Struggling with nutrition in patients with advanced cancer: nutrition and nourishment—focusing on metabolism and supportive care

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Patients with advanced cancer are at high risk of losing vital body resources resulting in malnutrition, immunodeficiency, impaired quality of life and worse clinical outcome. Prominent among the diverse factors contributing to this complex condition are metabolic derangements characterized by systemic inflammation, catabolism and accumulating changes in body composition. Because cure in advanced cancer still remains elusive, optimal supportive and integrated palliative care are required to allow patients to tolerate aggressive or long-term anticancer treatments, to maintain an adequate quality of life or to stay the course of advancing disease. Support needs to address and focus on all physical, psychological and social problems interfering with food intake, digestion and anabolism to maintaining adequate body resources and functions. Reliable screening for malnutrition, adequate assessment of the nutritional and metabolic status, and individualized multimodal care require the establishment of dedicated operating procedures involving experts and standardized pathways for communication among all participants involved in clinical cancer care. Therapeutic options include counseling, enriching foods, oral nutritional supplements, enteral and parenteral nutrition, metabolic modulation, exercise training, supportive care to enable and improve the intake of adequate amounts of food, as well as psycho-oncology and social support. Finally, to enable this new level of nutritional and metabolic patient care it appears necessary to establish common definitions and grading systems allowing not only for efficient treatment but allocating adequate medical resources to reach this goal.

Key words: advanced cancer, malnutrition, systemic inflammation, supportive care, muscle mass, multimodal care

Introduction

In many patients with advanced cancer body resources are being endangered and increasingly lost, resulting in malnutrition, compromised immune competence, impaired quality of life, reduced physical activity and worsened clinical outcome, including increased treatment toxicities and decreased overall survival [1, 2] (Table 1).

A diverse spectrum of interacting factors is contributing to this complex condition [1, 3]. Prominently among these, metabolism in patients with advanced cancer is frequently characterized by a systemic inflammatory response syndrome (SIRS) driving catabolism and redistribution of body resources [3]. Comprehensive and individually adequate care of this syndrome requires knowledge of the possible causes and the presently available treatment options [4].

Because cure in most cases of advanced cancer still remains elusive, optimal supportive and integrated palliative care will be required to guide and allow patients to tolerate aggressive and/or long-term anticancer treatments as well as the constant threat of considering treatment failure, tumor recurrence and approaching the end of life [5]. As important components of supportive care, nutritional and metabolic care are facing limits of their own. Today, there is still no golden bullet available to terminate malnutrition and catabolism. Thus, support needs to address and focus on all physical, psychological and social problems interfering with food intake, digestion and anabolism to maintaining adequate body resources and functions [1].

Setting

Weight loss is frequent in advanced cancer, being among the first symptoms in more than 50% [6] and occurring in up to more
than 70% during the further course of the disease [1]. The major factor leading to weight loss appears to be inadequate food intake [7] which may result from a number of different causes. Derangements in digestion and absorption may contribute but have not been studied extensively. Energy expenditure in cancer patients may be higher than normal in the resting state but due to reduced physical activity total daily energy expenditure in patients with advanced cancer usually is similar to that of healthy controls [8]. Similarly, draining of energy or substrates by hyperactive tumor tissues cannot reasonably explain weight loss, since the presence of small tumors may produce weight loss when host tissues outweigh the tumor by a factor of 1000 or more [9].

While inadequate food intake inexorably is followed by weight loss, the presence of an advanced cancer frequently is associated with an SIRS, which in turn promotes catabolism and especially protein breakdown in skeletal muscles [3]. Systemic inflammation-induced fatigue contributes to decreased physical activity and thus reduces anabolic signals promoting further muscle loss [10] (Figure 1).

