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Nutrition in oncologic patients during antiblastic treatment

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1. ABSTRACT

Cancer may induce weight loss and cachexia, and cancer treatment may contribute to nutritional impairment. Here, we review the literature on the mechanisms of cancer cachexia and the pharmacological interventions both in use in clinical practice and currently under development. Based on this analysis, several nutritional proposals for cancer patients are suggested and the importance of good nutritional status in candidates for hematopoietic stem cell transplantation is highlighted.

2. INTRODUCTION

Cancer can cause profound metabolic alterations that may affect the host's nutritional needs for protein, carbohydrate, fat, vitamin, and minerals (1). Symptoms such as anorexia, early satiety, changes in smell and taste, and disturbances in the gastrointestinal tract are common side effects of cancer treatment that can lead to an inadequate nutrient intake and subsequent malnutrition (2). Substantial weight loss and poor nutritional status are reported in more than 50% of patients at the time of diagnosis (3). Nutritional screening and assessment should

take place during treatment planning, with a focus on evaluation of dietary status and identification of treatment-related symptoms that may affect nutritional status. Such evaluation is particularly important when considering the data regarding the association among weight loss, cancer cachexia, and poor outcomes in cancer patients.

Over the past several years, research has helped elucidate the mechanisms behind cancer cachexia, and several pharmacologic agents that may reverse the syndrome are now available in clinical practice or under development. Cancer patients are often highly motivated to seek information regarding food choices and dietary supplements (DS) that may improve their treatment outcomes, quality of life, and survival. Thus, most patients use DS during all phases of cancer treatment, even though most conventional oncologists recommend complete avoidance of all supplements and have very little information regarding their effects (4). However, a closer look at the literature in this area does not support a blanket interdiction. A variety of DS may provide benefits to cancer patients, facilitating relief from such cancer-treatment associated symptoms such as mucositis, intestinal toxicity, neuropathy, and nausea.

An association between poor survival and increased morbidity has been identified in one specific patient population: malnourished patients undergoing hematopoietic stem cell transplantation (HSCT) (5). Due to this association and the high risk of malnutrition in HSCT candidates, nutritional status has gained particular relevance among clinicians aiming to develop HSCT conditioning regimens and avoid the development of therapy-related toxicity.

3. CACHEXIA

3.1. Impact on cancer

The weight loss frequently observed in advanced cancer patients has long been known to be associated with adverse outcomes. Up to 50% of cancer patients suffer from cachexia, defined as progressive atrophy of adipose tissue and skeletal muscle. Cachexia not only results in weight loss and reduced quality of life and survival but is also the direct cause of up to 20% of all cancer deaths due to immobility and cardiac/respiratory failure (6). Cancer cachexia may be clinically defined as the involuntary loss of more than 5% of pre-morbid weight within a 6-month period (7).

Loss of body weight in cancer patients is due to loss of fat and muscle in equal proportion (8). Cancer cachexia thus differs from simple starvation, in which more than three-quarters of body weight loss is due to loss of adipose mass, and only a small amount due to loss of muscle mass. In addition, cancer cachexia leads to specific loss of skeletal muscle, 75% of which may be depleted just prior to death, while visceral proteins are preserved and may even increase (9). In contrast, the losses of visceral mass and skeletal muscle in anorexia nervosa are proportional. Thus, although anorexia frequently accompanies cachexia, it is unlikely to play a major role in tissue loss, especially skeletal muscle (10).

3.2. Mechanisms of cancer cachexia

Although recent years have seen increased understanding of the mechanisms of loss of both adipose tissue and skeletal muscle in cancer cachexia, only the first step in the development of clinical therapy has been taken. Skeletal muscle wasting is now known to be due to decreased muscle protein synthesis, increased muscle protein degradation, or a combination of both.

Evidence suggests that cancer-related depression in skeletal muscle protein synthesis may be related to increased serum levels of tumor-released proteolysis-inducing factor (PIF), a 24-kDa sulfated glycoprotein produced by cachexia-inducing tumors (11). Similar to PIF, angiotensin II may contribute to decreasing muscle protein synthesis by affecting the initiation of protein translation (12). Cancer-related depression in skeletal muscle protein synthesis may also be attributed to decreased phosphorylation of intramuscular amino acid-signaling molecules of mammalian target of rapamycin and its downstream target p70 S6 kinase, which have a role in the translation-initiation phase of protein synthesis or in the decreased level of physical activity consequent to weakness and fatigue (13-14).

Increased skeletal muscle proteolysis in cancer may be attributable to several mechanisms, including activation of proteolytic systems within the skeletal muscle and increased levels of proinflammatory cytokines, tumor-released PIF, and angiotensin II. Two skeletal muscle proteolytic systems have been particularly implicated in cancer-related skeletal muscle protein degradation: the nonlysosomal calcium-dependent protease system, a member of a family of Ca^{2+}-activated cysteine proteases known as calpains, and the ATP-dependent ubiquitin–proteasome system (UPS) (15-16). Elevated serum levels of proinflammatory cytokines, in particular tumor necrosis factor-alpha (TNF-alpha), interleukin-1 (IL-1), and IL-6, are also reported to play a role in cancer-related skeletal muscle wasting (17-18). Similar to proinflammatory cytokines, PIF and angiotensin II cytokines increase muscle protein degradation by activation of the UPS (11, 13).

In a study of the adipose tissue pathways involved in the weight loss in cancer cachexia, Dahlman et al. detected 2 major pathways using gene expression profiling techniques (19). Specifically, they found that genes involved in pathways regulating energy turnover (i.e., regulating electron transport, fatty-acid degradation, oxidative phosphorylation, and the Krebs TCA cycle) were up-regulated, whereas genes involved in a number of pathways related to cellular adhesion and maintenance of the extracellular matrix and actin cytoskeleton were down-regulated. Moreover, they found that cachexia patients experienced no change in fat cell number but did experience a decrease in fat cell volume. Based on these findings, they hypothesized that changes in fat cell volume were secondary to increased lipid oxidation, enhanced lipid mobilization from adipose tissue, and adaptation of the

extracellular matrix. Interestingly, they observed no changes in the expression of inflammatory genes, suggesting that adipose tissue is not the source of the increased systemic inflammatory activity observed in cachexia patients. Consistent with these data, a lipid-mobilizing factor has been identified in both murine models and humans that acts as a mediator of fat cell lipolysis in cancer cachexia. However, increased expression of TNF-alpha, another possible mediator of direct lipolysis, has not been observed in cancer cachexia (20-21).

3.3. Medical management

The best means of management of cancer cachexia is cure of the cancer causing it. Unfortunately, this is an infrequent achievement in patients with advanced solid tumors. Nutritional intake to counteract weight loss may be another therapeutic option. However, enhanced nutrition is not able to reverse the wasting process associated with cachexia. Interestingly, nutritional supplementation, with or without appetite stimulants, increases body fat but fails to increase lean muscle mass in weight-losing cancer patients (22). Administration of pharmacological agents able to affect appetite or to target specific signaling pathways/cachectic mediators represents another manner of intervention. Progestagens (medroxyprogesterone acetate and megestrol acetate) appear to be able to increase body weight (mainly water and fat mass) and improve cenestesis and quality of life, but have not been proven to increase lean body mass (22-24). Corticosteroids appear equally effective and are widely used, but are not suitable for chronic use due to side effects (25).

Drugs able to inhibit the synthesis and/or release of cytokines, such as eicosapentaenoic acid and melatonin; inhibit cytokine activity, such as anti-cytokine antibodies (e.g., anti-TNF-alpha MoAb infliximab) and anti-inflammatory cytokines (e.g., IL-12 and IL-15); or inhibit proteasome activity (e.g., bortezomib) have failed to demonstrate exhaustive results in humans (26-28). Drugs currently under evaluation include 1) thalidomide, which is being studied due to its immunomodulatory and anti-inflammatory properties; 2) cyclooxygenase-2 inhibitors, which are being studied due to their role in suppression of systemic inflammation; 3) ghrelin, a peptide that stimulates GH secretion, promotes food intake, and decreases sympathetic nerve activity; 4) insulin, which increases body fat throughout the body, particularly in the trunk and leg compartments, but not lean tissue mass; 5) branched-chain amino acids, which appear to increase skeletal muscle wet weight and performance in experimental models of cancer cachexia; 6) oxandrolone, which affects lean body mass; 7) olanzapine, which exerts activity on weight and nutrition; and 8) PIF antagonists, which have been found to attenuate muscle wasting in both experimental cachexia models and clinical research (13, 29-37).

