2nd International Conference on Cancer Nutrition Therapy

Edinburgh Scotland
March 29-30, 2011

PROCEEDINGS BOOKLET

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2nd International Conference on Cancer Nutrition Therapy

The 2nd International Conference on Cancer Nutrition Therapy was held on March 29-30, 2011, at the historic 17th century Royal College of Physicians in Edinburgh, Scotland. This 2nd International Conference was held to build upon discussions from the 1st Conference convened last year in Istanbul, Turkey, where 170 attendees from 10 countries heard 12 key opinion leaders discuss cancer nutrition and how to bridge the gap between science and clinical practice in nutritional oncology. Additionally, Abbott Nutrition partnered with the Biochemical Society to support investigators and their research with an abstract submission program. This year, the conference was again chaired by **Kenneth C.H. Fearon, MD, FRCS (GLAS), FRCS (ED), FRCS (ENG)**, Professor of Surgical Oncology, University of Edinburgh, Scotland, and included 21 speakers and moderators from 14 countries with experience in surgical, radiation, and medical oncology, pediatric oncology, gastroenterology, and nutrition. One hundred sixty-five health care professionals including oncologists, surgeons, internists, palliative care specialists, hematologists, basic scientists, and dietitians from 27 countries attended this year's conference.

CONFERENCE VISION

The vision for this year's conference was to bring together professionals from multi-disciplinary fields involving nutrition and cancer in order to facilitate scientific exchanges and debates on bridging the gap between science and clinical practice in nutrition in cancer.

A Festschrift was held at the conference to honor **Michael J. Tisdale, PhD, DSc**, Aston University, Birmingham, United Kingdom, for his important contributions to the field of cancer cachexia and nutritional science.

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1. The biochemistry of cancer cachexia: What is there left to discover?

Professor Michael J. Tisdale, PhD, DSc, Aston Pharmacy School, School of Life and Health Sciences, Aston University, United Kingdom

LOSS OF FAT IN CANCER CACHEXIA

Cancer cachexia involves loss of both muscle and fat. Cachectic patients can lose up to 85% of their body fat[1] and most rapid loss of adipose tissue occurs within 3 months of death. This loss primarily involves increased lipolysis and response to lipolytic stimuli with no change in basal or insulin-stimulated lipogenesis. Expression of hormone sensitive lipase (HSL) is increased in both mRNA and protein. Beta-adrenergic receptor (β-AR) antagonists (atenolol and propranolol) possibly are involved in the process by reducing resting energy expenditure (REE), whole body oxygen uptake and CO_2 production.

Norton *et al* (1985)[2] showed that parabolic transfer of cachexia is mediated by a humoral factor. Multiple mediators play roles in cancer cachexia. One of these is tumor necrosis factor-α (TNF-α). It is well known that TNF-α can induce systemic lipolysis in humans mediated through TNF-R1 pathway and is involved in the stimulation of extracellular signal-regulated kinase (ERK) 1 and 2, mitogen activated protein kinase (MAPK), cJun N-terminal kinase and cAMP-dependent protein kinase (PKA). TNF-α also inhibits glucose transport, decreases lipogenesis, and increases lipid utilization through increased uncoupling protein-2 (UCP2) and UCP3 in skeletal muscle. Findings are not consistent regarding the TNF-α level in circulation.

Interleukin-6 (IL-6) is also extensively examined in cancer cachexia. IL-6 is associated with a moderate increase in lipolysis in human adipocytes.[3] Elevated serum IL-6 was observed in patients with head and neck cancer.[4] However, it is unclear whether circulating IL-6 correlates with severity of cachexia. Both TNF-α and IL-6 inhibit expression of lipoprotein lipase (LPL) in white adipose tissue (WAT), but no change in LPL in WAT of cachectic subjects.[5]

Zinc-α2-glycoprotein (ZAG), formerly known as lipid mobilizing factor (LMF), is secreted by adipose tissue, liver and cachexia-inducing tumors. It stimulates lipolysis directly through the interaction with a β-AR (most probably β3) and stimulates adenylate cyclase in a GTP-dependent process, leading to increased cAMP and activation of PKA and HSL. ZAG increases expression of both HSL and adipose

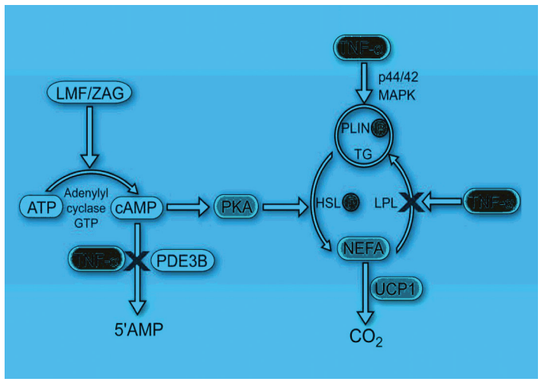


Figure 1: Mechanism of TNF-α and ZAG

triglyceride lipase (ATGL) in WAT and increases sensitivity to lipolytic stimuli. It is known that both ZAG and β3-agonists increase ZAG expression through interaction with a β3-AR. Marked increase in ZAG mRNA and protein in WAT is observed in patients with cancer cachexia, accompanied with a decrease in obesity. Thus, adipose-derived ZAG is inversely associated with body fat mass, which was demonstrated in *in vivo* and *in vitro* studies. For example, serum ZAG protein was increased in pancreatic cancer patients with cachexia.[6] When culturing murine epididymal adipocytes with extracts of MAC16 tumor, the free fatty acid (FFA) release increases over time. Glycerol release also increases with the ZAG concentration.

Loss of Fat – What is there left to discover?

1. *Is one or a combination of these factors involved in fat loss in human cachexia?*
2. *Can we attenuate fat loss in humans by interfering with the action of these factors?*
3. *Even if we could control fat loss would it benefit the patients' quality of life, or overall survival?*
4. *Are there more factors waiting to be discovered?*
5. *What role does anorexia play in loss of fat?*

LOSS OF MUSCLE IN CANCER CACHEXIA

Cachectic patients can experience a 75% loss in muscle mass, which is confined to skeletal muscle, while visceral protein is preserved.[7] The loss of myofibrillar protein is due to both a depression in protein synthesis and an increase in protein degradation through the ubiquitin-proteasome proteolytic pathway (illustrated in Figure 2).[8] In gastrocnemius muscle of weight losing mice bearing the MAC-16 tumor, phosphorylation of protein kinase R (PKR) and eIF2a increased with weight loss. A similar increase is observed in skeletal muscle of cancer patients.

