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Nutritional Interventions for Cancer-induced Cachexia

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Abstract

Cancer-induced cachexia remains a significant cause of morbidity and mortality in cancer treatment. Cancer research and development continues at an aggressive pace and yet a degree of cancer-induced cachexia is experienced by up to 80% of advanced stage cancer patients. Unfortunately, there are no established treatment regimens for this condition. Weight loss and fatigue consistently appear in patient oncologic histories and progress notes. However, few oncologists fully understand the pathologic mechanisms causing cachexia resulting in well-meaning advice to increase caloric intake with minimal results. Our goal is to describe the pathologic basis of cancer-induced cachexia and to detail accompanying metabolic derangements. Understanding the causes of cachexia sheds light on the subsequent need for multi-modality therapy including clinical intervention with specialized nutrition support, drug therapy, lifestyle and diet changes. In addition to nutrition support modalities, practicing oncologists may prescribe medical therapies designed to increase body weight and lean body mass, including megestrol acetate, tetrahydrocannibinol, oxandrolone, and non-steroidal anti-inflammatory drugs. A variety of experimental therapies are also being investigated for cancer-induced cachexia including tumor necrosis factor-alpha inhibitors and ghrelin infusions. We review the available data to support nutrition-oriented interventions in cancer-induced cachexia, including omega-3 fatty acids, amino-acid loading/protein supplementation, parenteral and enteral nutrition support, and food-derived compounds such as curcumin, reservatrol, and pomegranate.

Introduction

Cancer-induced cachexia (CIC) is experienced by up to 80% of patients with advanced stage cancer, particularly those with gastrointestinal, pancreatic, thoracic and head and neck malignancies.[i] CIC has been implicated in up to 20% of cancer-related deaths.[ii,iii] The definition of cachexia appears to be well-defined among the scientific community, however the term is liberally employed in clinical oncology practice. The 2006 Cachexia Consensus Conference, established cachexia as “a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass”.[iv] Many oncologists confuse cancer-induced cachexia with simple starvation, or physiologic processes such as sarcopenia (age-related loss of muscle mass).[v,vi] The clinical confusion regarding cachexia is understandable as most oncologists rely heavily on the patient's weight as an indicator of the degree of cachexia experienced. Both cachexia and starvation result in weight loss, however cachexia results from an altered metabolic state due to tumor-derived factors, loss of anabolic stimuli, and an increase in catabolic processes. Unlike starvation, where metabolism slows to conserve body mass, current data suggests that CIC cannot be

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reversed by feeding alone. The clinical picture is further compounded by muscle loss, a physiologic process as one ages, which may result in sarcopenia. The treating physician may see an elderly, frail, sarcopenic patient experiencing a degree of starvation due to the side effects of cancer therapy who is also cachectic secondary to presence of the tumor (Table 1).

Weight loss negatively affects a patient's ability to tolerate chemotherapy and radiation and ultimately can impact survival as well as quality of life during treatment.[vii,viii] As weight loss approaches 30% of baseline pre-treatment weight, death becomes imminent and is typically due to erosion of the diaphragm muscle resulting in pneumonia.[ix] In spite of this, accepted therapy for CIC does not exist, leading to a feeling of helplessness by both the patient and treating oncologist as weight continues to drop with each office visit. Therapeutic options for CIC are limited. While there are multiple medical therapies currently under investigation in both academic centers and in the private marketplace (celecoxib, tumor necrosis factor-alpha (TNF- α) inhibitors, interluekin antagonists, and omega-3 fatty acids), most oncologists would agree that more data is needed before prescribing these agents.

Pathogenesis of Cancer-induced Cachexia

Current scientific research implicates an inflammatory reaction to tumor that is predominantly local, but may also be systemic, as the basis for CIC. On a molecular level, proinflammatory cytokines including interleukins (IL) 1,2 and 6, interferon γ and TNF-α have been implicated in initiating a cascade of protein interactions that ultimately result in anorexia and catabolic processes such as muscle proteolysis and lipolysis.[x] Reduced muscle protein synthesis also occurs via activation of nuclear factor kappa-B (NF-κB), as well as TNF-α and interferon γ.[xi,xii] NF-κB signaling has been shown to contribute to CIC in animal models and a recent study compared 14 patients with gastric cancer to a control group and found that NF-κB subunit was elevated by 25% in the gastric cancer group and that NF-κB inhibition was depressed.[xiii] This process is termed an acute phase response (APR) which in includes a cascade of activity detailed in the diagram below (Figure 1).

Tumor cells initiate the production of pro-inflammatory cytokines: including multiple interleukins (varies by cancer type), interferon γ, and TNF –α and subsequently NF-κB.[xiv] These proteins initiate breakdown of both adipose and muscle tissue resulting in the clinical muscle wasting and fat loss seen with end stage cancer patients.[xv]

The presence of pro-inflammatory cytokines has been confirmed in multiple animal studies using TNF alpha, IL-1, IL-6 to induce cachexia in animal models, and attenuating cachexia using anti-TNF alpha or anti-IL-1 antibodies.[xvi] Additionally, transgenic IL-6 mice develop muscle atrophy that is reversed by anti-IL-6 receptor antibodies.[xvii] Human studies have confirmed the presence of these circulating cytokines. One study examined 87 patients with non-small cell lung (NSCL) cancer, 26 had lost more than 10% of their total body weight. The patients with weight loss had a greater inflammatory response, measured as a C-reactive protein (CRP) > 10 mg/L, with increased plasma concentrations of TNF receptor 55, IL-6, and CRP.[xviii] One retrospective study of 98 male patients examined the role of elevated CRP in conjunction with testosterone levels. Hypogonadism is associated with decreased muscle mass and survival. Their results showed an inverse correlation between testosterone and CRP levels. Survival of patients with testosterone levels < or = 185 ng/dL was decreased compared with that of those with levels >185 ng/dL. Patients with CRP levels >10mg/L had decreased survival compared with those with levels < or = 10mg/L.[xix]

The APR has also been shown to correlate with survival in pancreatic cancer patients. In one study, 102 patients with unresectable pancreatic cancer participated in a multivariate analysis using the serum concentrations of CRP, albumin, weight loss, age, sex, and disease

stage. Results showed that patient age, disease stage, serum albumin, and serum CRP were independent predictors of survival. The presence of an APR was the most significant independent predictor of survival. The median survival of those with an APR (CRP > 10 mg/L, n = 45) was 66 days compared with 222 days for those with no APR (n = 57). The metabolic disturbances associated with an APR are considered potential therapeutic targets.[xx]