4. GENERAL CONSIDERATIONS REGARDING NUTRITION AND FOOD CHOICES OF CANCER PATIENTS

Protein, carbohydrate, and fat contribute energy (calories) to the diet and are available from a wide variety of foods. Currently, the recommended level of fat intake in the diet ranges between 20% and 35% of total energy intake. Saturated fat intake should to be limited to less than 10% and trans-fatty acid intake to less than 3% of total energy intake (38). Intake of foods rich in omega-3 fatty acids (e.g., fish and walnuts) should be encouraged (39-41), as they have specific properties that ameliorate cachexia, improve quality of life, and even enhance the effects of some treatments and lower the risk of cardiovascular disease. Adequate protein intake is also essential. Intake of foods low in saturated fat (e.g., fish, lean meat, poultry, eggs, non- and low-fat dairy products, nuts, seeds, and legumes) is the best means to meet protein needs. An intake of 10% to 35% of energy from protein, or at least 0.8 g/kg of body weight, is recommended for the general population, and should be extended to cancer patients (38). Healthful carbohydrate sources are foods rich in essential nutrients, such as vitamins and minerals, which could potentially affect cancer progression, as well as in phytochemicals and fiber, and include vegetables, fruits, whole grains, and legumes. These foods, which should provide the majority of carbohydrates in the diet, are low energy density foods that promote satiety, and may thus promote healthy weight management (42). In the general population, the recommended level of carbohydrates in the diet ranges from 45% to 65% of the total energy intake (38). Sugars, including honey, raw sugar, brown sugar, high-fructose corn syrup, and molasses, together with beverages such as soft drinks and many fruit-flavored drinks, add substantial amounts of calories to the diet but do not contribute many nutrients, and should thus be limited in a balanced diet. In addition to fiber, whole grains are rich in a variety of compounds that have antioxidant activity, such as phenolic acids, flavonoids, and tocopherols; hormonal activity, such as lignans; and compounds that may influence lipid metabolism, such as phytosteroids and unsaturated fatty acids. All these compounds and their biological effects have been hypothesized to reduce the risk and the progression of cancer as well as cardiovascular disease (43).

5. DIETARY SUPPLEMENTATION AND CHEMOTHERAPY

Most cancer patients take DS during all phases of cancer treatment (4). Despite their increasing use by cancer patients, most oncologists recommend complete avoidance of all DS that are advocated by complementary and alternative medicine (CAM). However, a closer look at the literature in this area does not support a blanket interdiction (Table 1). Evidence of harm remains largely theoretical, while evidence of benefits in some cases may warrant active recommendation. One of the risks of CAM therapy that has been reported is refusal to undergo curative conventional treatment while undergoing CAM therapy. However, data show that only a minority of patients choose to use only CAM, while the vast majority uses CAM concurrently with conventional treatment (44). The use of contaminated or adulterated DS has also been suggested to be a risk, but efforts have been made to ensure DS quality and provide manufacturer guidelines.

In addition, relatively few herbal products have toxic components that are not recommended for general use. For example, hepato-toxicity has been reported to be

Table 1. Recommended dietary supplements during chemotherapy and their predominant action

Dietary supplement	**Field of action**
Alpha-tocopherol, beta-carotene, vitamin C, niacin, selenium, coenzyme Q, zinc	Antioxidants
Medical mushrooms and mushrooms-derived polysaccharide preparations (i.e. PSK, *Agaricus Blazei*, Avemar)	Immune Modulation
Glutamine	Mucositis, intestinal toxicity, neuropathy
Vitamine E (alpha-tocopherol)	Mucositis, neuropathy
Zinc supplementation	Mucositis
Probiotics (i.e. *Lactobacillus rhamnosus*)	Intestinal toxicity
Ginger	Nausea

associated with some common herbs, such as chaparral (*Larrea tridentate*), comfrey (*Symphytum officinale*), and kava (*Piper methysticum*) (45).

Oncologists have also raised concerns regarding herb–drug interactions and the interference of herbs with drug activity. The proposed mechanism of this interference is the ability of herbal products to affect the cytochrome P450 enzyme system, which is crucial in the metabolism of a number of chemotherapy agents. Other potential mechanisms that have been reported are the action of adenosine triphosphate-binding cassette transporters, such as P-glycoprotein, and multidrug resistance associated with protein-1 and breast cancer resistance protein (46). Based largely on preclinical data, specific cautions have been reported for garlic, ginkgo (*Ginkgo biloba*), soy (*Glycine max*), ginseng (*Panax ginseng*), valerian (*Valeriana officinalis*), and kava (46). However, these data have not been confirmed by human studies.

Moreover, the interference of DS and herbs in coagulation is largely based on case reports whose results have not been confirmed by pharmacological studies (49). Concerns about the use of herbal therapies with *in vitro* hormonal activity among patients with hormone-sensitive patients, such as black cohosh for breast cancer patients, has not been proven to be valid in human studies (50).

Oxidative stress, defined as a disturbance in the equilibrium between reactive oxygen species and detoxifying antioxidant systems, can be involved in the pathophysiology of many diseases, including tumors (51). A free radical is an atom or molecule that has at least one unpaired electron, and is therefore unstable and highly reactive. Free radicals generated during cancer treatments are responsible for cellular damage and the killing of malignant as well as normal cells. Antioxidants, which are defined as molecules that neutralize free radicals before vital molecules are damaged, include nutrients (e.g., vitamins A, C, and E; carotenoids; selenium; flavonoids/polyphenols; lycopene; lutein; lignans; coenzyme Q10; and glutathione) and enzymes synthesized in the body (e.g., superoxide dismutase, catalase, and glutathione peroxidise) that need the presence of micronutrients (e.g., copper, iron, manganese, zinc, and selenium) (52).

Although intake of antioxidant-rich foods is commonly associated with reduced risk for a variety of cancers, the use of antioxidants, either singly or in formulas, as preventative agents for cancers is not supported by large randomized trials (53). Clinicians cite fear of decreasing effectiveness of conventional therapy as a major concern for the use of antioxidants during chemotherapy and radiotherapy, and can refer to a large amount of pre-clinical data and limited data from human studies to support their fear. In fact, higher rates of local recurrence as well as higher all-cause mortality were found in a group of subjects with head-and-neck cancer undergoing radiation and taking a combination of antioxidants (400-IU alpha-tocopherol and 30 mg beta-carotene), compared to a group taking a placebo (54). Similarly, a trend toward reduction in disease-free survival ($p = 0.08$) was identified in a group of 90 women who had taken large doses of beta-carotene, vitamin C, niacin, selenium, coenzyme Q10, and zinc during conventional therapy in comparison with matched controls (55).

Other data have failed to demonstrate that antioxidant therapy causes harm to patients undergoing chemotherapy. In a study of a group of 136 advanced non-small cell lung cancer patients, a form of combined antioxidant therapy (6,100-mg ascorbic acid, 1,050-mg dl-alpha tocopherol, and 60-mg beta-carotene per day) neither improved the response rate nor increased toxicity (56). The greatest proponent of vitamin C use, Linus Pauling, asserted that terminal cancer patients can benefit from high-dose (10 gm) vitamin C therapy. Pauling based his assertion on his finding of a greater rate of male survival at 300 days and a greater number of survivors after 1 year (24% versus 0.4%) in a cohort of 100 untreatable cancer patients compared to a historical control group of 1,000 patients (57). Two subsequent randomized, controlled trials by other investigators failed to confirm any significant benefit from high-dose vitamin C therapy, but observed no significant toxicity with its use (58-59).