Similar to its role in the loss of fat during cachexia, TNF-α is also involved in muscle atrophy. Animal studies show that acute administration with TNF-α enhances protein degradation and decreases protein synthesis[9] and deficiency in TNF receptor protein 1 is associated with reduced wasting of skeletal muscle.[10] In addition, TNF-α induces muscle loss through oxidative stress,

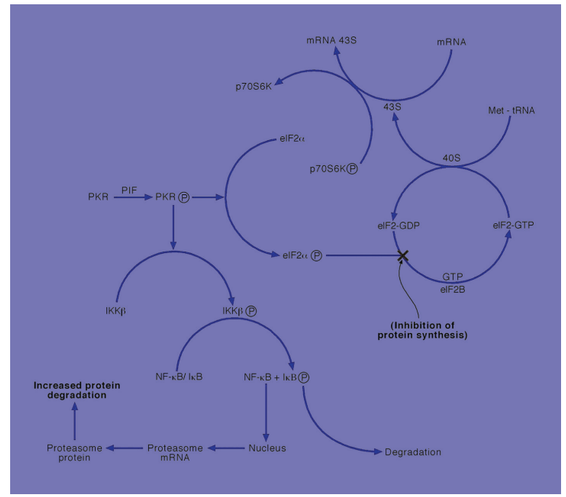


Figure 2: Muscle protein synthesis and degradation in cachexia

increases expression of ubiquitin and atrogin-1/MAFbx in skeletal muscle and inhibits myogenesis in vitro through NF-κB.[11, 12] However, clinical studies targeting the TNF-α pathway showed no effect on appetite or body weight/lean body mass in patients with cancer cachexia.

Muscle atrophy may also be associated with increased IL-6 as examined in transgenic mice. However, this association requires further investigation.

Activin type 2 receptor (ActRIIB) is recently reported to be closely associated with muscle wasting. It mediates signaling pathway of myostatin, activin, GDFII. Myostatin over expression leads to systemic muscle wasting in adult mice. Pharmacological blockade of ActRIIB pathway in several cancer cachexia models not only prevents further muscle wasting, but also completely reverses prior loss of skeletal muscle and cardiac atrophy.[13]

Proteolysis-inducing factor (PIF) is a tumor-produced sulphated glycoprotein. It induces loss of muscle mass specifically without an effect on adipose tissue mass.[14] PIF reduces muscle protein synthesis by increasing phosphorylation of eIF2α[15] and increases protein degradation through the ubiquitin-proteasome pathway and PKR-mediated NF-κB activation.[16] In addition, PIF also increases hepatic production of proinflammatory cytokines. In patients with non small cell lung cancer (NSCLC), PIF expression was positively correlated with weight loss and negatively associated with survival.[17] Further investigation of PIF and cancer cachexia is needed.

Loss of Muscle – What is there left to discover?

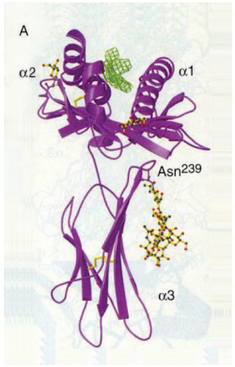
1. *Which of the factors (PIF, TNF, IL-6) are involved in muscle wasting in human cachexia?*
2. *Are any one of these factors alone or a combination required for activity?*
3. *Can better assays be developed for the measurement of PIF?*
4. *Are there more factors remaining to be discovered?*
5. *Should therapy be aimed at one or more of these factors and should it be combined with nutritional therapy?*

CONCLUSION

Tissue loss in cancer cachexia arises through increased catabolism and substrate utilization, rather than a reduction in energy intake, which is likely to have little effect on body weight, particularly lean muscle mass.

2. ZAG in adipose atrophy in cancer cachexia

Chen Bing, MB, PhD, Department of Obesity and Endocrinology, University of Liverpool, United Kingdom



ZAG

Cancer cachexia is a catabolic syndrome resulting in anorexia and the loss of muscle and adipose tissue. Extensive research has focused on muscle wasting while loss of fat tissue is poorly understood. Fat depletion starts from the loss of visceral fat followed by fat loss in legs and arms. Recent research suggests that a slight increase in body mass index (BMI) might protect against mortality due to cancer cachexia in certain cancers. However, the molecular mechanisms of fat loss in cancer cachexia are largely unknown.

Animal studies show that the size of adipocytes shrinks during cachexia with changes in their ultrastructure. ZAG is a potential mediator which acts as a lipid mobilizing factor to stimulate lipolysis in adipocytes.[18] ZAG is expressed by various adipose tissues and secreted by mature adipocytes.[19, 20] It has been shown that ZAG mRNA expression in WAT is negatively correlated with adiposity in humans.[20]

ZAG is closely associated with cancer cachexia. In a mouse cancer cachexia model, ZAG is up-regulated in WAT of MAC16 mice.[21] In humans, ZAG was found to be associated with decreased adipocyte size and with increased fibrosis in patients with pancreatic cancer.[6] In cachectic patients with GI cancer, higher ZAG secretion was associated with higher degree of weight loss.[22]

In addition, ZAG may locally modulate lipid metabolism by stimulating ZAG expression in human adipocytes.[22] ZAG-knockout mice were found to be susceptible to weight gain.[23] In GI cancer patients, ZAG mRNA levels were positively correlated with serum glycerol levels; administration of recombinant ZAG stimulated lipolysis.[22]

In summary, ZAG is a major adipokine expressed in mouse and human adipose tissues and is secreted abundantly by human adipocytes. ZAG expression and secretion by adipose tissue is up-regulated in cachectic cancer patients, which stimulates lipolysis. A large body of evidence indicates ZAG may contribute to fat loss in cancer cachexia.

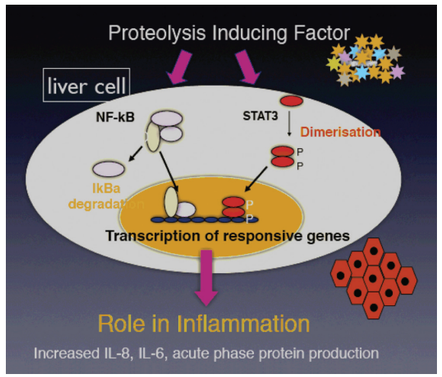
3. Proteolysis inducing factor-inflammation, cancer cachexia and survival

Jim Ross, BSc, PhD, School of Clinical Science and Community, University of Edinburgh, United Kingdom

This presentation discussed the effect of proteolysis inducing factor (PIF) on liver and its role in cachexia and the role of the gene encoding the PIF-core peptide (PIF-CP) in tumor biology.