Catabolism of muscle mass in CIC is considered the most detrimental aspect of the syndrome. Research has attributed the cause of muscle proteolysis in CIC to the ubiquitin – proteasome pathway [xxi] and to dysregulation of the dystrophin glycoprotein complex. Initiated by NF-κB, ubiquitin molecules attach to a muscle protein marking it for degradation in the large tube-like proteosome.[xxii] The proteosome produces amino acids which travel to the liver and support hepatic synthesis of acute phase proteins such as C-reactive protein, fibrinogen, and serum amyloid peptide. Baracos et al. observed that the ubiquitin–proteasome pathway is responsible for >80% of lean tissue wasting from cancer using a hepatoma-implanted animal model.[xxiii] Recently, two genes encoding ubiquitin-protein ligases have been identified and have been shown to increase during muscle proteolysis in murine models. These ligases are muscle atrophy F box (MAF bx)/atrogin-1 and muscle RING finger 1 (MURF1). Mice lacking either ligase were found to be resistant to muscle breakdown suggesting that the ubiquitin-proteasome pathway is a potential target for cancer-induced cachexia.[xxiv]

The dystrophin glycoprotein complex (DGC) is a collection of proteins that anchors muscle sarcomeres and protects them during muscle contraction. The deregulation of DGC has been shown to correlate positively with weight loss in patients with gastro-esophageal adenocarcinoma.[xxv] The specific mechanism by which DGC acts to induce muscle proteolysis has not been identified in animal studies at this time. More recently Zhou et al. have identified a potential target for CIC: the activin type-2 receptor (ActRIIB). ActRIIB is a transmembrane protein complex that is activated by ligands myostatin and activin A. The subsequent signal cascade results in increased expression of ubiquitin ligases MuRF1 and atrogin-1. These ubiquitin ligases stimulate degradation of myosin by the ubiquitin-proteasome system, resulting in muscle wasting seen in CIC. The breakdown of skeletal and cardiac muscle was both attenuated and reversed in animal models by blocking ActRIIB with a decoy receptor.[xxvi]

The loss of lean body mass that accompanies cancer-induced cachexia is often blamed for functional impairment and reduced quality of life. A 2007 study examined the non-exercise physical activity level (e.g. walking) of cachectic patients undergoing chemotherapy. The patients' median estimated total energy expenditure was 8% lower, median time spent upright was approximately two hours per day less, and median steps taken per day was 43% lower than that of the control group.[xxvii] These data illustrate the cycle of inactivity that initially begins with anorexia and fatigue and ultimately results in loss of muscle mass, decreased physical activity, and poor performance which directly impact a cancer patient's survival.[xxviii]

Multi-modality therapy

Understanding the pathogenesis of CIC is critical for identifying therapeutic targets. Modulation of the APR will require clinical intervention that includes both drug and diet therapy as well as lifestyle modification. We outline an approach to multi-modality therapy below and focus on medical and nutritional interventions currently under investigation.

Clinical intervention: Assessment

We have previously outlined a clinic-based approach to CIC to assist the practicing oncologist with management.[xxix] Our approach includes preliminary evaluation of the patient for starvation which can be reversed with feeding vs. cachexia which cannot. A summary of our recommendations follows:

1. Is the patient starving?—As mentioned, serum albumin and prealbumin concentrations are affected by many other conditions and neither should be used solely to determine nutritional state, nor treatment efficacy (Table 2). Albumin can however, provide a general idea of disease severity as it is affected by inflammation, the APR, and elevated CRP.[xxx,xxxi]

2. Is the patient cachectic?—Fearon et al. have proposed a working definition of CIC supported by the latest research that employs three factors: weight loss >= 10%, low caloric intake <= 1500 kcal/day and systemic inflammation as measured by a C-reactive protein >= 10 mg/L.[xxxii] Weight loss alone is an inadequate prognostic indicator. Clinical tools to assess cachexia may include:

- **a.** Serum C-reactive protein (CRP)
- **b.** Office scale to measure weight
- **c.** Isometric dynamometers to assess hand-grip strength which has been shown to predict all-cause mortality in elderly populations.[xxxiii]

Therapy

Initial treatment includes reversing the metabolic effects of starvation, which are treatable, with increased caloric intake. Oncologists are familiar with commercially available liquid or solid complete nutrient supplements as well as lifestyle modifications that include smaller, more frequent meals and encouraging hydration throughout the day. Increasing intake of fat and protein must also be encouraged, as amino acid intake is necessary to support muscle synthesis and many patients mistakenly continue on low-fat diets as part of disease prevention strategies. Unfortunately, there is no current standard-of-care for treatment of cancer-induced cachexia.

Nutrition Support

Oncologic providers often encourage nutrition support during cancer treatment and while logical, it is important to understand that significant increases in caloric intake, and use of enteral nutrition and parenteral nutrition, are not always beneficial. Often caretakers and patients themselves hold the perception that increased caloric intake will help the patient “fight the cancer”. In reality, the scientific data behind nutrition support in cancer care remains conflicting, in part due to an overall lack of rigorous randomized controlled clinical trials.

Ensuring sufficient caloric intake during cancer therapy is often accomplished by using temporary placement of nasogastric (NG) tubes or more permanent percutaneous endoscopic gastrostomy (PEG) tubes. In severe cases, when oral or gastrointestinal intake is not possible, parenteral nutrition is often administered. In earlier trials, in which parenteral nutrition caloric doses were considered excessive and hyperglycemia was common, parenteral nutrition was not associated with measureable clinical benefits and, in some studies, increased infectious complications.[xxxiv] Nutrition support either via parenteral route alone or given via the gastrointestinal tract as oral supplements or tube feedings, was shown to increase fat mass but did not impact patient survival in cancer – induced cachexia.[xxxv]

The timing of nutrition support during cancer therapy is also controversial, in part, due to lack of rigorous trials addressing this issue. Many surgical oncologists routinely use enteral nutrition support prior to gastric and pancreatic cancer surgery and studies show that this may reduce infections and hospital stays when compared to post-operative supplementation alone, particularly in patients with preexisting malnutrition.[xxxvi,xxxvii] One randomized trial examined the effects of at least ten days pre-operative total parenteral nutrition vs. enteral nutrition on postoperative complications and mortality. This study also employed a nutritionally- depleted control group as well as a non-depleted reference group. Depleted control patients suffered significantly more septic complications than did patients in the non-depleted reference group. No difference was noted in septic complications between either of the nutritional support groups and the non-depleted control group. In high risk patients, with weight loss >10% of body weight and over 500 ml blood loss during operation, a significant decrease in major complications was observed as a result of nutritional support.[xxxviii] Hyltander et al. examined the effects of enteral and parenteral feeding as compared to standard oral intake on the post-operative recovery of esophageal, stomach, and pancreatic cancer patients who had experienced preoperative weight loss. The patients who were randomized to oral intake served as controls. Consistent with prior studies, overall survival and length of hospital stay did not differ among the groups. Also consistent with prior studies, complication rates were higher among patients receiving artificial nutrition support modalities. Body weight and whole body fat declined similarly over time in all groups, whereas lean body mass was unchanged during follow-up as compared to preoperative values. Parenteral nutrition was associated with the highest rate of nutrition-related complications, whereas enteral feeding reduced quality of life.[xxxix] There are data to support early placement of PEG tubes for patients undergoing concurrent chemo-radiation in aerodigestive tract cancer[xl] and in many institutions prophylactic PEG tube placement is standard of care. However even these institutions report increases in infection and pain with greater than 10% of patients requiring PEG tube replacement.[xli] Nutrition support, given before and during chemotherapy has not been shown to reduce chemo-related toxicity, nor has it increased patient survival.[xlii,xliii,xliv,xlv] Efforts to arrive at formal nutrition support recommendations are confounded by several factors including a broad variety of nutrition indices, timing, patient populations and the nutrient composition of supplement products.

