Reviews

Nutritional Aspect of Cancer Care in Medical Oncology Patients

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ABSTRACT

Purpose: Awareness of advances in the nutritional aspects of cancer care and translation of this information into clinical practice are important for oncology practitioners to effectively couple oncologic and nutritional approaches throughout the cancer journey. The goal of this consensus statement by a panel of medical oncologists was to provide practical and implementable guidance addressing nutritional aspects of cancer care from the perspective of the medical oncologist.

Methods: A panel of medical oncologists agreed on a series of statements supported by scientific evidence and expert clinical opinion.

Findings: Participating experts emphasized that both poor nutritional intake and metabolic alterations underlie cancer-related malnutrition. The use of liquid and high energy-dense oral nutritional supplements may enable better patient compliance, whereas higher efficacy is more likely with the use of pharmaconutrient-enriched oral nutritional supplements in terms of improved weight, lean body mass, functional status, and quality of life, as well as better tolerance to antineoplastic treatment. A multimodal approach is currently believed to be the best option to counteract the catabolism leading to cancer-related malnutrition; this treatment is scheduled in parallel with anticancer therapies and includes nutritional interventions, multitarget drug therapies, and exercise and rehabilitation programs. Participating experts emphasized the role of the oncologist as a reference professional figure in the coordination of nutritional care for patients with cancer within the context of complex and different clinical scenarios, particularly for permissive-adjunctive nutritional support.

Implications: This review article provides practical guidance addressing major nutritional aspects of cancer care from the medical oncologist's perspective. Thus, this document is expected to assist oncology practitioners in terms of awareness of advances in the nutritional aspects of cancer care and translation of this information into their clinical practice to effectively couple oncologic and nutritional approaches as part of the continuum of care for

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Key words: Cancer cachexia, cancer patients, nutritional screening, nutritional support, medical oncologist's perspective, treatment.

INTRODUCTION

Cancer survivorship has become a long-term experience worldwide.[1] However, given the high prevalence of comorbid malnutrition and metabolic derangements in patients with cancer, a lack of appropriate concomitant nutritional management may limit the response to even the most effective anticancer therapies.[2] This limitation emphasizes the need for nutritional screening and the provision of appropriate nutritional support as important components of multifaceted cancer care.[2–4]

Progressive deterioration of nutritional status is a common feature of patients with cancer. Accordingly, >50% of hospitalized patients with cancer and up to 30% of cancer outpatients are estimated to be malnourished. Cancer-related malnutrition (CRM) is almost universal and occurs in 50%–80% of patients with cancer.[5–8]

CRM is estimated to be the immediate cause of death in 20%–40% of patients with cancer. Furthermore, CRM is not merely synonymous with weight loss; it is a multilayered, multifaceted process of complex etiology and involves weight loss as one of the clearly visible components.[9] Importantly, this process is characterized by an ongoing loss of skeletal muscle mass that cannot be completely reversed by conventional nutritional support and which leads to progressive functional impairment ("loss of mobility").[10]

Currently, in general oncology practice, nutritional support is provided only for the 30%–60% of patients with cancer who were already identified to be at risk of malnutrition,[4,11,12] which seems notable, given that CRM is a chronic wasting process resulting in progressive muscle depletion.[10,13,14] In this context, a correct and early diagnosis of CRM via screening and assessment of nutritional status and a multimodal therapeutic approach that targets nutrition together with other factors implicated in the pathophysiology of CRM are of utmost importance in the management of patients with cancer.[2,15]

However, despite the improved understanding of the importance of CRM over the past decade,[16] the condition often goes unrecognized by treating physicians,[17] and management has not been adequately addressed.[5,10] This oversight has been linked to certain contributing factors, such as a lack of strict definitive and diagnostic criteria for CRM and the multifactorial nature of the condition. Likewise, in a questionnaire-based survey among oncologists in Turkey, planning nutritional therapy simultaneously with the initial diagnosis of cancer was identified by 46.0% of oncologists and only for patients with noticeable weight loss (28.0%) or poor oral intake (23.0%).[18] The authors concluded that the diagnosis and practice patterns need to be improved in terms of the use of evidence-based malnutrition screening tools, consulting with clinical nutrition specialists on the provision and monitoring of nutritional support, and appropriate prescription of oral nutritional supplements (ONS). Accordingly, the current clinical management of CRM remains limited and complex,[10,19] despite the association of CRM with higher rates of hospital readmissions, longer hospital stays, poor tolerability of cancer treatment, reduced quality of life, and reduced survival in patients with cancer.[15,20–25]

CRM has been addressed in the recently published, evidence-based guidelines for nutrition care in cancer patients by the European Society for Clinical Nutrition and Metabolism (ESPEN),[2] as well as in the Academy of Nutrition and Dietetics[26] and American Society for Parenteral and Enteral Nutrition guidelines,[22] with emphasis on the high prevalence of malnutrition and its adverse impact on response to treatment, prognosis, and survival.[2,22,26]

Currently, the majority of medical oncologists consider weight loss and muscle loss to be an inevitable consequence of progressive tumor growth and thus focus on better control of tumor growth; a small minority consider the potential of nutritional intervention to improve the quality of life and life expectancy and await evidence-based data to enact a change in their clinical practice.[5] In this regard, it seems important to provide oncology practitioners with an awareness of advances in the nutritional aspects of cancer care and assistance with translating this information into their clinical practice to

effectively couple oncologic and nutritional approaches throughout the "cancer journey."[4,27]

The present consensus statement by a panel of medical oncologists thus aimed to provide a practical and implementable guidance document and a comprehensive framework for addressing nutritional aspects of cancer care from the medical oncologist's perspective in terms of definition, epidemiology, pathophysiology, adverse outcomes, and treatment (nutritional support, exercise, pharmacological interventions, and multimodal combined strategy) of CRM and the role of oncologists in the nutritional aspects of cancer care.