PIF was discovered by Prof. Michael J.Tisdale in 1996. It is a 24 kDa sulphated proteoglycan.[24] The human gene of PIF was patented as human cachexia associated protein (HCAP) gene by Incyte Pharmaceuticals in 1998. During cancer cachexia, the liver undergoes a continuous, prolonged acute phase response, which leads to increased protein degradation from the skeletal muscle and increased synthesis of acute phase proteins. PIF is a cachexia factor leading to muscle breakdown and weight loss in animal models with significant binding capacity to the muscle and liver. Bioactivity of PIF is dependent on glycosylation.[24] PIF can be isolated from urine of cachectic pancreatic cancer patients.

PIF has been shown to have direct effects on liver cells as well. In primary hepatocytes, PIF activates NF-κB and induces STAT3 activation leading to inflammatory response in liver cells with significant increase in IL-6, IL-8 and acute phase protein.[25] Therefore, it is concluded that PIF contributes to the proinflammatory effects on the liver by increasing acute phase response during cancer cachexia.



PIF may also be involved in other biological functions. PIF core protein is a survival promoting peptide (YP-30) in the medium of oxidatively stressed cells of nervous system origin.[26] The HCAP gene encoding PIF-CP and YP-30 is homologous with the gene sequence that encodes dermcidin, an antimicrobial peptide secreted by sweat glands which contains DCD-1 peptides.[27] In addition, the DCD-1 gene may be a candidate oncogene in breast cancer.

However, PIF expressed in some cell lines is not usually associated with wasting. PIF-CP expression provides a proliferative and survival advantage to tumor cells against apoptosis. The DCD expression may improve the ability of cancer cells to survive in areas of high oxidative stress and allow positive selection of cells with a survival advantage.

Studies have shown that placental factor, which is involved in survival of the developing thalamus, is identical to PIF-CP.[28] DCD/HCAP gene might participate in the regulation of placental function.[29] Thus, it was suggested that future research is needed to examine whether PIF-CP/YP-30 provides developmental cues for hepatocyte division, differentiation or survival. In conclusion, PIF contributes to tumor growth and cancer cachexia. Biological effects of PIF on other systems require further investigation.

4. Inflammation and cancer cachexia

Professor Josep M. Argilés, PhD, Cancer Research Group, University of Barcelona, Spain

Cancer is an inflammatory state with inflammatory status predicting survival. Glasgow Prognostic Score (GPS) measuring C-reactive protein (CRP) and albumin levels is a predictor of survival independent of tumor stage, performance status, or treatment.

Cytokines are involved in cancer cachexia and chronic inflammation causing metabolic changes, neuroendocrine alterations and anorexia. It was reported that in patients with advance cancer, CRP, fibrinogen, IL-6, TNF-α, and IL-1 are significantly increased and leptin is decreased.[30] Patients' performance status are negatively correlated with proinflammatory cytokines (especially IL-6) and positively related with leptin levels.[30]

Anti-inflammatory drugs and nutrients have been tested to attenuate cancer cachexia. For example, celecoxib, a COX-2 inhibitor, improved lean body mass (LBM) and grip strength in patients with cancer cachexia.[31] Similar positive results were reported using IL-6 and TNF-α blocking agents. Improved Kaplan-Meier survival was observed in patients with pancreatic cancer treated with thalidomide, a TNF-α blocking drug.[32] Nutrients targeting cancer cachexia include n-3 polyunsaturated fatty acids, leucine, arginine, methionine, β-hydroxy-β-methylbutyrate (HMB), resveratrol and oligosaccharides. Many studies show supplementation with a protein and energy dense n-3 fatty acid enriched oral nutritional supplement attenuated the loss of weight and LBM and/or inflammation in cachectic cancer patients.[33, 34] It was also noted that supplementing EPA alone at 2 g/day had no effect on weight, survival or nutritional variables.[35] Moreover, a combination of anabolic nutrients (high protein, leucine and fish oil) when tested in cachectic animal models significantly improved not only body weight but also muscle synthesis markers.[36] In addition, this combination plus oligosaccharides reduced inflammatory cytokines.

It is suggested that cancer cachexia is a result of energy imbalance due to reduced food intake and increased energy expenditure. The presence of tumor leads to energy wasting. Uncoupling protein (UCP) expression and activity are increased in skeletal muscle in subjects with cancer. ATP synthesis rate is significantly decreased although mitochondrial area is increased in tumor-bearing subjects. In addition, dysregulation of endoplasmic reticulum also contributes to energy wasting in cancer cachexia. Inflammatory cytokines may modulate the energetic efficiency and protein metabolism through intracellular signaling pathways (Figure 3).

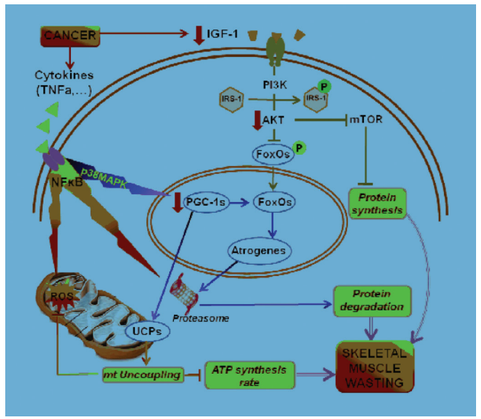


Figure 3: Intracellular signaling during cancer cachexia (Argiles et al, Int J Biochem, 2008.)

5. Biomarkers: Utility in the early diagnosis and histological diagnosis of lung cancer

Rafael Molina Porto, MD, Cancer Unit, Laboratory of Biochemistry, Hospital Clinic, Barcelona, Spain

This presentation described the utility of biomarkers to assist in the diagnosis of lung cancer and subsequently, to increase surgical probabilities, increase survival and decrease cost and morbidity.

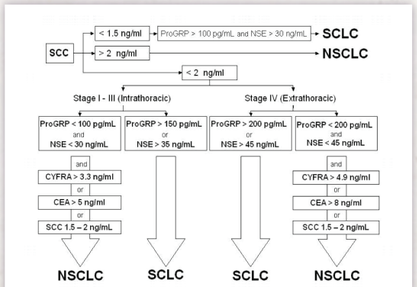


Figure 4: Algorithm to suggest lung cancer histology (Molina R, et al, Tumor Biol. 2009)

First, an algorithm using squamous cell carcinoma antigen (SCC), pro-gastrin-releasing peptide (proGRP), neuron-specific enolase (NSE), cytokeratin 19 fragment (CYFRA), and carcinoembryonic antigen (CEA) tumor markers to differentiate lung cancer histology was introduced (Figure 4).[37] Studies were conducted to examine specificity and sensitivity of a combination of these markers in 1047 patients with suspicious signs of lung cancer from four medical centers. Three hundred and eighty five patients were confirmed with no malignancy. Using cut-off values of CEA 10 ng/ml, CYFRA 5 ng/ml, NSE 30 U/ml, CA 15.3 50 U/ml, and ProGRP 100 pg/L, the specificity was 83.9%. This was relatively low and it may be attributed to the fact that a large proportion of patients had abnormal values of these tumor markers as a result of other pathologies. It was recommended to use these markers with signs, symptoms, and image results. In addition, the trend of these markers overtime may also suggest whether a malignancy exists.