A variety of natural products have been shown to provide benefits to cancer patients, either in terms of overall quality of life or relief of specific symptoms associated with cancer treatment, such as mucositis, intestinal toxicity, neuropathy, and nausea.

Medicinal mushrooms and mushroom-derived polysaccharide preparations have been investigated as immune modulators and adjuvant agents in cancer in both *in vitro* and animal studies, as well as in some human clinical trials. One of the best-studied preparation has been a protein-bound polysaccharide extract (PSK) of the medicinal mushroom *Trametes versicolor*, also called

Coriolus versicolor. A randomized trial of 207 stage II and III colorectal cancer patients showed that administering 3 g/day of PSK during the provision of conventional therapy significantly increased the 5-year disease-free survival rate ($p = 0.038$) and decreased the relative risk of regional metastasis (60-61). These results were confirmed by a meta-analysis of 3 trials involving 1,094 patients with colorectal cancer that found a significant improvement in overall survival ($p = 0.006$) and disease-free survival ($p = 0.003$) in those taking PSK (62). PSK therapy was also found to significantly increase survival rate ($p = 0.0180$) in a meta-analysis of 8,009 gastric cancers patients in 8 randomized, controlled trials (63). A number of other medicinal mushrooms that have been tested in cancer patients have yielded variable results. In one study, administration of an extract of the mushroom *Agaricus blazei* to 100 patients with gynecological cancers (cervical, ovarian, or endometrial) undergoing conventional chemotherapy (carboplatin, etoposide, or taxol) was found to increase NK activity ($p < 0.002$), as well as decrease many chemotherapy-related effects, such as appetite loss, alopecia, and weakness (64). Avemar, a fermented wheat germ extract standardized to methoxy-substituted benzoquinones and registered as medical nutriment, has also been shown to benefit cancer patients. In a cohort trial, 66 patients with colorectal cancer who took 9 g/day of Avemar for 6 months experienced fewer recurrences, new metastases, or death and a significant increase in both disease-free and overall survival compared to a control group of 104 colorectal cancer patients undergoing conventional treatment (65).

Mucositis is a common side effect of chemotherapy that contributes significantly to patient morbidity via decreased quality of life and interference with proper nutrition. Administration of glutamine, both intravenously and orally as a swish-and-swallow mouthwash, appears to prevent and treat oral mucositis.

In one study, head-and-neck patients treated with 0.4 g/kg/day of intravenous glutamine while undergoing chemotherapy experienced lower incidence of mucositis ($p = 0.035$) and less severe mucositis ($p = 0.007$) and pain ($p = 0.008$) (66). In another study, only 1 of 9 patients with inflammatory breast cancer receiving 0.5 g/kg/day of oral glutamine and neoadjuvant methotrexate followed by adriamycin experienced grade 1 mucositis, and all showed a good response to chemotherapy and no glutamine-related toxicity (67). However, in a large phase III trial of 134 subjects undergoing 5-fluorouracil chemotherapy, administration of 4 g of oral glutamine twice a day did not decrease the severity of symptoms or pain (68). The possible reasons for the failure to find benefit may have been pretreatment with ice, the short retention time in the mouth, or the minor effectiveness of the 5-fluorouracil chemotherapy.

Topical application of 100 mg of vitamin E to the mouth of children receiving a variety of different chemotherapeutic agents has been found to improve mucositis significantly (69). Likewise, administration of 400 mg/ml of Vitamin E oil twice per day to 18 patients undergoing a variety of different chemotherapy regimens resolved pre-existing mucositis in all but one patient (70). Zinc supplementation has been shown to be effective in preventing and treating mucositis in head-and-neck patients during radiation therapy (71). Herbal therapies (e.g., aloe vera; chamomile extract mouthwashes; and Traumeel, a homeopathic remedy containing *Arnica montana* and other substances) have shown mixed results (72-74). Administration of proteolytic enzymes, such as papain, trypsin and chymotrypsin, appears beneficial in preventing mucositis and skin reactions in head-and-neck patients undergoing radiation therapy (75).

Intestinal toxicity in the form of gut mucosa disruption leading to leaky gut or diarrhea is common during chemotherapy. Again, glutamine has shown benefit in preventing chemotherapy-related intestinal toxicity in some studies. Approximately half of 51 subjects undergoing 5-fluorouracil chemotherapy with leucovorin who also took 30 g/day of oral glutamine were found to have a significantly lower intestinal permeability score ($p < 0.001$), and a lower percentage of these subjects experienced grade 2 to 4 mucositis (9% versus 38%; $p < 0.001$) compared to controls (76). Moreover, among 70 gastrointestinal cancer subjects undergoing 5-fluorouracil therapy, the group also receiving glutamine (18 g/day for 5 days before and until 15 days after chemotherapy) experienced decreased incidence of diarrhea and use of loperamide tablets ($p = 0.09$ and $p = 0.002$, respectively) compared to a control group receiving a placebo. Patients undergoing combined glutamine therapy and chemotherapy also experienced decreased permeability and increased intestinal absorption ($p = 0.02$) compared to a control group (77). However, 33 patients with advanced breast cancer experienced no decrease in diarrhea incidence after taking 30 g/day of glutamine in 3 divided doses for 8 days during the interval between doxifluridine chemotherapy (78). Despite these mixed results regarding the efficacy of glutamine therapy, there is no evidence that it decreases response to chemotherapy.

Probiotics have been used to decrease gastrointestinal toxicity resulting from both chemotherapy and radiotherapy. Colorectal cancer patients receiving one of two 5-fluorouracil-based chemotherapy regimens, who were also randomized to receive either *Lactobacillus rhamnosus* at a dose of 1 to 2 × 10 organisms or 11 g/day of guar gum experienced fewer episodes of high-grade diarrhea (22% versus 37%; $p = 0.027$) and less abdominal discomfort, needed less hospital care, and required fewer reductions in chemotherapy dosage due to bowel toxicity. No toxicity has been noted with the *Lactobacillus* therapy (79).

Peripheral neuropathy is a potentially debilitating side effect caused by a number of chemotherapeutic agents, especially platinum-based drugs and taxanes. In a nonrandomized, controlled clinical trial, 33 patients administered 10 g of glutamine 3 times a day for 4 days starting 24 hours after chemotherapy together with high-dose paclitaxel experienced a significant decrease in severity of sensory neuropathy in terms of both dysesthesia and numbness ($p < 0.05$), better motor function, lower incidence and severity of motor weakness ($p = 0.04$), and

less disturbance in gait ($p = 0.016$) in comparison with 12 patients receiving only conventional care (80).

Among 86 metastatic colon cancer patients undergoing oxaliplatin-5-fluoruracil chemotherapy, reduced incidence of moderate-grade neuropathy after 2 (17% versus 39%), 4 (5% versus 18%), and 6 (12% versus 32%) cycles of treatment, less interference with activities of daily living (17% versus 41%), and less reduction in chemotherapy due to neuropathy (7% versus 27%) was reported for 44 patients administered 15 g of glutamine twice a day for the first 7 days of chemotherapy (81).

Concurrent administration of vitamin E (alpha-tocopherol) with platinum- and taxane-based chemotherapy has also shown benefit in preventing chemotherapy-related neuropathy. In one study, 13 of 27 subjects receiving 300 mg of alpha-tocopherol twice a day throughout treatment with cisplatin experienced both decreased incidence (31% versus 86%; $p< 0.01$) and severity of neurotoxicity ($p < 0.01$) compared with patients receiving conventional care (82). No differences in survival and tumor response were observed between the 2 groups, and both groups received a standard antiemetic on the first day. After the first cycle, patients were crossed over to the alternate protocol. Ginger as well as metoclopramide has been shown to delay nausea with less restlessness, in addition to conventional antiemetics have not improved acute efficacy (83).

6. NUTRITIONAL RECOMMENDATIONS IN HEMATOPOIETIC STEM CELL TRANSPLANTATION

Referring to an array of intensive therapies, including allo- and auto-grafts of bone marrow or peripheral hemopoietic stem cells, HSCT is the standard treatment provided when attempting to cure a large variety of hematological disorders, chemo-sensitive solid tumors, and severe autoimmune diseases (84).