MATERIALS AND METHODS

The present expert panel of medical oncology specialists, who were members of the Medical Oncology Active Nutrition Platform, met to develop a consensus opinion regarding the nutritional aspects of cancer care from the perspective of the medical oncologist. The Medical Oncology Active Nutrition Platform was created by one of the authors (S.Y.), with no funding source, to actively increase the knowledge and awareness of medical oncologists regarding the nutritional care of oncology patients. The participating experts (professors, as well as international speakers and national influencers), who had at least 15 years of experience in medical oncology and participated in research on nutrition from different provinces of the main geographical regions of Turkey, were invited to the platform. All experts were informed about the study via e-mail by the sponsor and then participated in the consecutive meetings supported by the sponsor to achieve the proposed consensus. The panel critically analyzed recommendations from international guidelines, systemic reviews and meta-analyses, and published results of randomized controlled trials focusing on the nutritional aspects of cancer care; they agreed on a series of statements supported by scientific evidence and expert clinical opinion to assist clinicians in oncology practice.

The proposed consensus planned to provide a practical and implementable guidance document addressing nutritional aspects of cancer care in terms of the following: (1) an overview of CRM (definition, epidemiology, pathophysiology, and adverse outcomes); (2) treatment and monitoring of CRM (management algorithm, therapeutic targets, and end points); (3) nutritional support (nutritional screening, nutritional counseling, planning nutritional support, routes of delivering nutritional support, types of nutritional supplements, and nutritional requirements); (4) the therapeutic role of exercise; (5) pharmacological interventions (potential modalities according to the site or mechanism of action, first-line drugs with confirmed efficacy including glucocorticoids and progestational agents, and second-line unproven/investigational drugs such as NSAIDs, cannabinoids, and pharmaconutrients); (6) a multimodal strategy (combined nutritional and pharmacological approaches); and (7) the role of oncologists in the nutritional aspects of cancer care.

OVERVIEW OF CRM

Definition and Epidemiology of CRM

Although the terms "malnutrition," "weight loss," and "cachexia" have been used interchangeably for many years, the term "cancer-related malnutrition" is believed to be more appropriate for patients with cancer because cachexia suggests that the patient is in the terminal stage of cancer. Given that poor nutrient intake and metabolic alterations underlie CRM, standard optimized nutritional support can only prevent further deterioration of nutritional status unless combined at an early stage with anabolic/anticatabolic agents.[23,28]

Weight loss due to chemotherapy-related anorexia, nausea, and vomiting should be distinguished from CRM, as they require different therapeutic interventions[29]; the weight loss–related changes in body composition (eg, reduction in skeletal muscle mass) also differ from anorexia (eg, predominant loss of fat mass).[29,30]

Accordingly, CRM is defined as a complex multifactorial process characterized by weight loss and an alteration in body composition, a key feature of which is a severe and specific loss of skeletal muscle mass with relative preservation of the visceral protein mass that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment.[1,10,15,31–34] The major hallmarks of CRM include anorexia, inflammatory processes, metabolic and endocrine alterations, increased tissue protein turnover, and loss of muscle mass[15,31–34] (Figure 1).

A progressive classification system for CRM has also been proposed to improve the ease with which clinicians can recognize CRM and includes