While body resources are catabolized rapidly when an inadequate intake is combined with a reduction of anabolic and an overabundance of catabolic signals, there has still no general agreement been reached on how to best diagnose and grade these derangements [11, 12]. Definitions and grading systems of clinical entities may alert the clinician to a reliably recognizable problem, enable comparability of statistical data and guide treatment strategies as well as reimbursement policies. Unfortunately, a fairly large number of different diagnostic systems and frameworks has been proposed to conceptualize involuntary weight loss in disease states, including associating different definitions with terms such as ‘malnutrition’, ‘cachexia’, ‘anorexia-cachexia’, and ‘sarcopenia’ [13–17]. While recently a tendency emerges to associate ‘malnutrition’ more generally with weight loss, ‘cachexia’ with a combination of weight loss and systemic inflammation, and ‘sarcopenia’ with a very low muscle mass, a consensus on a comprehensive and pathophysiology-based system of definitions still is awaited.

Malnutrition, sarcopenia and cachexia, when used as described above, all are associated with poor clinical outcome in patients with advanced cancer [1, 3, 18]. This requires to direct diagnostic procedures and treatment strategies at improving food intake, muscle mass and derangements of metabolism. While this, in principle, may be implemented without a firmly established system of definitions, it is important to recognize that without such an accepted classification system reimbursement issues and distribution of financial resources within our medical systems [19] will remain biased against nutritional and metabolic treatments.

### Systemic inflammation

Local inflammation is a driver of carcinogenesis and tumor growth by providing a microenvironment supportive of malignant growth [20, 21] and has been included as one of the hallmarks of cancer [22]. Malignant cells tend to recruit an accompanying stroma of myofibroblasts and inflammatory cells (stromatogenesis) [23] and in some cancers non-malignant stromal tissue may far outweigh malignant cells [24]. Tumors have been designated as ‘wounds that do not heal’ [25] and stromal inflammatory mediators may spill over into the systemic circulation initiating and maintaining a systemic inflammatory response [26]. When measured by the easily obtainable parameters of C-reactive protein (with a short half-life of ~20h) and serum albumin (long half-life of some 20 days) using the modified Glasgow Prognostic Score (mGPS, Table 2), poor clinical

### Table 1. Impact of malnutrition in patients with advanced cancer

<table>
<thead>
<tr>
<th>Biomarkers</th>
<th>Redistribution of body resources</th>
<th>Decreased muscle mass</th>
<th>Lean body mass (LBM) lost during chronic treatments</th>
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<tr>
<td>Functional parameters</td>
<td>Accumulation of immune defects</td>
<td>Impaired quality of life (QoL)</td>
<td>Impaired mobility, decrease of daily activities</td>
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<td>Clinical outcome</td>
<td>Increased treatment toxicities</td>
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outcome has been associated with an increased Score in more than 60 clinical trials involving more than 13 000 cancer patients [27].

In chronic inflammatory states energy regulation is disturbed due to the vast fuel consumption of an activated immune system [28]. The negative impact of systemic inflammation on clinical outcome has been attributed to the resulting metabolic shift toward catabolism, the appearance of insulin resistance and of anabolic resistance [29] as well as the promotion of malnutrition by inducing anorexia and fatigue [2, 3]. The adaptive response of protein conservation seen in simple starvation is lost resulting in increased loss of muscle mass [30]. SIRS has similarities with sepsis and is associated with relevant immune suppression thus predisposing to repeated bouts of infections [31]. By exerting this multitude of effects, systemic inflammation has a major impact on quality of life, decreasing physical and mental activity, performance index, activities of daily life, concentration, communication with family and friends, self-reliance, affecting eating habits and the self-image and inducing distress in patients and families [32].

Because systemic inflammation is associated with the presence of malignant tissue, effective anticancer treatments may relieve or diminish the negative effects.

**Anorexia, negative energy balance and weight loss**

Anorexia is one cause of a negative energy balance and weight loss. Anorexia may be induced by systemic inflammation, but also by other factors and symptoms (often referred to as ‘nutrition impact symptoms’) frequently present in cancer patients, such as nausea, vomiting, alterations or loss of taste and smell, abdominal discomfort like pain and bloating as well as changes in bowel function like constipation or diarrhea [33]. Chronic pain will diminish the appetite as will psycho-social distress caused by, e.g. fear, anxiety, insecurity, helplessness, depression, dependency, loneliness, and the experience of being abandoned.