Specificity of Markers in Lung Cancer

SQUAMOUS CRITERIAS Mo
- S CC >1.5; CEA (-): 82%
- S CC >1.5; CEA (+); CEA/SCC ratio <15: 86%
- S CC<1.5; CEA (-); CA 15.3 (-); YFRA (+): 81%

Squamous CRITERIAS stage IV
- S CC >5: 92.9%
- S CC 2-5; CYFRA (+); CEA (-): 87%
- S CC 2-5; CEA(+), CEA/SCC ratio <2: 100%

Adenocarcinoma CRITERIAS Mo
- S CC <1.5; CEA (+), CA 15.3 (+): 86.7%
- S CC <1.5; CEA (+); CA 15.3 (-); CYFRA (-): 86%
- S CC < 1.5; CEA (+); CA15.3 (-); CYFRA (+); CEA/CYFRA ratio >2: 80%

Adenocarcinoma CRITERIAS stage IV
- S CC <5; CEA (+); CA 15.3 (+): 93%
- S CC <2; CEA (+) and >7 ng/mL; CA 15.3 (-); CYFRA (+): 91.6%
- S CC <2; CEA (+); CA 15.3 (-); CYFRA(+);

The sensitivity of the tumor markers were examined as well. It was shown that in 545 patients with NSCLC, the sensitivity of CYFRA was 9%. When 3 markers, CEA, CYFRA 21-1, and SCC-CA 15.3 were used together, the sensitivity reached 75% for Stage I-III and 92% for Stage IV NSCLC. In patients with SCLC, ProGRP and NSE are most sensitive whereas SCC is not present in SCLC. The sensitivity to diagnose SCLC was 86.7% for Stage I-III and 96.1% for Stage IV when NSE, ProGRP and CEA were combined. Although the sensitivity and specificity of these markers may not be adequate to use in diagnosis, they may be useful to identify patients with high risk. In addition, results of these markers can be obtained within two hours. Markers to distinguish adeno- and squamous cell carcinoma and associated specificity are summarized in the box on the left.

In summary, these results suggest that these markers are clinically applicable for lung cancer screening, diagnosis, and treatment.

6. The role of nutritional intervention in multimodal management of chronic wasting disease

Annemie Schols, PhD, Department of Respiratory Medicine, Maastricht University Medical Centre, The Netherlands

This presentation described the role of nutritional intervention in multimodal management of chronic wasting disease due to chronic obstructive pulmonary disease (COPD) and suggested that this approach may be useful in patients with lung cancer.

SYSTEMIC INFLAMMATION AND MUSCLE WASTING IN COPD AND LUNG CANCER

Systemic inflammation plays a role in skeletal muscle weakness and cachexia, which are symptoms shared by both COPD and lung cancer leading to decreased physical function and quality of life. Negative correlation between muscle strength and exercise capacity and systemic inflammation markers, such as levels of CRP, IL-6 and TNF-α, has been reported.[38, 39]

The relationship between systemic inflammation and muscle wasting was examined in patients with lung cancer at pre- and cachectic stages (defined as weight loss < 5% and ≥ 5%, respectively). In a cross-sectional study in 26 patients with untreated late stage (III/IV) non-small cell lung cancer (NSCLC) and matched healthy controls (n=22), it was found that cancer patients had significantly less area of type I and type IIa, IIx and IIa/IIx muscle fibers compared to healthy controls, whereas the muscle inflammatory signaling (IKB-α and TNF-α mRNA) and CRP levels were increased significantly. The muscle isokinetic peak torque and domains of Quality of Life (QLQ-30) were decreased in patients with cancer. These parameters were worse in cachectic patients than in patients who were pre-cachectic. This study suggests that systemic inflammation is associated with muscle function and quality of life in patients with lung cancer.

In another cross-sectional study, metabolic profile and exercise capacity were examined in patients with early stage NSCLC (n=18, mean age 65 y). Mean weight loss in these patients was <5%. No difference in lean body mass and muscle inflammatory signaling were observed between patients and age, gender, and smoking matched controls. However, enhanced systemic TNF-R55, CRF, and fibrinogen levels and decreased albumin and peak exercise capacity were noted in these early stage cancer patients. Therefore, multimodal metabolic management should be started at an early stage of cachexia.[40]

MULTIMODAL MANAGEMENT OF NUTRITIONAL INTERVENTION IN WEIGHT LOSING COPD PATIENTS

Dietary counseling and food fortification[41] and exercise plus nutrition[42] have been shown to be effective in improving body weight, walking capacity and quality of life in patients with COPD. However, these interventions did not change muscle mass and function.[41, 42] Resistance training and administration of anabolic agents had synergistic effects on improving mRNA levels of insulin-like growth factor-1 (IGF-1) .[43] Exercise plus branched-chain amino acid (BCAA) supplementation appears to be a promising way to improve weight gain and fat-free mass (FFM).[44] In addition,

exercise, education, nutrition and anabolic steroids showed the most increase in body weight, muscle mass and strength (Pi-max) versus single treatment.[45]

The anabolic response may be different even in a controlled clinical trial. This difference can be explained by the negative association between weight gain and systemic inflammation. EPA may down-regulate the NF-κB transcriptional activity to attenuate muscle protein loss. Exercise plus 8 weeks supplementation of polyunsaturated fatty acids containing fish oil improved muscle mass and strength and exercise capacity.[39]

Oxidative metabolism may be involved in muscle endurance capacity and overall exercise capacity. In COPD cachexia, expression of regulatory proteins of aerobic muscle metabolism, such as peroxisome proliferator-activated receptor-α (PPAR-α) and PPAR-γ, was decreased compared to controls.[46] Cell studies showed that TNF-α may decrease type I muscle fiber expression and activity of PPAR-γ coactivator-1 (PGC-1α), mitochondrial transcription factor A (Tfam) and PPAR-α.[47]

LESSONS FROM THE MANAGEMENT OF MUSCLE WASTING IN COPD

COPD patients gradually lose muscle mass and function influenced by disease severity, systemic inflammation, physical inactivity, and smoking. Exacerbation significantly accelerates the process. Many studies have been done to use the multimodal approach to help COPD patients attenuate the weight loss during clinically stable condition. This could be useful for patients with lung cancer. On the other hand, treatment for weight loss due to acute exacerbation is also needed to improve physical function and quality of life for these patients. Linking knowledge between COPD and lung cancer is particularly important to manage patients with nutritional needs.