A recent comprehensive review by August et al. of the American Society for Parenteral and Enteral Nutrition (A.S.P.E.N) effectively summarizes the current data on nutrition support and makes recommendations for adult cancer patients.[47] A.S.P.E.N does not recommend nutritional support for routine use in patients undergoing major cancer operations. The authors reviewed randomized controlled studies examining the use of parenteral nutrition (PN) as compared to a standard oral diet as well as enteral nutrition (EN). They note that a majority of studies show no or minimal difference in morbidity and mortality post-operatively when comparing PN to EN or oral diet. This report concludes that pre-operative nutrition support may reduce morbidity and mortality in moderate to severely malnourished patients but notes that this must be evaluated against the known metabolic, mechanical and infectious risks of specialized nutritional support and delaying a cancer operation.[47] A.S.P.E.N. also does not recommend administration of nutrition support routinely during chemotherapy nor during head and neck, abdominal or pelvic radiation therapy.[xlvi] Studies have shown that nutrition support during chemotherapy does not reduce toxicity nor improve patient survival and often cause increased rates of infection in immunocompromised patients.[xlvii,xlviii,xlix] Similar results have been obtained in studies examining the role of nutrition support with patients receiving radiation therapy. One retrospective review of head and neck cancer patients receiving EN before or during radiation therapy identified several predictive factors indicating the need for nutrition support which included stage 3-4 disease, performance status of 2-3, and smoking greater

than 20 cigarettes a day. The authors concluded that a combination of three factors predicted a 75% chance of needing EN.[l]

Rabinovitch et al. provided a secondary analysis of data from the Radiation Therapy Oncology Group (RTOG) 90-03, a prospective randomized trial of that evaluated four definitive radiation fractionation schedules in 1073 patients with locally advanced head and neck cancer. RTOG 90-03 prospectively collected data on nutrition support given before treatment, during treatment, and after treatment. Nutrition support included oral supplements, enteral nutrition via feeding tube, the combination of oral and enteral feedings, as well as parental nutrition. The patients receiving nutrition support before treatment experienced significantly less weight loss and less grade 3 to 4 mucositis than patients not receiving pre-treatment nutrition support. However, patients receiving nutrition support prior to treatment had a poorer 5-year locoregional control rate than patients in the other two groups and a poorer 5-year overall survival. Patients receiving pre-treatment nutrition support typically had larger tumors at diagnosis and worse performance status. However, when controlling for these differences at baseline, pre-treatment nutrition support remained an independent prognostic factor for increased locoregional failure and death.[li] The results of RTOG 90-03 are consistent with other studies showing that while nutrition support can stabilize weight and reduce the side effects of cancer therapy, nutrition support may decrease the effectiveness of therapy at the same time. [lii,liii,liv]

A.S.P.E.N. does not recommend routine specialized PN or EN for cancer patients, however they do recommend nutrition support for “patients receiving active anticancer treatment who are malnourished and who are anticipated to be unable to ingest and/or absorb adequate nutrients for a prolonged period of time”.[47] Their guidelines suggest that, once instituted, at least seven to fourteen days of specialized nutrition support be administered, noting that there are no comparative effectiveness studies that directly evaluate this recommendation. They also note that nutrition support is rarely indicated in palliative cases.[47]

Drug therapy

The clinical efficacy of medical therapy for CIC has been the subject of considerable research during the past several decades, beginning in the 1990's with an increase in AIDS – related wasting. Research originally focused on reversing starvation with the use of appetite stimulants such as megestrol acetate and tetrahydrocannabinol, which while effective had questionable impact on quality of life and no impact on survival. As AIDS and advanced cancer are catabolic states, studies have examined the role of specific growth factors as well as anabolic steroids, and these data are reviewed below. When the role of inflammation in cancer and the APR was discovered, attempts to attenuate neoplastic inflammation lead to work with non-steroidal anti-inflammatory drugs (NSAIDS) and TNF-α inhibitors. Research continues to progress with ghrelin and ghrelin agonists, and the identification of new targets such as the ubiquitin-proteasome pathway in hopes of maintaining lean body mass and preserving nutritional status in cancer patients.

Megestrol Acetate

Megace®, or megestrol acetate (MA), is a synthetic derivative of progesterone, and the most widely used drug used to treat CIC.[lv] The precise mechanism of action of MA is unknown but research in murine models suggests that its effect may be partially mediated by neuropeptide Y, a potent centrally acting appetite stimulant.[lvi] A number of human studies show that various doses of MA stimulate appetite and increase weight gain; however more detailed body composition studies suggest that the weight gain is largely an increase in fat mass, while performance status and QOL are generally not affected.[lvii, lviii]

A 2005 Cochrane Database Review of 30 trials with over 4000 patients evaluated the efficacy, effectiveness, and safety of megestrol acetate in CIC. The review showed a benefit of megestrol acetate with regard to appetite improvement and weight gain in cancer patients, but no statistically significant conclusion about QOL changes could be drawn due to heterogeneity.[31] There was insufficient information to define the optimal dose of megestrol acetate although therapeutic doses typically ranged from 100mg to 1600mg per day, with efficacy shown between 400-800mg daily.[lix] A 2008 review by Lésniak et al. noted that the cancer patient study population experiences high mortality and progressive weight loss regardless of treatment. There was no difference between MA and placebo on survival. MA increases appetite (number needed to treat (NNT): 3) and leads to weight gain (NNT: 8).[lx]

The side effects of megestrol acetate include an increased risk of thromboembolism at doses exceeding 800mg per day, hypogonadism, transient adrenal insufficiency, and edema.[lxi,lxii] Given that MA increases fat mass and edema with no improvement in quality of life or survival, use of this agent has started to be abandoned in favor of catabolic therapies aimed at increasing or maintaining muscle mass.