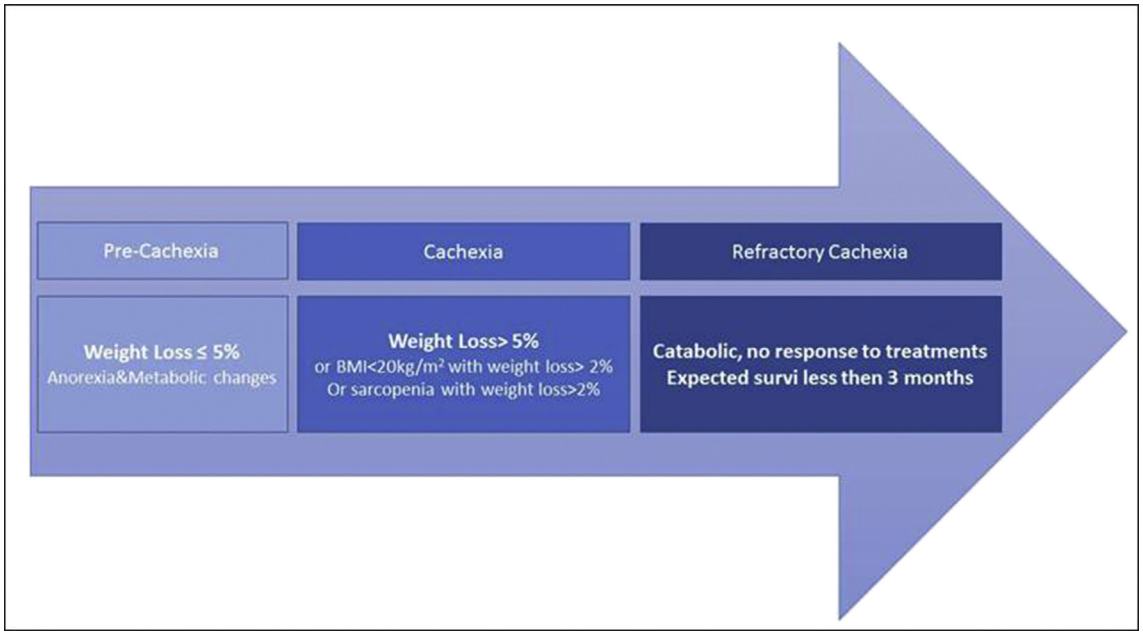

Figure 1. Classification and progression of cancer-related malnutrition. A progressive classification system for cancer-related malnutrition that includes precachexia, cachexia and refractory cachexia relative to progressive weight loss. BMI = body mass index.

precachexia, cachexia, and refractory cachexia.[4,10,35] It is estimated that patients with cancer have already lost ~5% of their weight and are already in precachexia during the initial diagnosis; chemotherapy, surgery, adjuvant therapy, and palliative care steps have also been associated with additional weight loss[10] (Figure 1). The overall prevalence of CRM ranges from 40% at cancer diagnosis to 70%–80% in advanced phases of the disease.[15,36,37] Moreover, the prevalence of CRM is 83%–85% in pancreatic and gastric cancer; 54%–60% in lung, prostate, and colon cancer; and 32%–48% in breast cancer, sarcoma, lymphoma, and leukemia.[15,38]

Pathophysiology of CRM

The pathophysiology of CRM includes a series of complex metabolic mechanisms that are directly linked to the tumor–host interaction. Such mechanisms are responsible for metabolic and endocrine changes such as glucose intolerance, elevated hepatic gluconeogenesis, increased glucose turnover, reduced muscular intake of glucose, hyperlipidemia, increased lipolysis, increased protein turnover, increased proteolysis, insulin resistance, increase in counterregulatory hormones, and release of rapid-response inflammatory factors.[15] These changes are mediated by tumor-derived proteolysis-inducing factor, lipid mobilization factor, humoral cytokines (tumor necrosis factor α, interleukin 1 [IL-1], IL-6, and interferon gamma), neuropeptides (neuropeptide Y, serotonin, and melanocortin), hormones (insulin, glucagon, and leptin), and effects that may or may not be associated with structural or functional digestive factors (nausea, dysphagia, odynophagia, mucositis, constipation, malabsorption, and intestinal obstruction) that allow them to become established or consolidated.[15]

Adverse Outcomes of CRM

CRM has negative impacts on quality of life, tolerance, and response to antineoplastic treatments, leading to increased morbidity and mortality rates in patients with advanced cancer.[1,38–42] In other words, CRM can be considered a negative prognostic factor. It has been estimated that >50% of patients with

cancer die after developing CRM, whereas CRM can be the direct cause of death in up to 40% of all oncology patients.[15]

Weight loss >5% before the start of chemotherapy can be used to predict the risk of poor response to therapy and shortened survival,[5,38,43] whereas early nutritional intervention (before refractory cachexia) was shown to be associated with better tolerance to aggressive antitumor therapies, improved quality of life, and prolonged survival, at least in some clinical settings.[10,20,44,45] This evidence emphasizes that evaluation of nutritional status should be included in the multidimensional initial approach to patients with cancer.[20]

TREATMENT AND MONITORING OF CRM

Management Algorithm

The management algorithm for CRM consists of the following[10,46]: (1) screening for CRM (weight loss, body mass index [BMI], or direct measure of muscle mass/function); (2) detailed nutritional assessment to determine severity (according to degree of depletion of energy stores and body protein in combination with degree of ongoing weight loss); (3) detailed assessment for phenotype (based on domains of anorexia or reduced food intake, catabolic drive, muscle mass and strength, and functional and psychosocial impairment); and (4) development of a management strategy. The development strategy consists of: (1) close monitoring and early support to prevent CRM; and (2) a detailed multimodal management plan (repeated monitoring, vigorous nutritional support, anti-inflammatory treatment, exercise, treatment of secondary gastrointestinal (GI) symptoms and other causes of decreased oral nutritional intake, and evaluation of antineoplastic options to reduce the catabolic drive of the cancer, and formal nutrition, as well as palliative symptom management, psychosocial support, and ethical discussions on nutritional support during late stages of CRM [refractory cachexia]).