7. Assessment of mass and function of skeletal muscle in cancer cachexia: Sexual dimorphism?

Carolyn Greig, PhD, Department of Clinical and Surgical Sciences, The University of Edinburgh, Scotland

This presentation discussed the importance of assessing skeletal muscle mass and function in patients with cancer cachexia.

Muscle mass and function are associated with disease progression and response to treatment in patients with cancer. Muscle mechanical quality can be determined by muscle strength per unit cross sectional area (CSA) using CT scan. Muscle strength can be measured by maximum voluntary isometric knee extensor strength (IKES) or maximum voluntary lower limb extensor power (LLEP).

In patients with gastrointestinal cancer, men with cancer cachexia experienced an 18% decline in quadriceps muscle mass compared to controls and men with cancer without cachexia. In contrast, there was no decrease in muscle mass in women with cancer cachexia compared to those without cachexia. Quadriceps strength was significantly lower in both men and women with cachexia. No difference was observed in hand grip strength in patients with cancer compared to healthy controls indicating reduced sensitivity of this test as a functional marker of cachexia.

Muscle mechanical quality measured by strength/CSA was decreased in both men and women with cancer cachexia. The observation of different response in muscle mass and quality between men and women may be explained by sexual dimorphism.

8. Cancer cachexia: Developing multimodal therapy for a multidimensional problem

Neil MacDonald, MD, McGill Cancer Nutrition-Rehabilitation Program, Montreal, Canada

There is abundant evidence supporting multimodal approaches to stabilize and even improve the nutritional status, function and quality of life in at least a proportion of advanced cancer patients.[48] This presentation described a privately funded interdisciplinary program that offers early palliative care for patients with cancer.

The McGill Cancer Nutrition-Rehabilitation Program (CNRP) involves a physician, physiotherapist, dietitian, nurse, psychologist, occupational therapist, and social worker, as well as the patient and family. At program entry, a patient's psychological, nutritional, inflammatory and hormonal status is assessed. Rehabilitation tests are performed to assess endurance, strength, and balance.

Dietary Counseling of the McGill Cancer Nutrition-Rehabilitation Program (CNRP)

- **Remove dietary restrictions**
- **1.5-2.0 g protein/kg**
- **2 g EPA (n-3 fatty acid) if there is evidence of inflammation**
- **1000-2000 IU of Vitamin D**
- **Multivitamins if there is evidence of malnutrition**

The CNRP is 8-10 weeks with clear initial and end evaluation. Participants actively participate in a personalized care plan that includes nutritional counseling, an exercise program, psychological support, nursing intervention, and pharmaceutical therapy. Details of dietary counseling are listed in the box on the left. Participants are encouraged to exercise 1-2 times/ week for cardiovascular and resistance training, and meet other team members every two weeks. Caregivers also receive information and education from the center. General approaches are taken to correct symptoms such as mouth care, anxiety, pain, and constipation.

Exercise is expected to lead to multiple benefits as listed below. In addition, exercise may improve inflammatory status and possibly impact tumor growth and attenuate cancer cachexia.

- Physical Benefits – muscle mass, muscle strength, flexibility, cardiovascular fitness and fatigue;
- Psychological Benefits – stress, anxiety, sleep quality, depression;
- Sociological Benefits - self esteem, efficacy, connectedness, activity of daily living and quality of life; and
- General Health Benefits - circulation, immune response, lipid profiles.

Drug therapies are selectively used to improve appetite (prednisolone, megestrol and cannabinoids) and muscle growth (hypogonadism replacement and nonsteroidal anti-inflammatory drugs).

In summary, high patient satisfaction is obtained from participation in the program. Appetite, weight and function are improved at the completion of the program. Future studies may consider standardizing populations and time entry as well as offering dietary and drug therapy consistently. Novel compounds targeting inflammation need to be included in the program. More importantly, it is suggested that oncology research needs to be prioritized to assess effects of anti-tumor/cancer cachexia programs.

9. Resting energy expenditure in head and neck cancer patients during radiotherapy

Jacqueline A.E. Langius, RD, VU University Medical Center Amsterdam, The Netherlands

Head and neck cancer is a common cancer worldwide. Malnutrition is a well-known problem in these patients. This presentation reported preliminary research data on whether hypermetabolism contributes to weight loss in head and neck cancer patients.

STUDY OBJECTIVES

To determine whether resting energy expenditure (REE)

- is elevated in head and neck cancer patients before radiotherapy;
- is dependent on tumor stage, acute phase reaction and prior tumor surgery;
- changes during radiotherapy.

METHODS

Seventy-one (71) patients with head and neck cancer receiving primary or postoperative radiotherapy (RT) for > 4 weeks were included in the study. No subjects had distant metastases, thyroid or inflammatory diseases. There were 40 healthy control subjects (20 men and 20 women) who were one-to-one matched to 40 (out of 71) patients by gender, age and fat free mass index (FFMI). REE (measured by indirect calorimetry), weight, and FFM were measured four times (before RT, 3 weeks, end of RT, and 3 months post RT).

RESULTS

There was no difference between controls and matched patients in age, gender, BMI and FFMI. REE was similar between controls and patients before RT (1619 vs 1568 kcal/day, respectively, $P = 0.29$). REE was not associated with tumor stage, prior surgery and CRP levels.

In patients with head and neck cancer , weight, FFM and REE decreased during RT. REE/kg FFM decreased at week 3 but increased at the end of RT and decreased again at 3 months post RT (Figure 5).

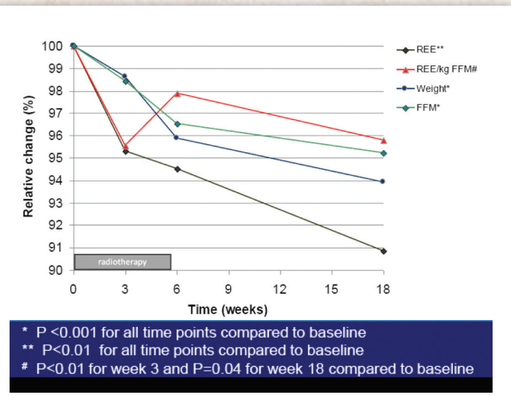


Figure 5: Weight, FFM, REE and REE/kg FFM over time

CONCLUSION

Patients with head and neck cancer had no hypermetabolism before RT. REE/kg FFM showed a transient decrease during RT. Weight decreased continuously during the entire study period.