Tetrahydrocannabinol (THC)

Tetrahydrocannabinol (THC) is the main psychoactive substance found in the *Cannabis sativa* plant. Synthetic THC is known as dronabinol and is available as a prescription medication as Marinol® which is prescribed for intractable cancer pain. The starting dose is 2.5 mg orally twice daily with titration up to 20 mg per day. THC has been found to influence the endocannibinoid system, a group of neuromodulatory lipids and their receptors, that are involved in pain perception, emesis and reward pathways.[lxiii,lxiv] Studies have shown that THC can stimulate appetite and promote food intake in healthy volunteers [lxv,lxvi] and patients with AIDS.[lxvii] A number of studies have been conducted to evaluate the effects of THC in patients with CIC. A phase III study involving 243 patients with advanced cancer experiencing cancer-related anorexia-cachexia were randomly assigned (2:2:1) to receive cannabis extract (standardized for 2.5 mg THC and 1 mg cannabidiol) or THC (2.5 mg) or placebo orally, twice daily for 6 weeks. Appetite, mood, and quality of life (QOL) were monitored and cannabinoid-related toxicity was assessed. An independent review board recommended that the trial be closed after interim analysis of 156 patients due to insufficient differences in the primary end point: change in appetite from week 0 to week 6 assessed with the visual analog scale. Subsequent intent-to-treat analysis showed no statistically significant differences between the three arms for appetite, cannabinoid-related toxicity or QOL.[lxviii]

A North Central cancer treatment group trial examined 499 patients with advanced cancer and self-reported appetite and weight loss were randomized to receive (1) oral megestrol acetate 800 mg/day liquid suspension plus placebo, (2) oral dronabinol 2.5 mg twice a day plus placebo, or (3) both agents. Megestrol acetate provided superior anorexia palliation and weight gain among advanced cancer patients compared with dronabinol alone. Combination therapy did not appear to confer additional benefit. However, even at low doses (5 mg daily), dronabinol alone improved appetite in almost 50% of patients. Toxicity was comparable between groups.[lxix]

Growth Hormone and Anabolic Steroids

With the understanding that MA increased fat mass with no improvement in performance status or survival, research focused on maintaining the cachectic patient's lean body mass in efforts to improve performance status and quality of life. Anabolic factors such as growth hormone (GH) and steroid hormones were investigated. GH has been shown consistently to stimulate muscle protein synthesis in catabolic states and historically was prescribed to

AIDS and chronic obstructive pulmonary disease (COPD) patients suffering from cachexia.[lxx,lxxi] Prior animal studies had shown that the GH–IGF-1 system plays a role in the development and progression of cancer and there has been hesitation among oncologists to use GH for treatment of CIC owing to concern that GH may stimulate tumor growth.[lxxii] It is important to note that this hypothesis has not been proven in either animal or human studies. The rationale behind this theory is based on historical data when a hypophysectomy (along with oopehorectomy and adrenaletomy) were part of a complete endocrine ablative therapy for breast cancer. The hypothesis also develops from epidemiologic data showing that healthy persons with increased height (> 175cm) and rapid growth during adolescence were at higher risk for breast, prostate and colon cancer.[lxxiii, lxxiv]

Testosterone and its derivatives are steroid hormones that exert their effect through binding to cytosolic receptors, leading to an increase in protein synthesis and muscle mass.[lxxv] Testosterone also inhibits the macrophage mediated release of pro-inflammatory cytokines like TNF α, IL- 1β and IL-6 [lxxvi,lxxvii] and stimulates the release of IL-10, an anti-inflammatory cytokine.[lxxviii] Studies have shown positive effects of these anabolic agents on body weight, lean body mass and functional parameters in cachectic patients. However, most studies have been largely limited to patients with COPD and HIV-AIDS.[lxxix,lxxx] In these trials testosterone was prescribed as either testosterone cipionate or testosterone enanthate and administered intramuscularly or dermally to treat hypogonadal men. No trials have been conducted to date investigating the use of testosterone in patients with CIC. The side effects of testosterone limit its use.

Oxandrolone, a modified testosterone derivative, has been used as an oral anabolic agent for both men and women with weight loss associated with surgery, infection and other catabolic conditions including cancer.[lxxxi] Oxandrolone is 95% protein bound and relatively resistant to liver biotransformation resulting in high plasma concentrations and less risk of liver toxicity. Oxandrolone was used in the bodybuilding community for years and has a marked anabolic effected with minimal androgenic effects.[lxxxii] Oxandrolone will not aromatize, so there is no increase in estrogen levels, removing the risk of gynecomastia in men and other hyper-estrogenic concerns. In addition, oxandrolone binds fewer androgen receptors, so there typically is no virilization. Women appear to tolerate oxandrolone well, and it historically has been used in the treatment of osteoporosis. More importantly, at low doses (10 mg), it does not appear to suppress gonadotropin-releasing hormone.[lxxxiii]

A recent phase III trial conducted in 155 adult patients with solid tumors and weight loss demonstrated that patients treated with oxandrolone (10mg twice daily) experienced an increase in lean body mass, a reduction in fat mass and anorectic symptoms when compared to patients receiving megestrol acetate (800mg daily).[lxxxiv] An 2003 study by Tchekmedyian et al. with 131 cancer patients who received 20 mg oxandrolone daily for four months. Eighty percent of the cancer patients gained an average of four pounds of lean body mass. In addition, Eastern Cooperative Oncology Group (ECOG) scores improved from an average of close to 2 (unable to perform work) to nearly 1 (able to perform light work), showing the impact of increased lean body mass when compared to appetite stimulants.

Oxandrolone provides an FDA-approved therapeutic option for increasing LBM in cachectic patients, assuming there are no contraindications to use. Oxandrolone can interact with other medications, such as oral anticoagulants, oral hypoglycemic agents, and adrenal steroids.[lxxxv] Side effects of oxandrolone in clinical trials have included elevated transaminase levels and decreased high-density lipoprotein levels which appear to resolve when administration is stopped.[lxxxvi] Oral hypoglycemics, anti-coagulants, as well as adrenal steroids may require dose modification when administered with

oxandrolone.[lxxxvii,lxxxviii] All anabolic steroids are Schedule III controlled substances, which may impact an oncologist's decision to prescribe oxandrolone.

NSAIDS and TNF-alpha

NSAIDs have been shown to reduce the APR as well as resting energy expenditure and preserve body fat in patients with advanced cancer. Lundholm et al. evaluated the effect of anti-inflammatory treatment on tumor progression in 135 patients with solid tumors. Patients were randomized to receive placebo, prednisolone (10 mg twice daily), or indomethacin (50 mg twice daily) until death. Indomethacin prolonged mean survival compared to placebo-treated patients. Survival analysis on all patients treated with either indomethacin or prednisolone demonstrated a significantly prolonged survival by anti-inflammatory treatment compared to placebo. Indomethicin prolonged survival when compared to the placebo group from 250 +/- 28 days to 510 +/- 28 days.[lxxxix] Lai et al. conducted a phase II clinical pilot trial investigating the effect of a 21-day course of Celebrex® (celecoxib) on body composition, inflammation, and quality of life (QOL) in 11 patients with cancer cachexia. Body composition, resting energy expenditure, QOL, physical function, and inflammatory markers were measured on days 1 and 21. Patients receiving the celecoxib had significant increases in weight and body mass index (BMI), and increases in QOL scores. The investigators noted that compliance was good with no adverse events.[xc]

Mantovi et al. also initiated a prospective phase II clinical trial to test the effectiveness of celecoxib (300mg/day) for four months in 24 patients with advanced cancer. Endpoints included lean body mass, resting energy expenditure, and serum cytokine levels. There was a significant increase of lean body mass and decrease of TNF-alpha levels. In addition, the patients showed an improvement in grip strength, quality of life, and performance status. No grade 3 or 4 toxicities were reported.[xci] COX-2 inhibition is currently one of the more promising areas of CIC research as this medical therapy directly targets the inflammatory APR of CIC and has shown to be well-tolerated with minimal side-effects.