Undergoing allogeneic or autologous HSCT should be considered a stressful event requiring a high level of energy. The energy requirements differ in allogeneic or autologous HSCT recipients and are affected by patient characteristics, including age, performance status, and presence of co-morbidities, such as metabolic diseases; disease features, such as presence of solid or hematological cancer and disease stage and status; type of transplant, whether autologous or allogeneic transplant from family or unrelated donors; type and intensity of conditioning regimen, whether calling for myeloablative or non-myeloablative treatment, associated chemotherapy and immunotherapy, or radiotherapy; and the quality, number, and type (i.e., peripheral, bone marrow, or cord blood-stem) of re-infused stem cells. The different combination of these variables results in different transplantation outcomes and a wide range and degree of short- and long-term complications.

Conditioning regimens affect not only tumor cells but also non-tumor cells, especially rapidly replicating cells, such as enterocytes, colonic epithelial cells, and lymphocytes. The conditioning regimen thus induces very important changes in the gastrointestinal tract and the immune system and, as a consequence, produces important metabolic and nutritional alterations (85).

HSCT complications affecting a patient's nutritional status may be mainly summarized as 1) digestive (e.g., diarrhea, mucositis, anorexia, nausea, vomiting, and taste and smell alterations), 2) graft-versus-host disease (GVHD), and 3) hepatic veno-occlusive disease (sinusoidal obstruction syndrome). GVHD is a severe complication of allogeneic HSCT that occurs when immune-competent graft cells react against host-cell antigens, and may be acute or chronic. In its acute form, GVHD appears with signs and symptoms affecting the gastrointestinal system, skin, and liver (86-87). Gastrointestinal involvement may be characterized by intestinal crypt destruction followed by profuse diarrhea with severe nitrogen loss and mucosal ulcers with possible perforation requiring emergency surgery (88). This situation prevents administration of oral nutrition, forcing clinicians to start total parental nutrition (TPN), and contributes to the development of infections. The same scenario is experienced by approximately 16% to 25% of patients with chronic GVHD who develop gastrointestinal involvement several months or years post transplant. Hepatic veno-occlusive disease is histologically characterized by stenosis and occlusion of hepatic venules with hepatocyte damage as a result of the toxic effects of chemotherapy. Generally developing within 3 weeks after autologous or allogeneic transplantation, hepatic veno-occlusive disease is usually accompanied by weight gain and high bilirubin and serum transaminase levels, followed by oliguria, sodium and water retention, ascites, hepatic failure, and liver encephalopathy (89).

Nutritional status and the role of nutritional screening before transplantation are typically not well investigated in patients undergoing autologous or allogeneic HSCT in clinical practice. However, experts agree with the inclusion of a nutritional assessment in the pre-transplantation work-up (90). Notably, impaired nutritional status before transplantation is reported as a negative prognostic factor for outcome after HSCT, having been associated with increased length of hospital stay and prolonged time to engraftment, and is of particular concern among elderly HSCT candidates (91-94).

Once-a-week nitrogen balance measurement is considered the most accurate way of assessing nutritional status in HSCT candidates, as it evaluates the direct expression of the imbalance between protein breakdown and synthesis. Moreover, daily monitoring of weight (primarily to judge hydration status), along with measurement of blood glucose, serum electrolyte, BUN/urea, and serum creatinine levels and calorie and protein intake, is advised. Finally, twice weekly measurement of liver function to detect abnormalities caused by TPN and weekly monitoring of serum albumin, serum transferrin (reflective of amino acid intake for visceral protein synthesis), and serum triglyceride levels may be suggested (95).

Table 2. Nutritional requirements in HSCT. Modified from ([99])

Nutrients	Severe malnutrition: severe complications	No severe malnutrition: mild complications
Proteins (g x kg^{-1} x d^{-1})	1.8-2.5	1.5-1.8
Carbohydrates (g x kg^{-1} x d^{-1})	3-4	3-5
Lipids (g x kg^{-1} x d^{-1})	1.8-2	1.5-2
Glutamine (g x kg^{-1} x d^{-1})	0.35-0.55	0.35-0.55
ω-3 Fatty acids	20% of total lipids	20% of total lipids
Vitamins E and C	Yes	Yes
Selenium	Yes	Yes

Nutritional requirements in patients undergoing transplantation are increased due to intense catabolism (96). There is consensus that the energy requirements of transplant recipients may increase up to 130% to 150% of estimated basal energy expenditure, corresponding to a 30% to 50% increase in kcal/kg of body weight per day (89, 96-97). Protein needs are also elevated above the typical amino acid dose of 1.5 to 2 g/kg/day. A mixture of long chain triglycerides containing saturated fatty acid moieties of 20 to 40 carbons and medium-chain triglycerides of 6 to 12 carbons should provide 30% to 40% of non-protein energy (Table 2) (98-99). Electrolytes, vitamins, and trace elements (e.g., chromium, zinc, copper, manganese, and selenium) should be added to TPN according to the recommended daily amount.

Despite the need for more research into the topic, low-microbial diets are indicated to prevent sepsis in transplant recipients. In particular, patients should avoid foods containing yeast or gram-negative bacteria and foods intrinsically contaminated with microorganisms, such as raw eggs, raw or rare-cooked meat, fish, seafood, and unpasteurized milk (100).

Moreover, provision of a specialized form of nutritional support may have a role in HSCT. For instance, some authors have found that administration of glutamine, a non-essential amino acid, improves nitrogen balance and immune system function while appearing to reduce risk of infection and compromising the intestinal mucosa. As a precursor of central nervous system neurotransmitters, glutamine also appears to have a role in mood improvement, and has been associated with shorter length of hospital stay (101-104). While several investigators have found glutamine to be safe and have positive metabolic effects, other investigators believe that its clinical usefulness has not been demonstrated (105).

Clinicians have also studied the role of dietary compounds in inflammatory response modulation, increased rate of immunocompetence restoration, and preservation of the integrity and function of the gastrointestinal mucosa. Among these, several nutrients with antioxidant properties, such as vitamin E and beta-carotene, have been shown beneficial in preventing oxidative damage and apoptosis in animal models (106). Lipids and newer lipoids emulsions containing oleic acid and omega-3 fatty acids have been demonstrated to provide an immunomodulatory effect obtained via decreased cytokine production and control of carbohydrate intolerance (107-108).

As concerns the route of artificial nutrition administration, TPN is largely favored to enteral nutrition (EN) in HSCT patients in clinical practice. In fact, nausea, vomiting, oro-esophageal mucositis, and intestinal GVHD prevent the insertion and subsequent tolerability of nasogastric tubes, percutaneous endoscopic gastrostomy, or surgical jejunostomy. Reported TPN complications are typically metabolic or related to the central venous catheter. Metabolic complications include abnormal liver function (i.e., elevation of transaminase, serum bilirubin, and alkaline phosphate levels) that enters in differential diagnosis with drug toxicity, infections, veno-occlusive liver disease, GVHD, or relapse of malignancy as other common causes of elevated liver enzymes during HSCT. Central-venous catheter complications include not only infections but also venous thromboembolism, mechanical obstruction, and dislodgment and leakage of the catheter (95). Studies comparing the effects of TPN and EN in HSCT patients found increased rates of morbidity, diarrhea, and hyperglycemia and delayed time to engraftment but less weight loss with TPN (109-112). EN may be associated with a decreased risk of severe GVHD (113). Notably, the oral route should be employed whenever possible and artificial support should be initiated only when oral intake proves to be insufficient.

Patients receiving HSCT are liable to develop malnutrition because of their underlying disease, the conditioning regimen, and treatment-related toxicity. In conclusion, due to the increase in morbidity and mortality reported in malnourished patients receiving HSCT, appropriate nutritional evaluation of patients should be encouraged during all transplantation phases.