Other causes, all of which may be induced by the tumor or by anticancer therapies, may decrease food intake like poor dentition, stomatitis, dysphagia, gastrointestinal ulcerations and mucositis, motility disorders including stenosis of the head and neck region or the upper or lower gastrointestinal tract.

When judging whether energy intake is adequate or insufficient, it is necessary to refer to standard requirement tables (Table 3). However, individual requirements may deviate from average values and data presented in these tables should be taken to give a rough initial estimate. Supply needs to be adapted according to the individual effects observed during follow-up visits.

**Fatigue, inactivity and muscle loss**

Systemic inflammation typically leads to fatigue, decreases in physical activity and subsequently less anabolic signals and an increased protein breakdown with muscle loss [1]. Other frequent causes of fatigue in cancer patients are anemia, infections, cancer treatments, chronic pain, nausea and vomiting and psycho-social distress. Compared with healthy controls, cancer patients have a lower performance index [34], take fewer steps per day [35] and have a lower physical activity level [8]. The tendency to lose muscle mass by inactivity, reduced energy intake as well as anabolic resistance induced by systemic inflammation may at least partly be addressed by increasing the supply of protein and amino acids [29]. Thus, high amino acid infusions may overcome anabolic resistance in patients with advanced lung cancer, and it is being suggested by international guidelines to increase protein intake in these patients to above 1 g/kg body weight and possibly to as high as 1.5–2.0 g/kg per day [4].

**Gastrointestinal dysfunction**

Food needs to be transported through the gastrointestinal tract, digested and absorbed. Deficits at any step may compromise the amount available to the body. There are few high-quality data in cancer patients; however, it appears reasonable to assume relevant problems of absorption in patients with severe intestinal mucositis associated with cancer treatments or gastrointestinal infections. Peritoneal carcinomatosis may affect transport and absorption by either rapid transit, slow transit, multiple stenoses and vascular insufficiencies. Post-surgical short-bowel syndrome or fistulas bypassing large sections of the small bowel may induce watery diarrhea and a loss of absorptive capacity, requiring parenteral fluids and nutrition.

**Pain**

Chronic pain may abolish appetite. While clinical experience firmly supports this relationship, there are few data comparing it quantitatively. The observation of a negative association of chronic pain and food intake, however, is presented by major online cancer sites (e.g., Canadian Cancer Society: http://www.

Psychosocial distress

Eating serves not only to ensure the intake of energy and nutrients but has an important role in maintaining psychological balance by providing pleasure. In addition, eating in all societies is associated closely with the opportunity for social contact and integration. Changes in eating habits or in chewing, swallowing or digestive functions may severely compromise psychological benefits and social contacts [32].

Anorexia may stir up distress in both patients and families when desperate or resolute caregivers try to force patients to eat [36]. It is mandatory for the health care team, in these situations to communicate carefully but clearly an understanding of the processes responsible for appetite regulation as well as the strain associated with eating against one’s will [37].

Weight loss of sufficient degree will negatively affect not only the physical performance and thus self-reliance and the immune competence and thus resilience but also the self-image of a patient and have a potentially serious effect on the individual quality of life, making the patient feel insecure and being not herself, losing confidence and recognizing an obvious sign of approaching death [32].

Treatment options

Screening for malnutrition

Though detected in many patients with advanced cancer, if analyzed routinely, malnutrition is overlooked frequently in routine clinical care [38, 39]. International clinical guidelines ask for standard screening of all cancer patients for the presence of malnutrition or the risk of malnutrition [4, 40]. Screening should best be carried out in every inpatient and at each out-patient visit [1]. Screening should be rapid, valid, preferably low-cost and easy enough to be carried out reliably by non-specialists. Several questionnaire tools have been developed to quickly detect patients with the presence or an impending risk of developing malnutrition, e.g. Nutrition Risk Screening (NRS) [41], Subjective Global Assessment (SGA) [42], Malnutrition Universal Screening Tool (MUST) [43], Mini Nutritional assessment (MNA) [44], and others. These tools collect easily available and mostly semi-quantitative or qualitative information on, e.g. food intake, recent weight loss, body mass index and metabolic stress level. Deviations from normal prompt further observation or immediate referral to nutritional assessment and therapy [1].