Therapeutic Targets and End Points

Treatment of CRM in terms of anorexia and metabolic disturbances is based on nonpharmacological (nutritional support and exercise) and pharmacological (pharmaconutrients and specific drugs) approaches.[15,47] Therapeutic targets include anticatabolic (directed toward both fat and muscle) and anabolic (leading to the synthesis of macromolecules) factors to control food intake and neutralize alterations in metabolism and in the rate of skeletal muscle protein breakdown.[47]

CRM monitoring is a key point during therapy with consideration of different parameters related to anorexia and metabolic disturbances. Although body weight is the most important end point, body composition (which reflects the impact of the treatment) should also be taken into consideration and analyzed via bioelectrical impedance analysis, dual-energy X-ray absorptiometry, or computed tomography scanning.[47]

Nutritional Support in the Management of CRM

The nutritional armamentarium in the management of CRM ranges from dietary counseling to home (total) parenteral nutrition or home enteral tube feeding, with ONS (standard or enriched), enteral nutrition (tube feeding), and parenteral nutrition (intravenous supplementation) in-between.[48]

Worldwide consensus exists regarding the implementation of nutritional support with the diagnosis of cancer after screening-based evidence of malnutrition or nutritional risk rather than routine support as an adjunct to chemotherapy or irradiation in patients with cancer.[23] This practice emphasizes the awareness of the oncologist about simple and validated nutritional screening tools.

Notably, however, due to the multifactorial etiology of CRM, optimizing nutritional counseling and support does not guarantee the improvement of nutritional status in every patient. Assessment of nutritional status for each indication eventually depends on the resources/facilities of the institution, given that it can be a time-consuming procedure that requires special expertise.[48]

Nutritional Screening

Simple and validated nutritional screening tools are available, including the Nutrition Risk Screening 2002 (NRS-2002),[49] Malnutrition Universal Screening Tool (MUST) or Malnutrition Screening Tool (MST),[50,51] and Mini Nutritional Assessment Short Form Revised.[52] Among the available screening tools, NRS 2002 is believed to be stronger in terms of risk identification and a more suitable tool for screening

nutritional risk in patients with cancer.[23,53] Patient-generated subjective global assessment (PG-SGA)[54] and the NRS 2002[49] are the most commonly used tools for the assessment of nutritional status.[23]

Because the assessment of nutritional status is a complex and time-consuming procedure that should be performed by specifically trained professionals, screening for nutritional risk seems more feasible in daily oncology practice, reserving complete assessment for selected patients. The MST is a simple, short screening questionnaire and has similar sensitivity and slightly lower specificity than the PG-SGA.[15,50,51] An MST score ≥ 2 detects risk of malnutrition, and if necessary, the evaluation can be completed with a broader nutritional assessment, such as the PG-SGA scale.[15]

Nutritional Counseling

Identifying the particular needs of each patient and provision of nutritional support in accordance with an individualized nutritional plan developed by professional health care teams (including oncology physicians, nurses, and dietitians) is believed to be crucial for improving the nutritional status of cancer patients.[46] Counseling is an effective and inexpensive intervention in combination with other nutritional interventions,[46,55] leading to improved nutritional intake in patients undergoing chemotherapy and improved quality of life in patients undergoing radiotherapy.[46,56,57]

Planning Nutritional Support in Patients With Cancer

To detect nutritional disturbances at an early stage, ESPEN recommends that nutritional intake, weight changes, and BMI be evaluated regularly, beginning at the time of initial cancer diagnosis. In patients found to be at nutritional risk on screening, objective and quantitative assessment of nutritional intake, nutritional impact symptoms, muscle mass, physical performance, and the degree of systemic inflammation is recommended. The total energy expenditure of patients with cancer, if not measured individually, can be assumed to be similar to that of healthy subjects, generally ranging between 25 and 30 kcal/kg per day, and protein intake should be > 1 g/kg per day and, if possible, up to 1.5 g/kg per day.[2]

Routes of Delivering Nutritional Support

Nutritional intervention is recommended to be individualized based on the nutritional status of patients and should include dietary advice, treatment of symptoms and derangements impairing food intake (nutrition impact symptoms), and nutritional support.[1,2] Nutritional support is given as ONS, enteral nutrition tube-feeding via gastric or jejunal routes, or parenteral nutrition when oral and enteral routes are unavailable for any reason.[23]

From a practical point of view, once the indication has been recognized (if undernutrition already exists or if food intake is markedly reduced for >7−10 days), the nutritional approach should rely on the integrity of the GI tract and GI function: ONS or enteral nutrition should be used for patients with intact GI function or access, and parenteral nutrition should be used in patients with impaired GI function or access.[1,13,23,58] Enteral nutrition is always preferred for patients with cancer with a (relatively) intact digestive tract due to a lower risk of complications, such as catheter-related infections and intestinal bacterial translocation, improved quality of life, and lower costs compared with parenteral nutrition.[13,59,60]

Benefits of ONS

Nutritional intervention with ONS has several benefits: (1) it can improve energy intake and reduce weight loss in patients with cancer[2]; (2) it can improve quality of life outcomes in malnourished patients with cancer[61]; (3) it can improve compliance with anticancer therapy and reduce the side effects of the treatment[6]; and (4) it may result in cost savings in patients with cancer.[2,62]

Nonetheless, due to the inconclusive evidence, no clear recommendations for specific nutrients are provided by any of the major cancer societies; only omega-3 (ω-3) fatty acids are modestly supported in some guidelines as they may help stabilize weight in patients with progressive unintentional weight loss.[2] Therefore, clinicians routinely recommend standard ONS (either high calorie, high protein, or both) consistent with the complexity of disease pathology due to varied types and stages and lack of enough conclusive randomized controlled trials.