7. CONCLUSIONS

Cachexia is a particularly debilitating syndrome characterized by progressive atrophy of the adipose tissue and skeletal muscle that affects up to 50% of cancer patients and is associated with adverse outcomes. In this study, we reviewed the physiopathology of cachexia and the pharmacological agents in clinical practice or under evaluation that may have a role in cancer cachexia management.

Based on our review, we presented general considerations regarding nutritional and food choices for cancer patients. In our review of the literature on the use of DS and CAM during chemo-radiotherapy, we found that the harmful effects remain largely theoretical while there is evidence of some benefits. Few herbal products contain

toxic components, and few studies on herb–drug interactions are reported in the literature. We reported on antioxidant properties of certain foods and their role in the relief of specific cancer symptoms, such as mucositis, intestinal toxicity, neuropathy, and nausea. We concluded by examining the increasing interest in nutritional status assessment in HSCT, particularly as malnourished patients undergoing HSCT have increased risk of morbidity and mortality.

9. REFERENCES

1. M Schattner, M Shike. Nutrition support of the patient with cancer, in Shils ME, Shike M, Ross AC (eds). Modern nutrition in health and disease. 10th ed. Philadelphia, PA: Lippincott Williams & Wilkins; pp. 1290-1313 (2006)

2. G Nitemberg, B Raynard : Nutritional support of the cancer patient: issues and dilemmas. *Crit Rev Oncol Hematol* 34, 137-168 (2000)

3. K McMahon, G Decker, FD Ottery: Integrating proactive nutritional assessment in clinical practises to prevent complications and costs. *Semin Oncol* 25, 20-27 (1998)

4. GM D'Andrea: Use of antioxidants during chemotherapy and radiotherapy should be avoided. *CA Cancer J Clin* 55, 319-321 (2005)

5. WH Navarro, FR Jr Loberiza, R Bajorunaite, K van Besien, JM Vose, HM Lazarus, JD Rizzo: Effect of body mass index on mortality of patients with lymphoma undergoing autologous hematopoietic cell transplantation. *Biol Blood Marrow Transplant* 12, 541-551 (2006)

6. BHL Tan, KCH Fearon: Cachexia: prevalence and impact in medicine. *Curr Opin Clin Nutr Metab Care* 11, 400-407 (2008)

7. A Inui: Cancer anorexia-cachexia syndrome. Current issues in research and management. *Cancer J Clin* 52, 72-91 (2002)

8. SH Cohn, W Gartenhaus, A Sawitsky, K Rai, I Zanzi, A Vaswani, KJ Ellis, S Yasumura, E Cortes, D Vartsky: Compartmental body composition of cancer patients with measurement of total body nitrogen, potassium and water. *Metabolism* 30, 222-229 (1981)

9. KCH Fearon: The mechanisms and treatment of weight loss in cancer. *Proc Nutr Soc* 51, 251-265 (1992)

10. SB Heymsfield, CB McManus: Tissue components of weight loss in cancer patients. *Cancer* 55, 2238-2242 (1985)

11. MJ Lorite, HJ Smith, JA Arnold, A Morris, MG Thompson, MJ Tisdale: Activation of ATP-ubiquitin-dependent proteolysis in skeletal muscle in vivo and murine myoblasts in vitro by a proteolysis-inducing factor (PIF). *Br J Cancer* 85, 297-302 (2001)

12. ST Russell, PM Sanders, MJ Tisdale: Angiotensin II directly inhibits protein synthesis in murine myotubes. *Cancer Lett* 231, 290-294 (2006)

13. HL Eley, ST Russell, MJ Tisdale: Effect of branched-chain amino acids on muscle atrophy in cancer cachexia. Biochem J 407, 113-120 (2007)

14. MJ Tisdale: Clinical anticachexia treatments. *Nutr Clin Pract* 21, 168-174 (2006)

15. K Baar, G Nader, S Bodine: Resistance exercise, muscle loading/unloading and the control of muscle mass. *Essays Biochem* 42, 61-74 (2006)

16. L Combaret, OA Adegoke, N Bedard, V Baracos, D Attaix, SS Wing: USP19 is a ubiquitin-specific protease regulated in rat skeletal muscle during catabolic states. *Am J Physiol Endocrinol Metab* 288, E693-E700 (2005)

17. M Figueras, S Busquets, N Carbó, V Almendro, JM Argilés, FJ López-Soriano: Cancer cachexia results in an increase in TNF-alpha receptor gene expression in both skeletal muscle and adipose tissue. *Int J Oncol* 27, 855-860 (2005)

18. JM Argilés, R Moore-Carrasco, S Busquets, FJ López-Soriano: Catabolic mediators as targets for cancer cachexia. *Drug Discov Today* 8, 838-844 (2003)

19. I Dahlman, N Mejhert, K Linder, T Agustsson, DM Mutch, A Kulyte, B Isaksson, J Permert, N Petrovic, J Nedergaard, E Sjölin, D Brodin, K Clement, K Dahlman-Wright, M Rydén, P Arner: Adipose tissue pathways involved in weight loss of cancer cachexia. *Br J Cancer* 102, 1541-1548 (2010)

20. PT Todorov, TM McDevitt, DJ Meyer, H Ueyama, I Ohkubo, MJ Tisdale: Purification and characterisation of a tumor lipid mobilizing factor. *Cancer Res* 58, 2353-2358 (1998)

21. MP Thompson, ST Cooper, BR Parry, JA Tuckey: Increased expression of the mRNA for hormone-sensitive lipase in adipose tissue of cancer patients. *Biochim Byophys Acta* 1180, 236-242 (1993)

22. JP Simons, AM Schols, JM Hoefnagels, KR Westerterp, GP ten Velde, EF Wouters: Effects of medroxyprogesterone acetate on food intake, body composition, and resting energy expenditure in patients with advanced, nonhormone-sensitive cancer: a randomised, placebo-controlled trial. *Cancer* 82, 553-560 (1998)

23. EG Berenstein, Z Ortiz: Megestrol acetate for the treatemnet of anorexia-cachexia syndrome. *Cochrane Database Syst Rev* CD004310 (2005)

24. RA Femia, RE Goyette: The science of megestrol acetate delivery: potential to improve outcomes in cachexia. *BioDrugs* 19, 179-187 (2005)

25. JC Willox, J Corr, J Shaw, M Richardson, KC Calman, M Drennan: Prednisolone as an appetite stimulant in patients with cancer. *Br Med J (Clin Res Ed)* 288, 27 (1984)

26. A Dewey, C Baughan, T Dean, B Higgins, I Johnson: Eicosapentaenoic acid (EPA, an omega-3 fatty acid from fish oils) for the treatment of cancer cachexia. *Cochrane Database Syst Rev* CD004597 (2007)

27. B Wiedenmann, P Malfertheiner, H Friess, P Ritch, J Arseneau, G Mantovani, F Caprioni, E Van Cutsem, D Richel, M DeWitte, M Qi, D Jr Robinson, B Zhong, C De Boer, JD Lu, U Prabhakar, R Corringham, D Von Hoff. A multicenter, phase II study of infliximab plus gemcitabine in pancreatic cancer cachexia. *J Support Oncol* 6, 18-25 (2008)

28. A Jatoi, SR Alberts, N Foster, R Morton, P Burch, M Block, PL Nguyen, J Kugler ; North Central Cancer Treatment Group: Is bortezomib, a proteasome inhibitor, effective in treating cancer-associated weight loss? Preliminary results from the North Central Cancer Treatment Group. *Support care cancer* 13, 381-386 (2005)

29. JN Gordon, TM Trebble, RD Ellis, HD Duncan, T Johns, PM Goggin: Thalidomide in the treatment of cancer cachexia: a randomised placebo controlled trial. *Gut* 54, 540-545 (2005)

30. V Lai, J George, L Richey, HJ Kim, T Cannon, C Shores, M Couch: Results of a pilot study of the effects of celecoxib on cancer cachexia in patients with cancer of the head, neck, and gastrointestinal tract. *Head Neck* 30, 67-74 (2008)