Assessing the nutritional and metabolic status

Patients detected by screening to be at risk of malnutrition, should be assessed by a nutrition expert to objectively judge (1) the present nutritional and metabolic state and (2) factors endangering this status, i.e. checking for the presence and intensity of factors impeding food intake, absorption and entry into anabolic processes [4]. Such an assessment should quantitate body composition, daily physical activity and the metabolic state of the patient; it also needs to include an estimate of nutritional intake, eating habits, food tolerance and preferences of the individual patient; the detection or exclusion of nutrition impact symptoms, the presence of gastrointestinal dysfunctions and an evaluation of the presence of psychological and social distress [4]. The assessment should best be written as a formal note and made available for the whole medical team and be included in the medical discharge letter.

Individualized multimodal care

Individualized nutritional and metabolic care should be based on and follow from the preceding assessment. Because the complex pattern of nutrition impact symptoms, impeding factors, catabolic drivers and psycho-social situation will differ vastly from patient to patient, any care needs to be individualized focusing on the detected set of problems and aiming for relieving each derangement as best as possible. If aiming for optimal effect, the general approach will by necessity be multimodal, targeting to normalize the intake of energy and nutrients, increasing and maintaining regular physical activity, supporting anabolism over catabolism and alleviating psycho-social distress [3, 45]. This will require to involve professional health care workers with different expertise and training and to initiate and maintain adequate contact and exchange among and between the involved experts [1, 46]. The complex treatment concept should be composed in a transparent way, documented formally and included in the discharge letter.

Evaluate and adapt care

While initiating nutritional and metabolic therapy is of primary importance, only follow-up and adaptation of the components of the individualized multimodal care (IMC) will ensure continuity of optimal care. This process requires reliable scheduling of follow-up visits, repeated assessment of the patient to monitor treatment effects as well as further communication among the involved treatment faculties to adapt their individual contributions aiming at further improvement for the patient.

Counseling

The most basic but critically important step in improving food intake is diligent but compassionate and usually repeated counseling by a professional nutrition expert. The goal is to ensure an adequate energy and nutrient intake by considering the individual food habits, tolerances and preferences as well as the presence of nutrition impact symptoms and derangements expected during the course of planned or ongoing anticancer treatments [47, 48]. Establishing and maintaining rapport with the patient is an essential component and requires adequate training of the expert as well as sufficient time and a supportive atmosphere during the counseling sessions. When counseling is provided by experts, beneficial effects are observed on energy intake, body weight and quality of life [49, 50]. It would be most appropriate to document these sessions, present the information to the oncology team and include it in the discharge letter.
Enriching foods
To improve energy and protein intake when appetite is decreased or satiety appears early, it is advisable to use techniques to increase the energy density of foods, thus supplying more nutrients in a smaller volume [51]. One option is to choose more energy-dense (e.g. high-fat vs low-fat) and protein-rich vs protein-poor products (meat, dairy products and legumes vs fruits and vegetables). Enriching foods with proteins or fats may be achieved by, e.g. adding protein powders (10–30 g/day) to liquids and cream or oils to foods and sauces [52]. Taste and tolerance need to be taken into account on an individual basis.

Oral nutritional supplements
Another option to improving energy intake is by offering commercially available balanced oral nutrition supplements. These products are either liquids or creamy or powders to be reconstituted with liquids to yield milky or sweet drinks or aromatic soups. Some products are highly concentrated to provide more than 3 kcal/ml. Guidelines recommend using standard formulas [4]; however, in addition specialized products are available, enriched in protein, selected amino acids, fats, N-3 fatty acids and other components. Evidence to support using specialized instead of standard products in cancer patients is sparse and heterogenous and today at best suggests a potential benefit of protein-rich oral nutritional supplements (ONS) with a high content of N-3 fatty acids when supplied to patients undergoing chemotherapy [4].

While no reliable data are available in patients with cancer cachexia, dietary supplements high in protein, especially branched-chain amino acids, enhance whole body protein synthesis and might improve mortality in malnourished patients with cardiac or pulmonary disease [53].