Use of liquid supplements (due to less satiating effects and easier ingestion) and higher energy-dense

products (≥2 kcal/mL, due to consumption of smaller volumes) have been associated with high patient compliance.[23,63] Standard ONS have been shown to significantly increase total energy and nutritional intake, with clinical benefits becoming apparent when the intake was in the range of 250−600 kcal/d. This finding seems notable given the positive association between dietary energy density, energy balance, and survival and the negative association with systemic inflammation in patients with advanced cancer.[23,64]

Specific ONS Ingredients for Patients With Cancer

ω-3 Fatty Acids

ω-3 Fatty acids, including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have been associated with improved immunocompetence and reduced inflammatory responses.[23,65] In addition to the effects on prostaglandin synthesis and cyclooxygenase-2 inhibition, ω-3 fatty acid− enriched ONS have been effective in reducing the proinflammatory cytokines involved in CRM, and they are associated with increased incorporation of EPA and DHA not only in the liver and gut mucosa but also in tumor tissue in patients with solid GI tumors.

Specific Amino Acids in Addition to β-Hydroxy-β-Methylbutyrate

The use of branched-chain amino acids (leucine, isoleucine, and valine) was proposed based on the rationale that increased hypothalamic serotonergic activity could play a role in the development of anorexia and that branched-chain amino acids might slow the entry of the serotonin precursor tryptophan into the brain by competing for the same transport system across the blood−brain barrier.[23]

Certain branched-chain amino acids (particularly leucine) have been shown to act as nutrient signals themselves to modulate cellular processes, leading to an acceleration of protein synthesis[23]; leucine-enriched supplements are believed to be promising in the management of CRM.[23,66] In addition, the use of an ONS with a combination of β-hydroxy-β-methylbutyrate (HMB) (3 g/d), arginine (14 g/d), and glutamine (14 g/d) for 6 months was reportedly associated with a considerable gain in body mass and fat-free mass, whereas the isonitrogenous control group had progressive weight loss.[67]

A combination therapy of HMB, arginine, and glutamine was reported to be associated with an increase in lean body mass after 4 weeks in a study of patients with advanced solid tumors, whereas it had no benefit on lean body mass in a large sample of patients with advanced lung cancer and other cancers after 8 weeks.[67−69]

Current evidence suggests the association of HMB treatment with stimulation of regenerative events, inhibition of protein degradation, and activation of signaling pathways preceding protein synthesis and skeletal muscle growth.[70] Accordingly, on the basis of data from preclinical studies, HMB has been suggested to act on key regulatory events driving cancer-related malnutrition leading to improved muscle growth/preservation.

Arginine

Arginine supplementation is believed to augment specific and nonspecific antitumor mechanisms, such as retarding tumor growth and prolonging survival, because arginine is essential for normal T lymphocyte function.[23,71] In a clinical study, perioperative enteral nutrition with an arginine-enriched formula was shown to increase the long-term survival of patients with head and neck cancer undergoing surgery and chemotherapy.[72]

The use of arginine supplementation (plus fish oils and nucleotides in some studies) in the treatment of CRM in patients with cancer was reportedly associated with an increase in BMI and albumin and prealbumin levels,[73] as well as improved overall survival,[72] in patients with head and neck cancer and reduced length of hospital stay in patients with GI cancers.[74]

Glutamine

Glutamine supplementation has also been shown to improve nitrogen balance and intracellular glutamine concentration after major surgery.[75] However, it remains unclear whether the decrease in glutamine levels during severe illness is caused by glutamine depletion alongside the controversy regarding the role of glutamine supplementation in catabolic conditions.[2] The observed safe level for supplemental glutamine in normal healthy adults is 14 g/d.[76]

Given the marked involvement of glutamine in several metabolic pathways and the likelihood that rapid uptake of glutamine by tumor cells contributes

to stabilizing the intracellular milieu against acidification,[77,78] recommending long-term and high dosage supplementation with glutamine in patients with cancer requires additional dedicated studies and more robust efficacy data.[79]

Nutritional Requirements (Substrates) for a "Cancer-Specific" Nutritional Regimen

Energy

Adequate energy goals for bedridden and ambulatory patients with cancer are suggested to be 20−25 kcal/kg per day and 25−30 kcal/kg per day, respectively, to improve lean body mass and increase hepatic production of anabolic proteins[2,10,59,80] (table).

Fluids

The volume of fluid is generally recommended not to exceed 30−35 mL/kg body weight per day; the range may change depending on a patient's hemodynamic condition, presence of fever, or body fluid losses.[13,59]

Macronutrients

According to recent guidelines, protein intake should be > 1 g/kg per day and, if possible, up to 1.5 g/kg per day in patients with cancer. In subjects with normal kidney function, protein intake at doses up to and above 2 g/kg per day are safe; in patients with acute or chronic renal failure, protein supply should not exceed 1 or 1.2 g/kg per day, respectively[10,23,59,81−83] (table).

Consistent with the oxidative rate of glucose, recommended carbohydrate (glucose) intake is < 5 g/kg per day.[10,59] Current guidelines suggest that optimal carbohydrate intake in patients with cancer should not exceed 40%−50% of nonprotein energy requirements; in weight-losing patients with cancer with insulin resistance, it is recommended to increase the ratio of energy-from-fat to energy-from-

Table. Calorie, protein, and micronutrient intake recommendations for patients with cancer.