31. F Strasser, TA Lutz, MT Maeder, B Thuerlimann, D Bueche, M Tschöp, K Kaufmann, B Holst, M Brändle, R von Moos, R Demmer, T Cerny: Safety, tolerability and pharmacokinetics of intravenous ghrelinofor cancer-related anorexia/cachexia: a randomized, placebo-controlled, double-blind, double-crossover study. *Br J Cancer* 98, 300-308 (2008)

32. NM Neary, CJ Small, AM Wren, JL Lee, MR Druce, C Palmieri, GS Frost, MA Ghatei, RC Coombes, SR Bloom: Ghrelin increases energy intake in cancer patients with impaired appetite: acute, randomized, placebo-controlled study. *J Clin Endocrinol Metab* 89, 2832-2836 (2004)

33. K Lundholm, U Körner, L Gunnebo, P Sixt-Ammilon, M Fouladiun, P Daneryd, I Bosaeus: Insulin treatment in cancer cachexia: effects on survival, metabolism, and physical functioning. *Clin Cancer Res* 13, 2699-2706 (2007)

34. K van Norren, D Kegler, JM Argilés, Y Luiking, M Gorselink, A Laviano, K Arts, J Faber, H Jansen, EM van der Beek, A van Helvoort: Dietary supplementation with a specific combination of high protein, leucine, and fish oil improves muscle function and daily activity in tumour-bearing cachectic mice. *Br J Cancer* 100, 713–722 (2009)

35. GJ Lesser, D Case, F Ottery, R McQuellon, JK Choksi, G Sanders, R Rosdhal, EG Shaw, Wake Forest University Community Clinical Oncology Program Research Base: ASCO Meeting. A phase III randomized study comparing the effects of oxandrolone (Ox) and megestrol acetate (Meg) on lean body mass (LBM), weight (wt) and quality of life (QOL) in patients with solid tumors and weight loss receiving chemotherapy. *Proc Am Soc Clin Onc* 26(15S), 505s (2008)

36. F Braiteh, S Dalal, A Khuwaja, H David, E Bruera, R Kurzrock: Phase I pilot study of the safety and tolerability of olanzapine (OZA) for the treatment of cachexia in patients with advanced cancer. *J Clin Oncol* 26, abstr # 20529 (2008)

37. Tisdale MJ: Are tumoral factors responsible for host tissue wasting in cancer cachexia? *Future Oncol* 6, 503-513 (2010)

38. Institute of Medicine: Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids (Macronutrients). *Washington, DC: National Academy Press* (2002)

39. CA Gogos, P Ginopoulos, B Salsa, E Apostolidou, NC Zoumbos, F Kalfarentzos: Dietary omega-3 polyinsaturated fatty acids plus vitamin E restore immunodeficiency and prolong survival for severely ill patients with generalized malignancy: a randomized control trial. *Cancer* 82, 395-402 (1998)

40. Hardman WE: (n-3) fatty acids and cancer therapy. *J Nutr* 134, 3427S-3430S (2004)

41. American Heart Association Nutrition Committee, AH Lichtenstein, LJ Appel, M Brands, M Carnethon, S Daniels, HA Franch, B Franklin, P Kris-Etherton, WS Harris, B Howard, N Karanja, M Lefevre, L Rudel, F Sacks, L Van Horn, M Winston, J Wylie-Rosett: Diet and lifestyle recommendations revision 2006: a scientific statement from the America Heart Association Nutrition Committee. *Circulation* 114, 82-96 (2006)

42. BC Tohill, J Seymour, M Serdula, L Kettel-Khan, BJ Rolls: What epidemiologic studies tell us about the relationship between fruit and vegetable consumption and body weight. *Nutr Rev* 62, 365-374 (2004)

43. Slavin J: Why whole grains are protective: biological mechanisms. *Proc Nutr Soc* 62, 129-134 (2003)

44. BR Cassileth, EJ Lusk, TB Strouse, BJ Bodenheimer: Contemporary unorthodox treatments in cancer medicine. A study of patients, treatments, and practitioners. *Ann Intern Med* 101, 105-112 (1984)

45. LB Seeff: Herbal hepatotoxicity. *Clin Liver Dis* 11, 577-596, vii (2007)

46. A Sparreboom, MC Cox, MR Acharya, WD Figg: Herbal remedies in the United States: potential adverse interactions with anticancer agents. *J Clin Oncol* 22, 2489-2503 (2004)

47. P Smith, JM Bullock, BM Booker, CE Haas, CS Berenson, WJ Jusko: The influence of St. John's wort on the pharmacokinetics and protein binding of imatinib mesylate. *Pharmacotherapy* 24, 1508-1514 (2004)

48. RH Mathijssen, J Verweij, P de Bruijn, WJ Loos, A Sparreboom: Effects of St. John's wort on irinotecan metabolism. *J Natl Cancer Inst* 94, 1247-1249 (2002)

49. BW Beckert, MJ Concannon, SL Henry, DS Smith, CL Puckett: The effect of herbal medicines on platelet function: an in vivo experiment and review of the literature. *Plast Reconstr Surg* 120, 2044-2050 (2007)

50. K Raus, C Brucker, C Gorkow, W Wuttke: First-time proof of endometrial safety of the special black cohosh extract (Actaea or Cimifuga racemosa extract) CR BNO 1055. *Menopause* 13, 678-691 (2006)

51. R Mahdavi, E Faramarzi, E Seyedrezazadeh, M Mohammad-Zadeh, M Pourmoghaddam: Evaluation of oxidative stress, antioxidant status and serum vitamine C levels in cancer patients. *Biol Trace Elem Res* 130, 1-6 (2009)

52. GJ Van den Berg, HT Wolterbeek, JJ De Goeij, AC Beynen: Absorption and retention studies of trace elements and minerals in rats using radiotracers and whole-body counting. *Lab Anim* 29, 66-77 (1995)

53. P Shekelle, ML Hardy, I Coulter, J Udani, M Spar, K Oda, LK Jungvig, W Tu, MJ Suttorp, D Valentine, L Ramirez, R Shanman, SJ Newberry: Effect of the supplemental use of antioxidant vitamin C, vitamin E and coenzyme Q10 for the prevention and treatment of cancer. *Evid Rep Technol Assess (Summ)* 75, 1-3 (2003)

54. I Bairati, F Meyer, E Jobin, M Gélinas, A Fortin, A Nabid, F Brochet, B Têtu: Antioxidant vitamins suplementation and mortality: a randomized trial in head and neck cancer patients. *Int J Cancer* 119, 2221-2224 (2006)

55. ML Lesperance, IA Olivotto, N Forde, Y Zhao, C Speers, H Foster, M Tsao, N MacPherson, A Hoffer: Mega-dose vitamins and minerals in the treatment of non-metastatic breast cancer: an historical color study. *Breast Cancer Res Treat* 76, 137-143 (2002)

56. AK Pathak, M Bhutani, R Guleria, S Bal, A Mohan, BK Mohanti, A Sharma, R Pathak, NK Bhardwaj, KN Prasad, V Kochupillai: Chemotherapy alone vs. chemotherapy plus high dose multiple antioxidants in patients with advanced non small cell lung cancer. *J Am Coll Nutr* 24, 16-21 (2005)

57. E Cameron, L Pauling. Supplemental ascorbate in the supportive treatment of cancer: reevaluation of prolongation of survival times in terminal human cancer. *Proc Natl Acad Sci USA* 75, 4538-4532 (1978)

58. CG Moertel, TR Fleming, ET Creagan, J Rubin, MJ O'Connell, MM Ames MM.: High-dose vitamin C versus placebo in treatment of patients with advanced cancer who have had no prior chemotherapy. A randomized double-blind comparison. *N Eng J Med* 312, 137-141 (1985)

59. ET Creagan, CG Moertel, JR O'Fallon, AJ Schutt, MJ O'Connell, J Rubin, S Frytak: Failure of high-dose vitamin C (ascorbic acid) therapy to benefit patients with advanced cancer. A controlled trial. *N Engl J Med* 301, 687-690 (1979)