10. Impact of nutritional status on QOL: The value of intervention in cancer

Paula Ravasco, PhD, Unit of Nutrition and Metabolism, Institute of Molecular Medicine, Faculty of Medicine of the University of Lisbon, Portugal

This presentation addressed the value of nutritional (dietary) intervention in multimodal cancer therapy and association with quality of life (QOL).

NUTRITION AND QOL

Decreased dietary intake is an independent determinant of QOL in patients with cancer.[49] When a patient's GI tract is functional, dietary counseling and supplements need to be considered. When dietary intake is insufficient (≤50% of requirement), artificial nutrition support (enteral or parenteral) may be initiated after assessment of duration, nutritional status and disease severity. It is important to be recognized that food intake is essential to patients to maintain activity, energy and function. Oral nutrition should be one of treatment priorities.

KEY COMPONENTS OF HIGH-QUALITY NUTRITION SUPPORT

- Involvement of nutritional professionals to provide individualized, evidence-based quality nutrition therapy;
- Utilization of structured and validated methods to assess nutritional intake and status, individual needs, psychological status, and symptoms
- Adjustment of nutritional therapy by disease state, symptom and progression;
- Respect of patients' usual dietary pattern;
- Use of nutritional prescription as needed.

IMPACT OF NUTRITIONAL COUNSELING

Nutritional counseling improves outcomes in patients with colorectal cancer receiving radiotherapy (data in press). During a 6-year follow up, patients who received nutritional counseling experienced less toxicity symptoms and better survival rate. Adequate nutritional intake and status were associated with highest QOL scores whereas worsened QOL was found in patients with deteriorated nutritional intake and status. Similar improvement in nutritional and functional outcomes was also reported in patients with GI cancer receiving radiotherapy and individualized nutritional counseling.[50]

ESPEN guidelines (2006) recommended intensive dietary counseling with regular foods and/or oral nutritional supplements to improve diet intake, prevent therapy-associated weight loss and treatment interruption in patients with GI or head and neck cancer undergoing radiotherapy with and without chemotherapy.[51] However, implementation of dietary counseling requires further involvement of health care professionals.

11. Nutrition in the health system

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Risk of malnutrition exists in a significant number of hospitalized patients worldwide. However, more than half of hospitals do not have or communicate a nutritional care plan at discharge. A recent study from the UK revealed that the cost of managing malnourished patients after hospital discharge was more than twice that of managing non-malnourished patients due to increased use of healthcare resources.[52] Significant cost occurred in general physician consultations, hospital admissions and uses of medical devices.[52] Therefore, improving nutritional care during hospital admission may play a role in reducing the healthcare cost incurred after discharge.

Many nutritional guidelines have been published to improve nutritional therapy in the healthcare system. For example, the COUNCIL OF EUROPE- COMMITTEE OF MINISTERS adopted Resolution ResAP (2003)3 and provided nutritional assessment and treatment for hospitals. A.S.P.E.N. and ESPEN also published series of evidence-based medical guidelines on nutrition support. The European Nutrition for Health Alliance (ENHA) unites European stakeholders to raise awareness, change policy priorities and help improve nutritional care. Political support, reimbursement for nutritional support and nutrition care plans are being planned by ENHA. The World Health Organization (WHO) is also planning hospital nutrition network activities and plans.

In summary, nutritional care should be an intrinsic part/component of prevention and disease management in the health system. Nutritional care should be a priority in the political agenda.

12. Screening and assessment for early intervention

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Malnutrition is a state of nutrition in which a deficiency or excess of energy, protein, and other nutrients causes measurable adverse effects on tissue/body form and function, and clinical outcome.[53] It is prevalent in oncology patients associated with increased morbidity and mortality and decreased quality of life.

Cachexia is a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass. The prominent clinical feature of cachexia is weight loss. Anorexia, inflammation, insulin resistance and increased muscle protein breakdown are frequently associated with this wasting disease.[54] Cachexia can be diagnosed by weight loss ≥ 5% within 12 months plus abnormalities in muscle strength, fatigue, anorexia, low FFM and/or abnormal biochemistry.[54] Recently published by the European Palliative Care Research Collaborative (2010), cachexia is diagnosed by weight loss > 5% over the last 6 months (in absence of simple starvation) or BMI < 20 and any degree of weight loss (i.e., > 2%) or abnormal appendicular skeletal muscle index (males < 7.26 kg/m^2, females < 5.45 kg/m^2) and any degree of weight loss (i.e., > 2%).[55]

Many nutritional screening tools are developed to identify patients at high risk for malnutrition. One of the tools is Malnutrition Screening Tool (MST) which gives a score of 0 to 5.[56] The positive predictive value of the tool is 98.4% and the negative predictive value is 72.7%.

Early nutritional assessment is recommended by A.S.P.E.N..[57] Subjective global assessment (SGA) is an easy and validated tool most commonly used to identify patients with protein-calorie malnutrition. SGA categorizes patients into one of the three groups:

A. Well nourished
B. Moderated malnourished
C. Severely malnourished

SGA score can also be useful to predict survival of patients. It is the current “gold standard” for defining malnutrition and is a tool proposed by ESPEN.

Therefore, MST and SGA satisfy constraints of good tools for screening and assessment. In the Croatian nutrition support guidelines, it is suggested that a patient with an MST score ≥ 2 should by assessed by SGA. Nutrition support should be considered for oncology patients whose SGA score is B or C. Enteral nutrition plus EPA (2.2 g) plus megestrol acetate (400-800 mg/day) is recommended for patients with an MST score of 4 or 5.

13. Classification, assessment and early intervention for cancer cachexia

Professor Kenneth C.H. Fearon, MD, Department of Surgical Oncology, University of Edinburgh, Scotland

This presentation discussed the consensus statement which defines and classifies cancer cachexia.[40] This was developed by a panel of world-renowned experts that was recently published in *Lancet Oncology* in 2011.

DEFINITION

“Cancer cachexia is a multifactorial syndrome defined by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment. The pathophysiology is characterized by a negative protein and energy balance driven by a variable combination of reduced food intake and abnormal metabolism.” [40]

DIAGNOSIS

Cancer cachexia can be diagnosed by one of the following three criteria presented in Box 1. The severity of cachexia can be determined by the baseline BMI and weight and the degree of depletion of energy stores/protein mass as well as degree and rate of weight loss.