TNF-alpha Inhibotors: Infliximab, Etanercept, Adalimumab

Anti-TNF-alpha therapies are currently employed for inflammatory conditions such as rheumatoid and psoriatic arthritis and Crohn's disease. As TNF-alpha has become increasingly implicated in the pathogenesis of CIC, thus, interest in evaluating these drugs as a possible therapy has evolved. Saraceno et al. used a population of patients under treatment for psoriatic arthritis to evaluate the effect of anti-TNF-alpha therapy on body mass index (BMI). The investigators examined the effect of either infliximab, etanercept, or adalimumab (experimental group) against a control group of patients on efalizumab or methotrexate which both are traditionally used for psoriatic arthritis treatment. The patients were treated for 48 weeks. At week 24 a significant increase in body weight and BMI in the anti-TNF-alpha treatment group compared to the control was observed.[xcii]

In another trial using rheumatoid arthritis patients, etanercept was evaluated for its effect on body composition. Twenty-six patients were randomly assigned to 24 weeks of treatment with etanercept or methotrexate (considered first-line therapy for rheumatoid arthritis). Body composition, physical function, disease activity, systemic inflammation, and the circulating insulin-like growth factor (IGF) system were measured at baseline (week 0) and at follow-up (weeks 12 and 24). Overall, no important changes in body composition were observed. Secondary analysis of six patients who gained weight during follow-up showed that patients receiving etanercept had an increase in fat-free mass. The investigators concluded that etanercept was not superior to methotrexate for the treatment of rheumatoid cachexia. But did note that TNF blockade seems to normalize the anabolic response to overfeeding and could be useful in treating anorexia and weight loss.[xciii]

There are several trials evaluating the addition of infliximab to chemotherapy regiments in patients with advanced cancer. Wiedenmann et al. lead a multicenter, randomized, placebo-controlled study of 89 cachectic patients with stage II-IV pancreatic cancer to receive either placebo or 3 - 5 mg/kg of infliximab at weeks 0, 2, and 4 and then every 4 weeks until week 24. Patients also received concurrent gemcitabine weekly from weeks 0-6 and then for 3 of every 4 weeks until disease progression. The primary endpoint was change in lean body mass at 8 weeks from baseline. The mean change in lean body mass at 8 weeks was +0.4 kg for patients receiving placebo, +0.3 kg for those receiving 3 mg/kg of infliximab, and +1.7 kg for those receiving 5 mg/kg of infliximab. The investigators concluded that adding infliximab to gemcitabine to treat cachexia in pancreatic cancer patients was not associated with statistically significant differences in safety or efficacy when compared with placebo.[xciv]

More recently, Jatoi et al. conducted a double-blind trial randomly assigned 61 patients to infliximab/docetaxel versus placebo/docetaxel. The primary endpoint was greater or equal to 10% weight gain. No patient gained or exceeded an increase of 10% baseline weight, and the lack of efficacy prompted early trial closure. Appetite improvement was negligible in both arms. However, infliximab/docetaxel-treated patients developed greater fatigue and worse global quality of life scores. Tumor response rate and overall survival, were not statistically different between groups. Genotyping for the TNF alpha -238 and -308 polymorphisms revealed no clinical significance of these genotypes, as relevant to the loss of weight or appetite.[xcv]

Ghrelin and ghrelin agonists

Ghrelin is a peptide hormone secreted by the stomach and pancreas in response to fasting. Ghrelin binds to the growth hormone receptor in the hypothalamus to stimulate the release of growth hormone from the anterior pituitary. Ghrelin also increases hypothalamic expression of the orexigenic neuropeptides such as neuropeptide Y.[xcvi] Studies have shown that cachectic cancer patients can have higher levels of ghrelin compared to cancer and non-cancer controls, why these levels remain insufficient to significantly increase appetite to arrest weight loss is unknown.[xcvii] Higher ghrelin levels have also been correlated with cancer severity stages.[xcviii]

Stasser et al. first attempted ghrelin administration to cachectic cancer patients. 21 patient were randomized to receive either 2 μg/kg or 8 μg/kg of human ghrelin as a 60-min infusion on two study days, seven days apart. A third study group was randomized to receive placebo on two study days, seven days apart. Ad libitum food intake tended to improve during ghrelin administration but this was not statistically significant. Nutritional intake did not differ between patients receiving ghrelin or placebo. No grade 3 or 4 toxicity or stimulation of tumor growth was observed. The peak increase of growth hormone, a biological marker of ghrelin action, was 25 ng/ml with lower-dose and 42 ng/ml with higher-dose ghrelin.[xcix]

Neary et al. administered a single dose of synthetic human ghrelin (5 pmol/kg/min × 90 min) versus placebo to 7 cancer patients with impaired appetite in a randomized crossover design study. A significant mean increase (+31%) in the consumption of calories from an ad libitum buffet meal offered immediately after ghrelin infusion was documented. No adverse effects of ghrelin were observed.[c]

Limited data is available on the effects of ghrelin receptor agonists. A phase I pilot study conducted by Garcia et al. examined an orally available ghrelin mimetic (RC-1291) at various doses daily and twice daily in healthy volunteers.[ci] Results showed that the agonist produced a dose-related increase in body weight without dose-limiting adverse effects. These authors also conducted a pilot double-blind trial in cachectic cancer patients and

administered oral RC-1291 (50 mg/day) over a twelve-week period. Results showed a significant 1.3% increase in lean body mass compared to placebo that RC-1291 was well tolerated.[cii]

DeBoer and colleagues implanted rats with sarcomas and then administered both ghrelin and a synthetic ghrelin agonist. The effect of ghrelin and synthetic ghrelin on food intake and body composition was measured. The rat hypothalami and brainstems were also harvested to assess the effect of ghrelin administration on appetite and inflammatory gene expression. They concluded that both ghrelin and the synthetic ghrelin receptor agonist increased weight and maintained lean body mass via effects on orexigenic neuropeptides and attenuation of inflammation. As ghrelin exhibits orexigenic effects due to its role as a potent growth hormone secretagogue, there remains concern about growth hormone-mediated stimulation of tumor growth in cancer patients. As previously mentioned, this concern has never been supported in the medical literature. The authors of this study noted that they observed no unexpected tumor growth in the rat models, but the study design had short intervals of tumor measurement.[ciii]

Nutrition and cancer

Dietary patterns are an important contributor to cancer pathogenesis and so logically are a consideration for cancer treatment as well as treatment of side effects. The current scientific literature supports a combination of genetics, environment, and diet as causes of cancer and dietary habits established over a period of years can directly modulate DNA – either as a direct mutagen or via a cascade of extracellular signaling.[29] Both in-vivo and in-vitro data support nutritional interventional for cancer treatment and side-effects, however numerous studies have failed to show success with single-nutrient intervention or the “more is better” approach typically taken by researchers. A classic example is the Selenium and Vitamin E Cancer Prevention Trial (SELECT) of 35,000 men with an average risk for prostate cancer. The SELECT researchers hypothesized that supplementation with daily selenium or daily vitamin E used alone or in combination, could reduce the incidence of prostate cancer. Neither selenium, vitamin E, nor the combination prevented prostate cancer after 5.5 years of follow up, with no effect on the risk of lung or colorectal cancer, nor overall cancer incidence. [civ] These studies exemplify the complexity in nutritional intervention for cancer which requires a multi-modality approach that unlike drug therapy, will likely depend on nutritional changes over an extended period of time.