60. S Ohwada, T Ogawa, F Makita, Y Tanahashi, T Ohya, N Tomizawa, Y Satoh, I Kobayashi, M Izumi, I Takeyoshi, K Hamada, S Minaguchi, Y Togo, T Toshihiko, T Koyama, M Kamio: Beneficial effects of protein-bound polysaccharide K plus tegafur/uracil in patients with stage II or III colorectal cancer: analysis of immunological parameters. *Oncol Rep* 15, 861-868 (2006)

61. S Ohwada, T Ikeya, T Yokomori, T Kusaba, T Roppongi, T Takahashi, S Nakamura, S Kakinuma, S Iwazaki, H Ishikawa, S Kawate, T Nakajima, Y Morishita: Adjuvant immunochemotherapy with oral Tegafur/Uracil plus PSK in patients with stage II or III colorectal cancer: a randomised controlled study. *Br J Cancer* 90, 1003-1010 (2004)

62. J Sakamoto, S Morita, K Oba, T Matsui, M Kobayashi, H Nakazato, Y Ohashi; Meta-Analysis Group of the Japanese Society for Cancer of the Colon Rectum: Efficacy of adjuvant immunochemotherapy with polysaccharide K for patients with curatively resected colorectal cancer: a meta-analysis of centrally randomised controlled clinical trials. *Cancer Immunol Imunother* 55, 404-411 (2006)

63. K Oba, S Teramukai, M Kobayashi, T Matsui, Y Kodera, J Sakamoto: Efficacy of adjuvant immunochemotherapy with polysaccharide K for patients with curative resections of gastric cancer. *Cancer Immunol Immunother* 56, 905-911 (2007)

64. WS Ahn, DJ Kim, GT Chae, JM Lee, SM Bae, JI Sin, YM Kim, SE Namkoong, IP Lee: Natural Killer activity and quality of life were improved by consumption of a mushroom extract, Agaricus blazei Murill Kyowa, in gynaecological cancer patients undergoing chemotherapy. *Int J Gynecol Cancer* 14, 589-594 (2004)

65. F Jakab, Y Shoenfeld, A Balogh, M Nichelatti, A Hoffmann, Z Kahán, K Lapis, A Mayer, P Sápy, F Szentpétery, A Telekes, L Thurzó, A Vágvölgyi, M Hidvégi: A medical nutriment has supportive value in the

treatment of colorectal cancer. *Br J Cancer* 89, 465-469 (2003)

66. LC Cerchietti, AH Navigante, MA Lutteral, MA Castro, R Kirchuk, M Bonomi, ME Cabalar, B Roth, G Negretti, B Sheinker, P Uchima: Double-blinded, placebo-controlled trial of intravenous L-alanyl-L-glutamine in the incidence of oral mucositis following chemoradiotherapy in patients with head and neck cancer. *Int J Radiat Oncol Biol Phys* 65, 1330-1337 (2006)

67. IT Rubio, Y Cao, LF Hutchins, KC Westbrook, VS Klimberg: Effect of glutamine on methotrexate efficacy and toxicity. *Ann Surg* 227, 772-778 (1998)

68. SH Okuno, CO Woodhouse, CL Loprinzi, JA Sloan, BI LaVasseur, D Clemens-Schutjer, D Swan, C Axvig, LP Ebbert, MR Tirona, JC Michalak, N Pierson: Phase III controlled evaluation of glutamine for decreasing stomatitis in patients receiving fluorouracil (5-FU)-based chemotherapy. *Am J Clin Oncol* 22, 258-261 (1999)

69. AA El-Housseiny, SM Saleh, AA El-Masry, AA Allam: The effectiveness of vitamin "E" in the treatment of oral mucositis in children receiving chemotherapy. *J Clin Pediatr Dent* 31, 167-170 (2007)

70. RG Wadleigh, RS Redman, ML Graham, SH Krasnow, A Anderson, MH Cohen: Vitamin E in the treatment of chemotherapy-induced mucositis. *Am J Med* 92, 481-484 (1992)

71. LC Lin, J Que, LK Lin, FC Lin: Zinc supplementation to improve mucositis and dermatitis in patients after radiotherapy for head and neck cancers: a double-blind randomized study. *Int J Radiat Oncol Biol Phys* 65, 745-750 (2006)

72. CK Su, V Mehta, L Ravikumar, R Shah, H Pinto, J Halpern, A Koong, D Goffinet, QT Le: Phase II double-blind randomized study comparing oral aloe vera versus placebo to prevent radiation-related mucositis in patients with head and neck neoplasms. *Int J Radiat Oncol Biol Phys* 60, 171-177 (2004)

73. W Carl, LS Emrich: Management of oral mucositis during local radiation and systemic chemotherapy: a study of 98 patients. *J Prosteth Dent* 66, 361-369 (1991)

74. M Oberbaum, I Yaniv, Y Ben-Gal, J Stein, N Ben-Zvi, LS Freedman, D Branski: A randomized, controller clinical trial of the homeopathic medication TRAUMEEL S in the treatment of chemotherapy-induced stomatitis in children undergoing stem cell transplantation. *Cancer* 92, 684-690 (2001)

75. MS Gujral, PM Patnaik, R Kaul, HK Parikh, C Conradt, CP Tamhankar, GV Daftary: Efficacy of hydrolytic enzymes in preventing radiation therapy-induced side effects in patients with head and neck cancers. *Cancer Chemother Pharmacol* 47, S23-28 (2001)

76. K Choi, SS Lee, SJ Oh, SY Lim, SY Lim, WK Jeon, TY Oh, JW Kim: The effect of oral glutamine on 5-fluorouracil/leucovorin induced mucositis/stomatitis assessed by intestinal permeability test. *Clin Nutr* 26, 57-62 (2007)

77. B Daniele, F Perrone, C Gallo, S Pignata, S De Martino, R De Vivo, E Barletta, R Tambaro, R Abbiati, L D'Agostino: Oral glutamine in the prevention of fluorouracil induced intestinal toxicity: a double blind, placebo controller, randomised trial. *Gut* 48, 28-33 (2001)

78. F Bozzetti, L Biganzoli, C Gavazzi, F Cappuzzo, C Carnaghi, R Buzzoni, M Dibartolomeo, E Baietta: Glutamine supplementation in cancer patients receiving chemotherapy: a double-blind randomized study. *Nutrition* 13, 748-751 (1997)

79. P Osterlund, T Ruotsalainen, R Korpela, M Saxelin, A Ollus, P Valta, M Kouri, I Elomaa, H Joensuu: Lactobacillus supplementation for diarrhoea related to chemotherapy of colorectal cancer: a randomised study. *Br J Cancer* 97, 1028-1034 (2007)

80. L Vahdat, K Papadopoulos, D Lange, S Leuin, E Kaufman, D Donovan, D Frederick, E Bagiella, A Tiersten, G Nichols, T Garrett, D Savage, K Antman, CS Hesdorffer, C Balmaceda: Reduction of paclitaxel-induced peripheral neuropathy with glutamine. *Clin Cancer Res* 7, 1192-1197 (2001)

81. WS Wang, JK Lin, TC Lin, WS Chen, JK Jiang, HS Wang, TJ Chiou, JH Liu, CC Yen, PM Chen: Oral glutamine is effective for preventing oxaliplatin-induced neuropathy in colorectal cancer patients. *Oncologist* 12, 312-319 (2007)

82. A Pace, A Savarese, M Picardo, V Maresca, U Pacetti, G Del Monte, A Biroccio, C Leonetti, B Jandolo, F Cognetti, L Bove: Neuroprotective effect of vitamin E supplementation in patients treated with cisplatin chemotherapy. *J Clin Oncol* 21, 927-931 (2003)

83. S Manusirivithaya, M Sripramote, S Tangjitgamol, C Sheanakul, S Leelahakorn, T Thavaramara, K Tangcharoenpanich: Antiemetic effect of ginger in gynaecologic oncology patients receiving cisplatin. *Int J Gynecol Cancer* 14, 1063-1069 (2004)