Box 1: Diagnosis of Cancer Cachexia

1. Involuntary weight loss >5% over last 6 months (in absence of simple starvation); or
2. Weight loss >2% with BMI <20; or
3. Weight loss >2% with an appendicular skeletal muscle index consistent with sarcopenia (males <7.26 kg/m^2; females <5.45 kg/m^2)*

** With fluid retention, a large tumor mass or overweight/obesity a direct measure of muscularity is particularly recommended.*

PHASES OF CANCER CACHEXIA

There are three phases of cancer cachexia: pre-cachexia, cachexia, and refractory cachexia. Patient assessment should include four domains which are summarized in Figure 6.

Pre-cachexia can be found in any stage of cancer and any stage of cancer therapy. Diagnosis criteria include weight loss ≤ 5% with metabolic/endocrine changes. Anorexia may be present. During this stage, the patient’s nutritional status should be closely monitored.

Cachexia, or cachexia syndrome, can also be observed in patients with any stage of cancer and at any stage of cancer therapy. Patients undergo active catabolism, which potentially responds to multimodal therapy. Diagnosis is based on >5% weight loss without simple starvation or > 2% weight loss with low BMI or sarcopenia. Once cachexia is diagnosed, a multimodal rehabilitation program should be initiated to preserve weight and quality of life.

Refractory cachexia is the most severe phase of cancer cachexia as a result of significantly high catabolism. Patients with very advanced and/or rapidly progressive cancer and unresponsive to anti-cancer therapy are classified in this stage. Once a patient enters this phase, life expectancy is < 3 months. Because multimodal therapy may no longer be beneficial, patient management should focus on symptom control and family support.

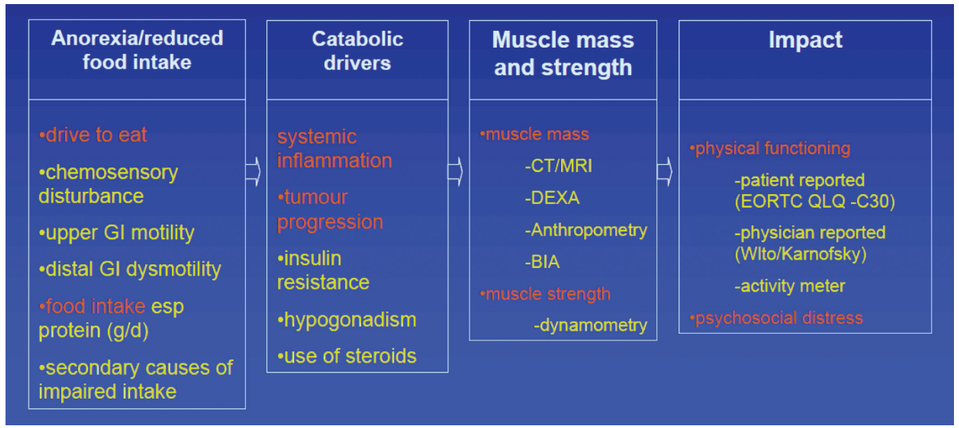

Figure 6: Assessment domains for cancer cachexia (adapted from the presentation).

EARLY INTERVENTION

Management of cancer cachexia is a multimodal approach. Early intervention plays an important role in the model. Ross *et al*[58] showed that in 418 patients with stage III/IV NSCLC, 58% had weight loss at presentation. Compared to patients who did not have weight loss, those who lost weight had significantly increased failure to complete 3 cycles of chemotherapy ($P = 0.003$) and higher frequency of anemia ($P = 0.0003$). The symptomatic responses ($P = 0.0001$) and survival duration ($P = 0.0009$, RR = 1.33) were significantly lower in those patients. Similar results were reported by other researchers. Therefore, early intervention for weight loss in patients with cancer may:

- reduce side-effects of surgery, chemotherapy, radiotherapy (e.g., infectious episodes);
- improve tolerance of surgery, chemotherapy, radiotherapy;
- increase dose intensity/total dose delivery;
- increase response rates;
- improve overall survival; and
- reduce symptom burden in survivors.

STRATEGIES FOR INTERVENTION IN CACHEXIA

Cachexia is frequently associated with anorexia and metabolic changes. Megestrol acetate and oral nutritional supplements (ONS) can be prescribed to increase food intake. Anti-inflammatory and anabolic agents, such as ibuprofen, EPA, and formoterol, are useful to modulate metabolism. A recent study conducted in patients with lung cancer receiving chemotherapy showed that EPA supplementation (2.5 g EPA + DHA/day) significantly maintained weight and tissue rate of changes (muscle, intermuscular adipose tissue and total adipose tissue) from baseline to after chemotherapy.[59] Additionally, van der Meij *et al*[60] showed that supplementation of an EPA-containing ONS maintained

weight and LBM in patients with lung cancer during chemo-radiation.

In summary, management of cancer-associated weight loss should use multimodal approaches which comprise four steps: (1) early assessment and optimization of symptoms to identify and treat problems; (2) dietary and exercise counseling to improve food intake; (3) utilization of ONS or artificial nutritional supplement when needed; and (4) combination therapies.

14. Nutrition intervention during chemo-radiotherapy

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Malnutrition or risk of malnutrition exists in many cancer patients at diagnosis, primarily in those with head and neck or gastrointestinal (GI) cancers. Chemo-radiotherapy is a risk factor for malnutrition in all cancer types. This presentation discussed the role of nutrition intervention during chemo-radiotherapy and reviewed ESPEN guidelines on enteral nutrition (EN) for cancer patients receiving chemo-radiotherapy.

EARLY NUTRITIONAL INTERVENTION

In 26 patients with advanced nasopharyngeal or hypopharyngeal cancer, nutritional intervention with standard ONS given to patients with SGA of B or C significantly decreased the severity of mucositis, dysphasia, and late effects of radiotherapy treatment. In another study of 40 patients with rectal cancer receiving chemo-radiotherapy, those who consumed an ONS enriched with EPA experienced less diarrhea than patients who did not consume the ONS (Kilic *et al*, presented at 3rd National Gastrointestinal Oncology Congress, Antalya, Turkey, April 2011). In addition, supplementation with an EPA-supplemented ONS starting a week before the chemo-radiotherapy for 13 weeks decreased the rate of weight loss; 33% experienced a median 1.2 kg/month weight gain (personal data). These data indicated that early nutrition intervention is beneficial in patients undergoing chemo-radiotherapy.

IMMUNONUTRITION

Some nutrients may possess immune modulating properties, which require further studies to examine their effects in cancer patients. These nutrients include arginine, glutamine, omega-3 fatty acids, RNA, β-hydroxy-β-methylbutyrate (HMB), and soluble fiber. It is possible that a combination of pharmaconutrients is useful to optimize immune response and improve outcomes in patients with cancer.