In the following discussion of nutrition and cancer, not only is the length of time of nutritional intervention important, but we must also discuss the general problems inherent in nutrition research with human subjects. First and foremost, most nutrition research is retrospective due to the difficulty in prospectively administering a diet to a group of patients. Retrospective review often relies on subjective patient reporting which calls into question the exact amount and type of many nutrients consumed. Nutrition data is also affected by recall bias and the “Hawthorne effect” as many patients often try to list foods considered “healthy” on their questionnaires or food journals and minimize intake of foods considered “unhealthy.[cv] In addition, experimental attrition is significant in any study with end stage cancer patients due to the morbidity and mortality associated with cancer and cancer treatment. High attrition is an obvious problem for enrollment, but also when analyzing the efficacy of a drug or nutritional therapy. Further, the randomized controlled trial design used as the “gold standard” for efficacy in drug intervention trials is not appropriate for nutritional intervention studies. Consensus on efficacy by researchers is often limited when considering the multi-factorial nature of an end-stage cancer patient's death process and the underlying metabolic derangements that make up cancer-induced cachexia.

As previously discussed, weight has historically been used to define CIC, specifically involuntary weight loss greater than 10% of baseline body weight as reported by the patient.[cvi] National Cancer Institute (NCI) Common Toxicity Criteria have been used by clinical researchers to assess CIC. Grade 1 is defined as 5% loss from baseline body weight, Grade 2 is a 10% weight loss and 20% weight loss for Grade 3, with Grade 4 defined as life-threatening.[cvii] These criteria focus on only weight loss and do not quantify the acute phase response and inflammation, nor assess fatigue, weakness, or the loss of muscle mass, which are the more detrimental aspects of CIC.[cviii] Studies on cachectic patients have used indirect measures of skeletal muscle such as prediction of total lean body mass from total body water, [cix] skin folds,[cx] and bioelectrical impedance [cxi,cxii] none of which distinguish skeletal muscle from other lean soft tissue. In general, short supplementation periods have failed to show efficacy in patients who are in advanced stages of cancer when it is unlikely that any type of intervention would be of benefit.

Nutrition Intervention for CIC

Any nutrition intervention must first involve assessment of the patient's current dietary habits, either with informal conversation or with the 3-day food journal mentioned previously. Data regarding the success of dietary counseling in cancer patients experiencing CIC has been conflicting in the past, though has recently become a more common intervention in medical and radiation oncology practices. French oncology guidelines require systematic screening for malnutrition since 2007 and recommendations include oral supplementation as well as “immune-enhancing diets”.[cxiii] Hopkinson et al. discuss the need for nutritional assessment to identify erroneous dietary beliefs held by the patient and caregiver. The authors emphasize that:

- a “healthy diet” as currently defined in our culture (i.e. low fat, high fiber, five portions of fruit and vegetables daily) has no proven benefit for someone with advanced cancer
- patients will typically eat more of the things they enjoy or find easiest to eat
- cold foods, soft foods and fluids can provide the same nutrients as cooked meals
- cancer causes metabolic change that suppresses appetite, these changes are out of the patient's control and should not serve as an indication of not trying to eat, emotional weakness or giving up
- and disagreements over food are common between patients and caregivers. [cxiv]

At this time, there is no agreed upon successful nutritional intervention for cancer-induced cachexia. Promising in-vitro and in-vivo data will be subsequently outlined, however need to be considered as part of a multi-modality approach.

Omega-3 Fatty Acids

The omega-3 fatty acids eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) are found in fish oil and are known for their ability to reduce inflammation in the human body. Omega-3 fatty acids as a nutritional intervention for cancer remains an area of intense interest particularly as it relates to the potential to improve response to cytotoxic treatments and reduce associated side effects, particularly muscle wasting. EPA and DHA are well recognized for anti-inflammatory properties[cxv,cxvi] and these actions, together with EPA's ability to block ubiquitin-proteosome induced muscle proteolysis, probably account for EPA's favorable effect on wasting syndromes. Omega-3 fatty acids are found in the phospholipid (PL) membrane of cells. Fatty acid composition of plasma PL and different cell types (erythrocytes, neutrophils) reflect short and long term patterns of dietary fatty acid consumption, and are frequently used as indices of fatty acid status.[cxvii] Studies have shown

that patients with advanced cancer have low amounts (<30% of normal values) of fatty acids in their plasma phospholipids.[cxviii] The potential impact of an essential fatty acid deficit is exemplified by data showing that survival is reduced by about half (approximately 8 months shorter) in cancer patients who have EPA below the range observed in an age matched healthy control group.[cxix] There is evidence to suggest improvement in muscle health when essential fatty acid supply is maintained. As discussed, sarcopenia is highly prevalent in the cancer population and affects patients in all body mass index (BMI) ranges (from underweight to overweight to obese). Sarcopenic individuals exhibit low concentrations of EPA and DHA in plasma.[111] Given that n-3 fatty acids are deficient in cancer patients experiencing weight and muscle loss, supplementing n-3 fatty acids may provide a benefit. A.S.P.E.N. also encourages supplementation with n-3 fatty acids of 2g daily to help stabilize weight.[47]

In-vitro data has consistently demonstrated the ability of omega-3 fatty acids to modulate the APR in cachectic murine models. Several human studies have been conducted using fish oil (EPA+DHA), or EPA alone either as part of an oral nutritional supplement or in purified form in an attempt to reduce weight and/or muscle loss in patients with advanced cancers. Studies using patients in advanced cancer stages report that supplementation with > 2g per day of EPA stabilizes weight loss,[110] attenuates lean tissue wasting,[cxx] and increases survival in patients with advanced cancer.[cxxi,cxxii] Significant improvements in weight, lean body mass, function, and to a lesser extent, appetite, have been reported[93,cxxiii,cxxiv,cxxv,cxxvi,cxxvii] Conversely, three large phase III trials have failed to demonstrate a clear benefit of EPA on body weight or lean tissue in cancer patients [125,128,cxxviii] There are several reasons for discordance including the time at which intervention is initiated, contamination between treatment arms, and indirect assessments of muscle mass. Moreover, patients with advanced cancer are often unable to complete the study and unable to consume the therapeutic dose of omega-3 fatty acids due to anorexia as well as dysguesia and dysphagia from chemotherapy and radiation. In general, short supplementation periods have failed to show efficacy in patients who are in advanced stages of decline when it is unlikely that any type of intervention would be of benefit. These limitations have prevented meaningful interpretation of the data in previous studies. The studies in this area have been reviewed [cxxix, cxxx] and overall, fish oil is safe in high doses and remains a consideration as part of multi-nutritional approaches to treatment of cachexia.