Calorie requirements	Energy: 20−25 kcal/kg/d (bedridden) and 25−30 kcal/kg/d (ambulatory)
	Carbohydrate: Glucose <5 g/kg/d; should not exceed 40%−50% of nonprotein energy requirements
	Lipids (LCT or MCT) 0.5 and 1.5 g/kg/d up to a maximum of 2 g/kg/d; should provide up to 50% of nonprotein calories
Protein requirements	Protein intake should be > 1 g/kg/d and, if possible, up to 1.5 g/kg/d in patients with cancer. In subjects with normal kidney function, intake of protein in doses up to and above 2 g/kg/d are safe; in patients with acute or chronic renal failure, protein supply should not exceed 1 or 1.2 g/kg/d, respectively
Micronutrients	
Vitamins	In physiological doses, without use of high-dose micronutrients in the absence of specific deficiencies
	For PN: balanced standard solutions, vitamin K (≥6−10 mg/d) vitamins B_1 and B_6 (>100 mg/d), antioxidants (vitamins A, C, and E)
Trace elements	Complete standard solutions
	Zinc (15−20 mg/d)
	Selenium (120 µg/d)
Electrolytes	Daily adaptation (sodium, potassium, and calcium)
	P (>16 mmol/d)
	Magnesium (>200 mg/d)

LCT = long-chain triglycerides; MCT = medium-chain triglycerides; PN = parenteral nutrition.
Adapted from Nitenberg et al[59] and Arends et al.[2]

carbohydrates to increase the energy density of the diet and to reduce the glycemic load.[2,10]

Lipids are efficiently mobilized and metabolized by patients with cancer and therefore represent a valid source of energy in this setting. Provision of up to 50% of nonprotein calories from fat is feasible and safe in patients with cancer.[13,23]

Micronutrients

Nutritional supplement formulas usually contain electrolytes. Blood electrolyte levels must be carefully monitored, and supplementation must be adjusted according to each patient's needs[13,59] (table).

Vitamins and minerals are recommended in physiological doses, whereas the use of high-dose micronutrients is discouraged in the absence of specific deficiencies.[2] Although vitamin D deficiency is frequently observed in patients with cancer and is associated with cancer incidence and prognosis, it remains unknown whether using supplements to normalize vitamin D levels in patients with vitamin D deficiency will improve prognosis in patients with cancer.[2,84,85]

Vitamin D likely plays a role in the reduction of cancer cachexia, as it has been shown to suppress IL-6, a proinflammatory cytokine that is a key mediator of the muscle wasting seen in cancer cachexia.[86] Vitamin D (2000 IU daily for 12 weeks following a 4-week placebo trial) was reported to improve muscle weakness in prostate patients with cancer[87]; it also reduced plasma concentrations and combined *z* scores for proinflammatory markers (C-reactive protein, tumor necrosis factor α, IL-6, IL-1β, and IL-8) in sporadic colorectal adenoma when used over a 6-month period at a dosage of 800 IU/d.[88]

THERAPEUTIC ROLE OF EXERCISE IN CRM MANAGEMENT

Physical exercise is believed to attenuate the effects of CRM by increasing insulin sensitivity; preserving muscle mass and function by enhancing protein synthesis, decreasing protein catabolism, and contributing to better muscle performance; and increasing antioxidative enzyme activity, while suppressing the inflammatory response through upregulation of the anti-inflammatory cytokines both in skeletal muscle and adipose tissue and enhancement of immune function.[1,46,89–92] There is evidence that endurance exercise ameliorates cancer-related fatigue, whereas resistance exercise attenuates muscle wasting in different catabolic conditions.[46]

PHARMACOLOGICAL INTERVENTIONS IN THE MANAGEMENT OF CRM

The current and emerging treatments for CRM prevention and therapy are based on nutritional intervention, appetite stimulation, anti-inflammatory agents, growth factors, anabolic agents, and pharmaconutrients (ω-3 fatty acids).[1,93,94]

In recent years, several potential agents have been studied in the pharmacological intervention of CRM based on the following sites or mechanism of action: (1) inhibitors of production/release of cytokines and other factors; (2) gastroprokinetic agents with or without antinausea effects; (3) blockers of the Cori cycle; (4) blockers of fat and muscle tissue wasting; (5) appetite stimulants with or without antinausea effects; and (6) antianxiety/depressant drugs.[15,46] Consistent with these sites or mechanisms of action, the potential modalities of pharmacological intervention are classified as first-line (established) treatments, including glucocorticoids (1,5) and progestational agents (1,5) and second-line (unproven/investigational) treatments, including cannabinoids (5), NSAIDs (1,5), ω-3 fatty acids (EPA and DHA) (1,4), cyproheptadine (5), branched-chain amino acids (4,5), metoclopramide (2,5), 5′-deoxy-5-fluorouridine (1), melatonin (1), thalidomide (1), β_2-adrenoceptor agonists (4), other anabolic steroids (4), pentoxifylline (1), hydrazine sulfate (3), statins (1,4), angiotensin-converting enzyme inhibitors (4), and selective androgen receptor modulators (4). These agents are selected on an individual basis according to the cause of CRM or the condition of the patient[46] (Figure 2).