Enteral tube feeding and parenteral nutrition
While most experts agree on preferring oral over enteral or parenteral nutrition [4], in a number of settings oral nutrition will not suffice to provide adequate amounts of nutrients and energy. Even when orexigenic pharmacologic agents like steroids or cannabinoids, anorexia and early satiety may make it impossible to motivate a patient to continually consume adequate amounts of (enriched or liquid) foods. If further worsening of malnutrition and subsequent impairment of clinical outcome is expected, the option of intermittent or supplemental tube feeding should be discussed with the patient [4]. This option has been studied most frequently in patients with head and neck cancers undergoing combined radio-chemotherapy, but may be offered for severe dysphagia or anorexia if gastrointestinal functions distal to the tube are known to be normal. Tubes may be placed via the nasal or percutaneous route. Both nasogastric tubes and either endoscopically (PEG) or radiologically inserted (RIG) gastrostomies carry a similar risk of regurgitation and aspiration (REF), but long-term (more than 3 weeks) placement is more reliable with PEG or RIG [4].

If inadequate oral food tolerance is combined with severe small bowel defects, like in peritoneal carcinosis, parenteral nutrition may ensure an adequate supply of energy and nutrients. Parenteral nutrition may be offered as a daily or several weekly supplements or may be used daily to supply the complete requirement of all nutrients (total parenteral nutrition) [54]. A large selection of pre-compounded multi-component (all-in-one, AIO) bags is commercially available [55]. In addition, mixtures designed individually for a patient may be compounded on-demand. In cooperation with well-trained home-care teams parenteral nutrition may be supplied within the home-setting over longer periods [56]. Infusion of macronutrients is limited by metabolic tolerance; therefore, the average daily requirement of fat, carbohydrates and amino acids may be infused within 6, 12, and 14 h, respectively. Thus, the on-line time for total parenteral nutrition is considerable and may favor over-night infusions [56].

Risks and burdens of parenteral nutrition may be serious and need to be taken into account. This includes limiting this form of nutrition to patients undergoing anticancer treatment or having an expected overall survival of more than a few weeks [4, 40, 57]. The potential benefits of avoiding malnutrition have to be discussed with the patient as well as the burden of long infusion times, strict hygiene techniques and complex preparations for starting and ending the infusions [56]. In addition, there are risks for serious complications, e.g. sepsis, catheter occlusion and thrombosis [58]. The risk of line infections may be as high as 3 per year even in highly experienced centers [56] with each episode associated with a mortality risk of up to 25% [59].

Metabolic modulation
To counter the catabolic effects of systemic inflammation, a diverse spectrum of anti-inflammatory and anabolic agents has been studied, including anticytokines, melatonin, cannabinoids, insulin, amino acids, proteasome inhibitors, β-receptor modulators, hydrazine, ATP, and anabolic steroids [60]. Thalidomide exerts some promising effects but is considered too toxic. Non-steroidal anti-inflammatory agents have been reported to improve body weight and muscle mass but trial quality has been low rendering results unreliable [61]. Corticosteroids may improve appetite and fatigue for short periods of up to 2 or 3 weeks but are associated among other effects with muscle loss, loss of immune competence and insulin resistance; progestins may increase appetite and weight gain while increasing the risk for thromboembolic complications; cannabinoids appear to be insufficient to stimulate appetite in cancer patients; data on androgens is heterogenous and not adequate for a recommendation [4].

N-3 fatty acids mainly obtained from cold water fish compete with N-6 arachidonic acid for conversion by cyclooxygenases and lipoxigenases, resulting in eicosanoids with only low or no inflammatory activity. In clinical trials N-3 fatty acids or fish oil may decrease inflammatory markers. The evidence to support the use of these fatty acids to counter cancer cachexia, however, is heterogeneous and still inconclusive [4]. While some small randomized trials in patients undergoing chemotherapy have reported improved physical activity, quality of life, appetite, energy intake, body weight and lean body mass; other larger randomized trials could not observe beneficial effects [4].

