on palliation; attempts to increase nutrition and physical activity are typically futile and reducing distress is essential.

When cachexia is refractory, efforts in nutrition and exercise to reverse the syndrome turn futile and can cause additional distress.[47] Cachexia often turns refractory after a multimodal treatment attempt.[48] It is helpful to prospectively announce this possible tipping point during multimodal treatment, when attempts to treat cachexia do more harm than good, because in this situation a change of treatment goal to symptom control should be discussed.

Now corticosteroids can be used to improve appetite and fatigue for a few weeks, despite their negative effect on muscle and cachexia. Diagnosing refractory cachexia and diagnosing dying is essential in PC, but hard criteria for the 'dying phase refractory cachexia' are lacking.[49] In this phase, artificial nutrition and hydration can cause additional harm.[8] Dying patients are bedridden and eat little to nothing. Now it is important to educate families that feeding is no longer helpful and that the patient is not eating because s/he is dying and not dying because s/he is not eating. Alternative forms of caring, such as mouth hygiene, massages or reading to the patients should be proposed. Compassionate care at end of life is more important than cachexia management.

Conclusion

Cancer cachexia remains challenging due to its difficulty to measure, numerous causes, and lack of robust treatments. Cachexia management needs multidisciplinary collaboration between physicians, nutritionists, physiotherapists, nurses, and other members of the interdisciplinary team. Early identification and multimodal treatment, together with patients and proxies, are key. Treatment strategy has to be modified throughout the illness trajectory in order to do no harm and avoid additional suffering.

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