THE ROLE OF THE ONCOLOGIST IN NUTRITIONAL ASPECTS OF CANCER CARE

A modern view of the nutritional aspects of cancer care considers nutritional care as an essential component of multimodal therapy for CRM,[34,95] with the role of nutritional intervention in cancer treatment potentially contributing beyond simply maintaining or restoring nutritional status.[20] Because oncologists

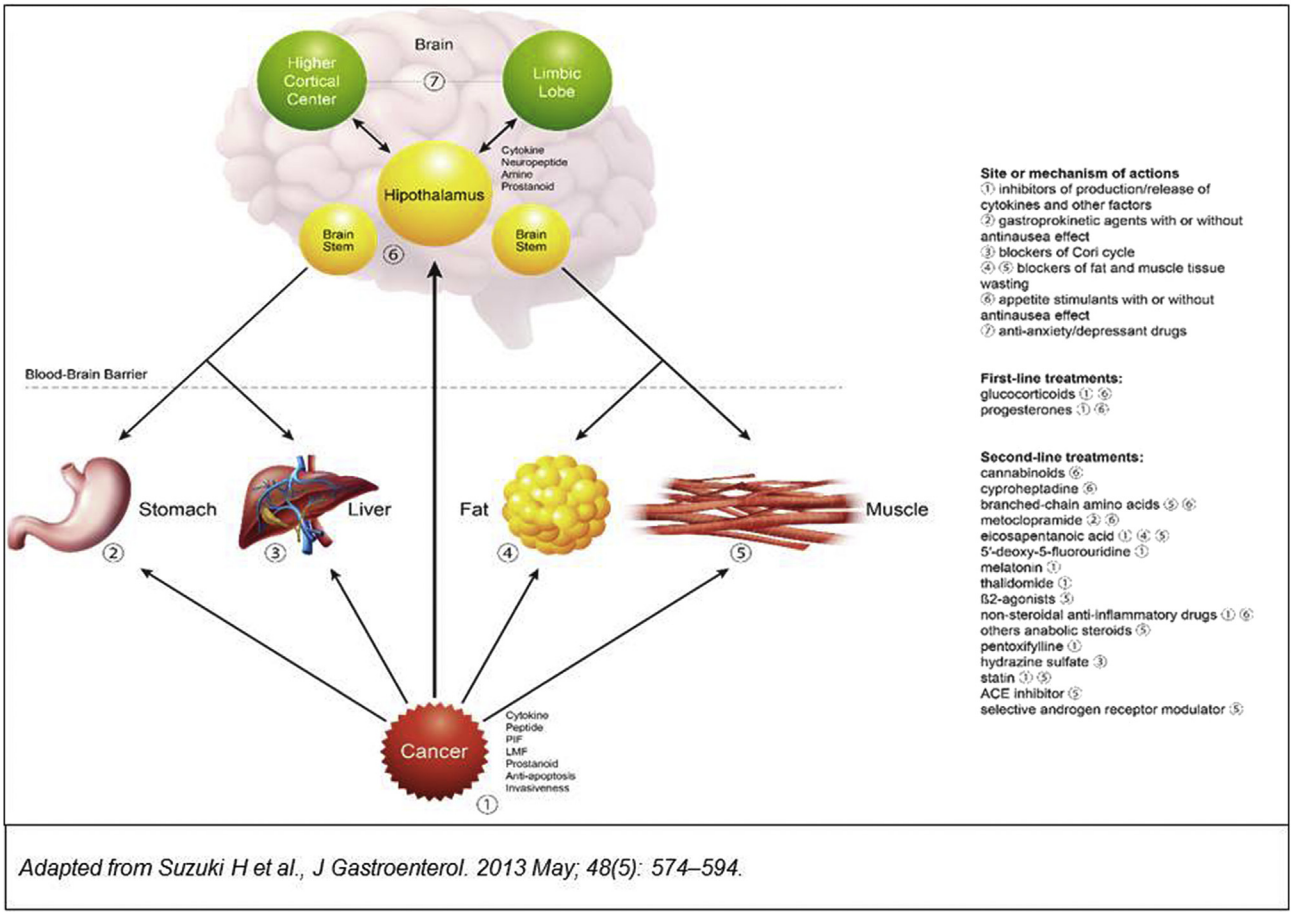

Figure 2. The potential modalities for pharmacological intervention of cancer-related malnutrition according to sites or mechanisms of action: (a) inhibitors of production/release of cytokines and other factors; (b) gastroprokinetic agents with or without antinausea effects; (c) blockers of the Cori cycle; (d) blockers of fat and muscle tissue wasting; (e) appetite stimulants with or without antinausea effects; and (f) antianxiety/depressant drugs. First-line (established) treatments: glucocorticoids (a,e) and progestational agents (a,e). Second-line (unproven/investigational) treatments: cannabinoids (e), NSAIDs (a,e), ω-3 fatty acids (eicosapentaenoic acid and docosahexaenoic acid) (a,d), cyproheptadine (e), branched-chain amino acids (d,e), metoclopramide (b,e), 5′-deoxy-5-fluorouridine (a), melatonin (a), thalidomide (a), β_2-adrenoceptor agonists (d), other anabolic steroids (d), pentoxifylline (a), hydrazine sulfate (c), statins (a,d), angiotensin-converting enzyme (ACE) inhibitors (d), and selective androgen receptor modulators (d). Adapted from Suzuki et al.[46]

are the clinicians who are most familiar with the particular natural history and clinical trajectory of the patients with cancer, they have a pivotal role in the nutritional aspects of cancer care.[48] The role of oncologists is crucial, particularly for permissive-adjunctive nutritional support, rather than perioperative nutrition and home total parenteral nutrition, for which the reference figures are more likely to be the surgeon and nutritionist, respectively.