The trials reviewed above did not enroll patients receiving chemotherapy or radiation, however the majority of cancer patients undergo some form of drug treatment, thus it seems important to address omega-3 fatty acid consumption as it might metabolically support patients during these treatments. Several experimental studies have reported an association between dietary fish oil and attenuation of side effects associated with anti-neoplastic therapies and enhanced cytotoxicity of drugs to tumor cells. There is emerging evidence from human studies suggest that n-3 fatty acids have a benefit for patients with advanced cancers undergoing chemotherapy.[cxxxi,cxxxii,cxxxiii] Low levels of essential fatty acids (both n-6 and n-3) in plasma and cell PL are evident in patients undergoing chemotherapy[cxxxiv] and patients with low EPA prior to receiving chemotherapy (i.e. at diagnosis) experienced more toxicities, treatment delays and dose reductions compared to patients with EPA within the reference range of age matched healthy adults.[cxxxv]

Low concentrations of EPA and DHA are independently and strongly related to the presence of sarcopenia and loss of muscle over treatment.[cxxxvi,cxxxvii] For example, patients with the lowest n-3 fatty acids in plasma PL experience muscle loss whereas those with the highest n-3 fatty acids gain muscle over the course of chemotherapy. This is important because evidence suggests that sarcopenic patients experience greater toxicity to a range of chemotherapy drugs that those with normal muscle mass. In studies where n-3

supplementation began at diagnosis, and CT images were used to precisely quantify muscle and fat mass in patients receiving the same type of chemotherapy for advanced cancer, a significant benefit to muscle mass was reported.[138] There is also data to support an enhanced toxicity to the tumor with n-3 supplementation. In one study, a third of patients (n= 45) undergoing standard of care treatment and not taking the n-3 fatty acid supplement, did not respond to first line chemotherapy and stopped treatment due to disease progression (Murphy, 2011 in press). Conversely, only 1 of 20 patients receiving n-3 supplementation did not respond to first line chemotherapy. Several potentially synergistic and diverse mechanisms have been proposed and reviewed.[cxxxviii,cxxxix] Overall, the beneficial effects observed with n-3 supplementation are likely due at least in part, to the n-3 supplement improving muscle health, the response of the tumor to chemotherapy and reducing toxicities. Approaches that increase tumor sensitivity to chemotherapy while not affecting non-malignant tissue would potentially improve prognosis and clinical outcomes of advanced cancer patients.

Amino Acid Loading

Even small changes in protein synthesis or protein degradation lead to large protein deficits because the rate of protein turnover for humans is high (240–310 g/day).[21] As previously outlined, there are currently no standardized means of minimizing the loss of skeletal muscle in CIC beyond aggressive treatment of the underlying illness and the experimental therapies described within. The loss of skeletal muscle in CIC is often coupled with patient fatigue/weakness from chemotherapy or radiation. Disuse of a muscle for even two weeks can result in reduction of its size by 20%. [cxl]

Logically, maintenance of skeletal muscle would require available amino acids as protein synthesis is stimulated only in the presence of available precursors, such as branched chain amino acids, leucine, and the appropriate hormonal milieu.[cxli] Many patients have been encouraged to increase their protein intake above the recommended daily allowance (RDA) of 0.8g/Kg/day for adults older than 19.[cxlii] Commercially available liquid supplements such as Boost® and Ensure® also offer high protein options. In-vivo data has supported the use of amino acid loading in an effort to support muscle synthesis by ensuring a constant supply of amino-acid precursors however in-vivo data has been conflicting. A phase III trial with over 400 advanced stage cancer patients with up to 10% weight loss randomized patients to receive an amino acid compound containing beta-hydroxl beta-methyl butyrate, glutamine, and arginine (HMB/Arg/Gin) or placebo (RTOG 0122). The amino acid mixture was taken twice daily for eight weeks and lean body mass was measured using bioimpedence and skin-fold measurements. 37% of enrolled patients completed the protocol with attrition due to patient preference. Using an intention to treat analysis, there was no significant difference in the 8-week lean body mass between the two arms. [cxliii]

Another parenteral branched amino acid product, Aminoleban®, has been used for patients with protein malnutrition resulting from liver cirrhosis. Meng et al. completed a prospective randomized controlled trial with fifty patients with hepatocellular carcinoma and a history of cirrhosis. After hepatic resection, patients were randomized to receive Aminoleban®, or an isonitrogenous, isocaloric placebo. There was no difference in morbidity or mortality in the post-operative period, however the study group did have improved liver function with higher albumin and lower bilirubin levels.[cxliv] One study evaluated the impact of dietary supplementation with a combination of high protein, leucine, and fish oil in tumor-bearing cachectic mice. The mice were divided into weight-matched groups: 1) control, 2) mice with adenocarcinoma, 3) mice with adenocarcinoma receiving the combination supplement. Mice with adenocarcinoma showed reduced muscle and fat mass as expected. Mice with adenocarcinoma receiving the combination supplement showed significantly reduced muscle and fat loss and improved muscle performance. In addition, 24-hour activity was assessed

and the experimental mice had increased performance.[cxlv] While data remains conflicting in humans, many oncologic nutritionists and practitioners continue to recommend increased protein intake for patients experiencing CIC based on the strong in-vitro data and known muscle synthesis processes.

Micronutrients

As noted above, current data regarding nutrition support for CIC is conflicting, however targeted nutritional intake with dietary components is a consideration. Multiple epidemiological and animal model studies show that consumption of fruit and vegetables decreases the occurrence of variety of cancers.[cxlvi,cxlvii,cxlviii,cxlix,cl] As previously mentioned however, the benefit of fruit and vegetable consumption, as well as various micronutrients, appears to be the result of lifelong dietary habits as opposed to increase in consumption during a short period of time. The specific anti-cancer effects of the micronutrients in fruits and vegetables continue to be research targets and are popular with the general media and public. While the best treatment for CIC remains treatment of the underlying cancer, a review of nutritional therapies does warrant a word on micronutrients. Use of micronutrients and ensuring good nutritional intake in CIC is also attractive when considering the cost of other interventions. Dietary consumption of foods and herbal medicines is a convenient method of administering phytochemicals in a cost effective manner with minimal side-effects. [cli]

Curcumin

Investigations into curcumin for CIC have been conflicting in mice. Researchers induced progressive muscle wasting in mice by implanting the MAC16 colon tumor and subsequent findings indicated that low doses of curcumin c3 (100 mg/kg body weight) was able to prevent weight loss and higher doses of curcumin c3 (250 mg/kg body weight) resulted in approximately 25 % weight gain when compared with the placebo-treated animals.[clii] A 2001 study was negative, with systemic administration of curcumin [1,7-bis(4-hydroxy-3-methoxyphenil)1,6-heptadiene-3,5-dione] (20 microg/kg body weight) for 6 consecutive days to rats bearing the highly cachectic Yoshida AH-130 ascites hepatoma. The curcumin inhibited tumor growth (31% of total cell number) but showed no improvement on muscle bulk. Both the weight and protein content of the gastrocnemius muscle in these mice significantly decreased as a result of tumor growth and curcumin was unable to reverse this tendency. The authors concluded that curcumin has little potential as an anticachectic drug in the Yoshida AH-130 ascites hepatoma tumor model.[cliii]