Despite at this time a lack of high-level evidence, anti-inflammatory, anticatabolic and anabolic pharmacologic interventions appear promising as components of multi-targeted and
Exercise training

Exercise has been proposed to modulate muscle metabolism, insulin sensitivity, and levels of inflammation and thus to attenuate the effects of cancer cachexia [62]. Physical activity is well-tolerated and safe at different stages of cancer [63] and patients with advanced stages of cancer are able and willing to engage in physical activity [64]. Resistance training at moderate intensity has been shown to improve immune activity and decrease inflammatory status in patients with cancer [27, 65]. Resistance and aerobic training, as well as a combined training program may increase muscle strength and maintain patients’ functional ability [46, 66]. Unfortunately, studies of exercise intervention in patients with cancer cachexia are very limited [67] and recommendations to implement exercise and muscle training within multimodal concepts of cachexia treatment are based on animal models and analogies [4, 46]. However, it is apparent, that desired self-reliance rests on adequate physical performance, which requires adequate functional muscle mass, which may not be maintained by nutrients alone without adequate muscle training. Clinical guidelines recommend that cancer patients should be advised to reduce inactivity and suggest individualized resistance exercise in addition to aerobic exercise to maintain muscle strength and muscle mass [4].

Trials in healthy volunteers have demonstrated that bouts of exercise increase and prolong the feeding-induced stimulation of muscle protein synthesis [68]. This supports the concept of combining exercise and feeding to maximize the anabolic effects on muscle.

Supportive care

Best supportive care in many patients may be the most important intervention to enable the intake of adequate amounts of food. This includes effective treatment of chronic pain, improvement of dental status, treatment of stomatitis and mucositis, elimination of nausea, dysphagia, gastrointestinal ulceration or stenoses, treatment of thrush and other infections, as well as of diarrhea or constipation. Enabling the consumption of food is as important as counseling the choices of energy- and nutrient-rich foods.

Psycho-oncology and social support

Health care professionals should empower patients and their care givers to understand the nature and course of malnutrition and cachexia. It is important to acknowledge the associated and frequently irreversible negative effects, including the loss of weight and appetite; this may improve the patient’s confidence and trust in the care relationship. Patients and their families prefer clear and honest information rather than a lack of information [69]. In fact, poor communication may weaken the confidence in the health care provider’s knowledge and thus impair hope and worsen quality of life [70]. Being unable—even despite pressure exerted—to persuade their loved one to eat and seeing food being rejected, this will elicit feelings of guilt, anxiety and frustration [36]. Simultaneously, the patient may experience food as a traumatic experience, possibly feeling coerced to escape by lying or choosing isolation [36].

Enteral or parenteral nutrition may relieve eating-induced distress within a family [71], this option, however, should only be discussed and offered if artificial nutrition is expected to improve a patient reported or clinical outcome. There are only a few controlled trials investigating and supporting beneficial effects of brief forms of psychotherapy, more complex psycho-social interventions as well as family-centered therapies in the management of cancer cachexia [72–76]. While small and biased by a number of shortcomings, these trials reported decreases in weight- and eating-related distress and thus support further interest in this direction of research.

Conclusion

Detect, assess and treat all factors endangering body resources and functions

Malnutrition and cachexia occur frequently in patients with advanced cancer. Contributing factors are an intolerance of adequate food intake, a relevant decrease in daily physical activity and metabolic derangements highlighted by systemic inflammation and resulting in sustained catabolism. It is recommended to screen all cancer patients regularly for signs of active or imminent malnutrition, assess thoroughly all those at-risk and design individualized multimodal treatments targeting all factors contributing in one patient to compromising body resources and functions.

Strive for a common classification and grading system of malnutrition

Finally, there remains the hope that the medical specialties of oncology and nutrition will approach each other close enough to agree on and establish a common set of defining parameters and a grading system of the depletion of body resources and functions which simultaneously allow guiding treatment of nutritional and metabolic derangements in patients with advanced cancer and allocating adequate medical resources to reliably and successfully perform the required diagnostic procedures and therapeutic interventions.

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References