The majority of oncologists are not comfortable, confident, or adequately prepared to provide nutritional counseling, a situation possibly related to suboptimal knowledge of basic nutrition and understanding of potential nutritional interventions.[23]

However, the oncologist knows the natural history of the disease and the severity and duration of toxicity of an oncological treatment; thus, the rationale is well placed to determine the need for nutritional support.

The oncologist should therefore be aware of the adverse effects of malnutrition on patient outcomes, be familiar with the main indications for nutritional support, provide the patient with simple nutritional support (ie, ONS), and refer the patient to the appropriate specialists (eg, radiotherapists, surgeons, dietitians, palliative care specialists) when necessary, based on a comprehensive clinical evaluation of the clinical status, prognosis, and patient expectations.[23,48,58]

More importantly, oncologists have a chance to recognize the problem at an earlier (precachexia) and more responsive phase, given that the vast majority of patients referred to the specialized units for nutritional support are in an advanced state of cachexia and are often unresponsive to treatment.[23] In addition, patient compliance with nutritional therapy has been suggested to be increased when it is prescribed and supervised by the oncologist rather than by nutritionists or dietitians.

Oncologists should include nutritional status assessment in the multidimensional initial approach to patients with cancer to be able to identify CRM at an earlier phase based on weight loss or an easy composite index, such as the NRS-2002, and to view nutritional support as an essential component of the therapeutic armamentarium alongside chemotherapy, radiation therapy, antiemetic drugs, and analgesic agents.[48] Notably, CRM is considered a comorbidity of cancer with practical and operational implications, favoring early recognition, diagnosis, and therapeutic interventions for cancer cachexia, and positively affecting survival, quality of life and health care expenses.[1]

In current practice, early identification of CRM, provision of early multimodal interventions, or the early referral to a specialist upon recognition of weight loss are believed to be among the oncologists' responsibilities.[58] In this regard, the ESPEN oncology expert group emphasized 3 key steps to update nutritional care for people with cancer: (1) screening all patients with cancer for nutritional risk early in the course of their care, regardless of BMI and weight history; (2) incorporation of measures of anorexia, body composition, inflammatory biomarkers, resting energy expenditure, and physical function into the nutrition-related assessment practices; and (3) use of multimodal nutritional interventions with individualized plans, including care focused on increasing nutritional intake, reducing inflammation and hypermetabolic stress, and increasing physical activity.[4]

CONCLUSIONS

The goal of the present consensus statement by the members of the Medical Oncology Active Nutrition Platform was to provide a practical and implementable guidance document and a comprehensive framework for addressing nutritional aspects of cancer care from the medical oncologists' perspective. This document may assist oncology practitioners in the awareness of advances in nutritional aspects of cancer care and in translating this information into their clinical practice to effectively couple oncologic and nutritional approaches throughout the "cancer journey."

The expert panel emphasized that "cancer-related malnutrition" rather than "cachexia" more appropriately defines the status in patients with cancer. This consensus statement recommends the use of a management algorithm, including screening for nutritional risk, staging of CRM, and developing a management strategy consistent with staging and phenotype. This management algorithm should include prevention measures for CRM such as nonpharmacological (nutritional support and exercise) and pharmacological (pharmaconutrients and specific drugs) interventions targeting both anticatabolic and anabolic measures, along with repeated monitoring of nutritional status.

Participating experts agreed that consistent with the multifactorial pathogenesis, a multimodal approach is currently believed to be the best option to counteract catabolism leading to CRM. This approach should be scheduled in parallel with anticancer therapies and include nutritional intervention, pharmaconutrients, and multitarget drug therapies as well as exercise and rehabilitation programs. This consensus statement emphasizes the role of oncologists as a reference professional figure in coordinating the practice of nutritional support in cancer patients within the context of complex and different clinical scenarios, particularly for permissive-adjunctive nutritional

support. Participating experts agreed that the oncologist should therefore be aware of the adverse effects of malnutrition on patient outcomes (including nutritional status assessment in the multidimensional initial approach to patients with cancer), be familiar with the main indications for nutritional support, recognize the problem at an earlier (beginning with the diagnosis) and more responsive phase, and view nutritional support as an essential component of the therapeutic armamentarium alongside chemotherapy, radiation therapy, antiemetic treatment, and pain management.

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DISCLOSURES

Dr. Sarioglu is an Abbott employee. Dr. Yalcin is the founder of The Medical Oncology Active Nutrition Platform and the members of the Platform were assigned by Dr. Yalcin. An honorarium fee was paid to each expert in accordance with Abbott's fair market value rates. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

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