84. P Ljungman, M Bregni, M Brune, J Cornelissen, T de Witte, G Dini, H Einsele, HB Gaspar, A Gratwohl, J Passweg, C Peters, V Rocha, R Saccardi, H Schouten, A Sureda, A Tichelli, A Velardi, D Niederwieser; European Group for Blood and Marrow Transplantation: Allogenic and autologous transplantation for haematological diseases, solid tumors and immune disorders: current practise in Europe 2009. *Bone Marrow Transplant* 45, 219-234 (2010)

85. FJ Ordonez, GJ Jemenez, JA Delgado. Parenteral nutrition in hematologic patients treated with hematopoietic stem cell transplantation. *Nutr Hosp* 15, 114-120 (2000)

86. NM Blijlevens, JP Donelly, BE De Pauw. Mucosal barrier injury: biology, pathology, clinical counterparts and consequences of intensive treatment for haematological malignancy: an overview. *Bone Marrow Transplant* 25, 1269-1278 (2000)

87. FG Fernandez Ortega, FJ Ordonez Gonzalez, AL Blesa Malpica: Nutritional support in the critically ill patients: to whom, how, and when? *Nutr Hosp* 20, 9-12 (2005)

88. ME Gomez Alvarez: Parental nutrition in hematopoietic stem cell transplantation. *Farm Hosp* 28, 116-122 (2004)

89. AA Pegram, LD Kennedy: Prevention and treatment of veno-occlusive disease. *Ann Pharmacother* 35, 935-942 (2001)

90. B Raynard, G Nitenberg, G Gory-Delabaere, JH Bourhis, P Bachmann, RJ Bensadoun, JC Desport, D Kere, S Schneider, P Senesse, P Bordigoni, L Dieu; FNCLCC: Summary of the Standards, Options and Recommendations for nutritional support in patients undergoing bone marrow transplantation (2002). *Br J Cancer* 89, S101-S106 (2003)

91. WH Navarro, FR Jr Loberiza, R Bajorunaite, K van Besien, JM Vose, HM Lazarus, JD Rizzo: Effect of body mass index on mortality of patients with lymphoma undergoing autologous hematopoietic cell transplantation. *Biol Blood Marrow Transplant* 12, 541-551 (2006)

92. P Horsley, J Bauer, B Gallagher: Poor nutrition status prior to peripheral blood stem cell transplantation is associated with increased length of hospital stay. *Bone Marrow Transplant* 35, 1113-1116 (2005)

93. M Hadjibabaie, M Iravani, M Taghizadeh, A Ataie-Jafari, AR Shamshiri, SA Mousavi, K Alimoghaddam, S Hosseini, A Ghavamzadeh: Evaluation of nutritional status in patients undergoing hematopoietic SCT. *Bone Marrow Transplant* 42, 469-473 (2008)

94. PO Iversen, F Wisloff, N Gulbrandsen: Reduced nutritional status among multiple myeloma patients during treatment with high-dose chemotherapy and autologous stem cell support. *Clin Nutr* 29, 488-491 (2010)

95. The EBMT handbook 5th edition revised edition: haematopoietic stem cell transplantation (2008)

96. ML Forchielli, N Azzi, S Cadranel, G Paolucci: Total parental nutrition in bone marrow transplant: what appropriate energy level? *Oncology* 64, 7-13 (2003)

97. B Raynard, G Nitenberg, G Gory-Delabaere, JH Bourhis, P Bachmann, RJ Bensadoun, JC Desport, D Kere, S Schneider, P Senesse, P Bordigoni, L Dieu: Standards, options and recommendations for nutritional support in bone marrow transplant patients. *Bull Cancer* 89, 381-398 (2002)

98. FJ Jiménez Jiménez, C Ortiz Leyba, JL García Garmendia, J Garnacho Montero, JM Rodríguez Fernández, I Espigado Tocino: Prospective comparative study of different amino acid and lipid solutions in parental nutrition of patients undergoing bone marrow transplantation. *Nutr Hosp* 14, 57-66 (1999)

99. M Martin-Salces, R de Paz, MA Canales, A Mesejo, F Hernandez-Navarro: Nutritional recommendations in hematopoietic stem cell transplantation. *Nutrition* 24, 769-775 (2008)

100. DA August, MB Huhmann, and A.S.P.E.N. board of directors: A.S.P.E.N. clinical guidelines: nutrition support therapy during adult anticancer treatment and in hematopoietic cell transplantation. *J Parenter Enter Nutr* 33, 472-500 (2009)

101. TM Coghlin Dickson, RM Wong, RS Offrin, JA Shizuru, LJ Johnston, WW Hu, KG Blume, KE Stockerl-Goldstein: Effect of oral glutamine supplementation during bone marrow transplantation. *J Parenter Enter Nutr* 24, 61-66 (2000)

102. DW Wilmore, PR Schloerb, TR Ziegler: Glutamine in the support of patients following bone marrow transplantation. *Curr Opin Clin Nutr Metab Care* 2, 323-327 (1999)

103. G Mercadal Orfila, JM Llop Talaverón, B Gracia García, C Martorell Puigserver, MB Badía Tahull, M Tubau Molas, R Jodar Masanes: Glutamine use for parental nutrition in the critically ill patient: effects on morbidity/mortality. *Nutr Hosp* 22, 61-67 (2007)

104. C Gómez Candela, R Castillo, AI de Cos, C Iglesias, MC Martín, MJ Aguado, E Ojeda: Effects of parental glutamine in patients submitted to bone marrow transplantation. *Nutr Hosp* 21, 13-21 (2006)

105. L Alonso Pérez, A Fernández Vázquez, MA Valero Zanuy, P Gomis Muñoz, M León Sanz, A Herreros de Tejada: Parenteral nutrition supplemented with glutamine in patients undergoing bone marrow transplantation. *Nutr Hosp* 25, 49-52 (2010)

106. A Hunnisett, S Davies, J McLaren-Howard, P Gravett, M Finn, D Gueret-Wardle: Lipoperoxides as index of free radical activity in bone marrow transplant recipients. *Biol Trace Elem Res* 47, 125-132 (1995)

107. RI Salganik, CD Albright, J Rodgers, J Kim, SH Zeisel, MS Sivashinskiy, TA Van Dyke: Dietary antioxidants depletion: enhancement of tumor apoptosis and inhibition of brain tumor growth in transgenic mice. *Carcinogenesis* 21, 909-914 (2000)

108. S Fuji, SW Kim, S Mori, T Fukuda, S Kamiya, S Yamasaki, Y Morita-Hoshi, F Ohara-Waki, O Honda, S Kuwahara, R Tanosaki, Y Heike, K Tobinai, Y Takaue: Hyperglycemia during neutropenic period is associated with a poor outcome in patients undergoing myeloablative allogeneic hematopoietic stem cell transplantation. *Transplantation* 84, 814-820 (2007)

109. M Lough, R Watkins, M Campbell, K Carr, A Burnett, A Shenkin: Parenteral nutrition in bone marrow transplantation. *Clin Nutr* 9, 97-101 (1990)

110. PO Mulder, JG Bouman, JA Gietema, H Van Rijsbergen, NH Mulder, S Van der Geest, EG De Vries: Hyperalimentation in autologous bone marrow transplantation for solid tumors. Comparison of total parental versus partial parental plus enteral nutrition. *Cancer* 64, 2045-2052 (1989)

111. PM Sheean, C Braunschweig, E Rich: The incidence of hyperglycemia in hematopoietic stem cell transplant recipients receiving total parental nutrition: a pilot study. *J Am Diet Assoc* 104, 1352-1360 (2004)

112. PM Sheean, SA Freels, WS Helton, CA Braunschweig: Adverse clinical cosequences of hyperglycemia from total parental nutrition exposure during hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant* 12, 656-664 (2006)

113. D Seguy, C Berthon, JB Micol, S Darré, JH Dalle, S Neuville, F Bauters, JP Jouet, I Yakoub-Agha: Enteral feeding and early outcomes of patients undergoing allogenic stem cell transplantation following myeloablative conditioning. *Transplantation* 82, 835-839 (2006)

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