Resveratrol

Resveratrol (trans-3, 4′, 5-trihydroxystilbene) is a naturally occurring polyphenol found in the skin of red grapes and other fruits. Resveratrol has been explored by cardiovascular researchers due to its anti-inflammatory properties and ability to inhibit platelet aggregation. Resveratrol has also shown have anti-cancer effects in-vitro and data regarding CIC is conflicting. The most notable cancer research has shown that dermal application of resveratrol on mice, after UVB exposure, inhibited skin damage and decreased skin hyperplasia. [cliv] Additional in-vivo data on reservatrol supports anti-tumor affects in breast, prostate, esophageal and colon cancer.[clv] Resveratrol also inhibits various tumor promotion proteins, including cyclooxygenase (COX) -2. [clvi] Its anti-inflammatory properties make it an attractive therapy for CIC. Recently, Olivan et al. examined the anti-muscle wasting effects of multiple nutraceuticals such as genistein, resveratrol, epigallocatechin gallate and diallyl sulphide (DAS) in muscle cell cultures submitted to hyperthermia. All the nutraceuticals tested inhibited muscle proteolysis, including reservatrol.[clvii]

Laboratory studies in mice have shown that resveratrol partially blocks skeletal muscle wasting by interfering with NF-κB activation in murine muscle models. Resveratrol also modulates the activity and of the ubiquitin-proteasome pathway [clviii] and significantly attenuates the weight loss and protein degradation observed in skeletal muscle of mice bearing the cachexia-inducing MAC16 tumor, adding to the data already discussed supporting inhibition of the nuclear translocation of NF-κB may prove useful for the treatment of muscle wasting in cancer cachexia. [clix]

Busquets et al. investigated the anti- muscle wasting properties of resveratrol on different animal models of cancer cachexia. Incubations of isolated extensor digitorum longus muscles in the presence of resveratrol caused a significant decrease in the rate of protein muscle degradation. However, administration of resveratrol in vivo to both rats bearing the Yoshida AH-130 ascites hepatoma and mice bearing the Lewis lung carcinoma had no effect on skeletal muscle mass or body weight. The researchers combined resveratrol and fish oil for administration, and reported that this combination was also unable to increase skeletal muscle weight.[clx]

Pomegranate

The pomegranate (Punica granatum L.) is a fruit grown throughout the Mediterranean, Southeast Asia, and in the United States where it is found predominantly in California and Arizona. Pomegranate has been explored by multiple medical specialties including cardiology, infectious disease, and urology for a variety of conditions. Data has shown that there are multiple constituents of the pomegranate of medical interest and it appears that their synergetic affect is superior to that of a single agent. The promegranate's actions are as an antioxidant, anticarcinogenic, and anti-inflammatory. Cold pressed pomegranate seed oil has been shown to inhibit both cyclooxygenase and lipoxygenase enzymes in vitro.[clxi] As previously discussed, COX-2 expression is increased in cachexia due to TNF-alpha's activation of NFκB.

Pomegranate research in oncology has primarily focused on chemoprevention, however a component of the seed, punic acid, may act similar to an omega-3 fatty acid contributing to an anti-inflammatory effect.[clxii] Adams et al. examined the effect of pomegranate in various forms on HT-29 colon cancer cells. Treatment of HT-29 colon cancer cells with pomegranate juice, total pomegranate tannins, or concentrated pomegranate punicalagin induced a significant decrease in COX-2 expression. Pomengranate juice resulted in the highest level of COX-2 suppression (79%) compared to treatment with single constituents. The effects are attributed to synergistic activity of the various pomegranate components necessary for anti-inflammatory and anti-carcinogenic activity.[clxiii]

Conclusions

It is well established in the medical literature that restoring nutritional status has beneficial effects on patient outcome after surgery and during chemotherapy and radiation. Despite this knowledge, no specific nutritional intervention has been defined for patients with advanced cancer who are undergoing treatment. Current serial assessment modalities of nutritional status lack the necessary sensitivity and specificity, making it difficult to identify patients at risk as well as those who may benefit from nutritional intervention. We have reviewed the pathogenesis of CIC as it is currently understood to explain why standard treatments such as megestrol acetate and other appetite stimulants have such poor efficacy. Intervention for CIC should be multi-modality and should consider drugs targeted at the underlying inflammatory process (such as NSAIDS) or anabolic therapy (oxandrolone) along with nutritional assessment and dietary and nutrient supplement recommendations. Possible macronutrient changes such as increased protein may be considered as well as

supplementation with omega-3 fatty acids and other micronutrients described. There is a need to optimize nutritional state and encourage repair of tissues not only during cancer surgery or procedures, but throughout the course of cancer therapy to decrease morbidity and increase quality of life. Proper identification and management of chemotherapy and radiation side effects, promotion of nutritional status, and prevention of muscle loss would be expected to reduce the considerable morbidity associated with CIC.

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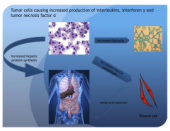

FIG 1. Please Supply Wording

Table 1

Starvation	Cachexia	Sarcopenia
May or may not occur due to disease or underlying pathology	Result of pathological process (e.g. neoplasm, heart failure, renal failure, etc).	May or may not occur due to disease or underlying pathology
Hypometabolic state	Hypo-, normo-, or hyper-metabolic state	Physiologic process that occurs with age, typically slowed metabolism within normal limits
Conservation of muscle mass, increased lipolysis	Characterized by both muscle proteolysis and lipolysis, as well as decreased muscle synthesis	Loss of muscle mass
Reversed by caloric intake	Not reversed with caloric intake	Variable, process can be delayed, but not avoided, with resistance exercise and amino-acid loading

Table 2

Identify treatment side effects and treat	Pain, nausea, dry mouth, ageusia, hyposmia and trismus
Obtain a 3-day food and activity journal	**Macronutrient intake:** Is the patient consuming sufficient calories? While caloric intake varies by body composition and activity, a quick reference for intake should be a minimum of 1700 calories for males and 1300 calories for females to support the basal metabolic rate.[i]
	Physical activity: Is the patient able to perform activities of daily living (ADL) and instrumental activities of daily living (IADL)?
Laboratory Tests	It must be noted that both albumin and pre-albumin are dependent on liver function and hydration status, however when evaluating a cancer patient's nutritional status they can provide a general idea of caloric intake.
	Serum albumin: half life of 14 to 20 days, less than 2.2 g/dL generally reflects severe malnutrition.
	Prealbumin(transthyretin): half-life of 24 to 48 hrs, <18 mg/dL reflects decreased caloric intake.

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