NUTRITIONAL INTERVENTION AND TUMOR GROWTH

Discrepancies exist in the relationship between nutritional intervention and cancer. Based on literature review, there is no data supporting that nutritional support has deleterious effect on outcomes in cancer patients. Regarding the effect of antioxidant supplementation during chemo-radiotherapy, currently, high dose supplementation is not suggested because of the possibility of tumor protection and reduced survival.[61]

> ***Fear for a disproportionate and excessive tumor growth should not prevent appropriate nutritional support when it is clinically indicated.***
>
> **- Diclehan Kilic**

ESPEN GUIDELINES

The goals of nutritional intervention for patients with cancer are to (1) prevent and treat malnutrition; (2) improve effects of anti-cancer treatment; (3) decrease complications of anti-cancer treatment; and (4) improve quality of life.[51] The major guidelines include the following.

- Frequent evaluation, early nutrition support (NS) when indicated;
- In already malnourished or will be unable to eat for > 7 days, start EN with standard formula;
- NS 10 – 14 days prior to major surgery, even if operation has to be delayed;
- Intensive dietary advice and ONS;
- Routine EN (tube feeding) is not indicated during chemo- or radiotherapy;
- Dietary counseling and ONS for patients with head and neck and GI cancer receiving radiotherapy;
- In patients with severe local mucositis, transnasal/percutaneous tube feeding may be considered; PEG is indicated during radiation mucositis;
- Medication in case of systemic inflammation in addition to nutritional intervention to modulation the inflammatory response.

15. Complex cancer surgery: Experimental paradigm for studies of immune function, nutrition and metabolism

Professor John Reynolds, MA, MB, BCh, FRCSI, Department of Surgery, St. James's Hospital and Trinity College, Dublin, Ireland

Malnutrition exists in a significant number of cancer patients undergoing surgery and is associated with worsened clinical outcomes. It has been shown that preoperative hypoalbuminemia (< 30 g/dL) was an independent marker of surgical site infection after gastrointestinal surgery.[62] Prognosis was worse in cachectic patients with resectable pancreatic cancer.[63]

Major surgery is a contributing factor of increased immune-inflammatory response and nitrogen excretion, and possibly, cancer-induced weight loss. Esophageal cancer surgery is associated with profound and predictable changes in nutrition, metabolism, immune function and quality of life. A large number of patients have significant weight loss (≥10%) 6 months after esophagectomy.

The gut immune function is affected during cancer and possibly after major surgery. In cancer patients, malnutrition effects intestinal barrier function and alters mucosal immunity, which correlates well with the acute phase response (C-reactive protein, IL-6).[64] Initiation of enteral feeding after surgery may attenuate the acute phase response and improve disease severity.[65] Current ESPEN Guidelines recommend the use of immune modulating enteral nutrition preoperatively for 5-7 days and its continuation for 5-7 days after uncomplicated surgery.[66]

Many studies indicate enteral nutrition supplemented with EPA decreases release of inflammatory cytokines and decreases severity of inflammation. It may also have an anabolic effect. In 200 weight-losing patients with advanced pancreatic cancer, supplementation of an EPA-containing ONS for at least 8 weeks significantly improved weight gain, lean body mass and quality of life.[33] Similar results were observed in patients after esophageal cancer surgery.[67] In addition, patients receiving EPA-containing ONS had significantly lower maximal body temperature and lower concentrations of TNF-α, IL-10 and IL-8 although there was no difference in postoperative complications.[67]

Obesity is a risk factor for the incidence of gastrointestinal and other types of cancer, possibly due to systemic inflammatory microenvironment. Obesity-like cachexia is associated with insulin resistance and metabolic disturbance. Release of inflammatory cytokines and chemokines from expanding adipose tissue has profound influence on immune cells both locally and systemically. There is evidence suggesting that in obesity M2 macrophages may shift to M1 macrophages promoting angiogenesis. In addition, the composition of T cell populations is also altered which influences the development of obesity-associated inflammation. The omentum is a rich source of activated immune cells and cytokines (INF-γ, IL-4, 10, 17, etc) in obese patients. High visceral fat area is associated with increased acute inflammatory response.

In summary, malnourished patients should be nutritionally replenished before surgery. Enteral nutrition should be used in patients undergoing cancer treatment. Impact of obesity in cancer therapy needs further investigation.

16. The use of a protein and energy dense eicosapentaenoic acid containing supplement for malignancy-related weight loss in children

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Many studies suggest dietary supplementation with eicosapentaenoic acid (EPA), an n-3 polyunsaturated fatty acid, may have beneficial effects in cancer patients by modulating the inflammatory response and attenuating weight loss and muscle wasting.[35] However, there is no data in the pediatric population. Therefore, a study was conducted to examine the clinical effect of a protein and energy dense, EPA containing oral supplement in pediatric cancer patients receiving active chemotherapy treatment.[68]

STUDY DESIGN

This was a prospective, randomized, single-center, open-label study. Fifty two (52) patients with newly diagnosed pediatric malignant diseases were included and were randomized to receive either a protein and energy dense EPA containing oral supplement (ProSure™) in addition to their normal dietary intake (n=33) or usual dietary care (n=19) for a total of 3 months. Twenty-three (23) subjects were followed for an additional 3 months. Subjects began to take the supplement orally at or shortly after clinical diagnosis of cancer. A nurse specializing in nutritional support was responsible to check whether the supplement was taken regularly both at home and in the clinic. The primary variable was the percent of subjects having body weight loss.

RESULTS

There were no tolerance or taste issues reported during the study. At 3 months, significantly fewer subjects in the treatment group showed loss of body weight and BMI, and negative deviation from weight percentile. At 6 months, fewer subjects in the treatment group lost body weight (6.7% vs 50%, $P = 0.033$). Comparison was done based on tumor types. Similar positive results were observed in patients with leukemia but not in patients with solid tumors. At 3 months, the remission rate in patients in the treatment group was significantly greater as compared to control patients (87.9% vs. 63.2%; $P = 0.036$). There was no difference in either the number of febrile neutropenic attacks or the percentage of patients having an attack between the treatment groups.

CONCLUSION

It was concluded that this specialized supplement was safe in children with cancer. Consuming the protein and energy dense, EPA containing oral supplement in addition to standard of care improved clinical outcomes. The different response between patients with leukemia and solid tumors may be due to selective differences in cancer cell sensitivities to EPA. It was recommended that this supplement can be considered a safe, adjuvant therapy as part of overall care for pediatric cancer patients.

Future work needs to determine if the administration of this nutritional supplement to children affects biochemical mechanisms that have been previously shown in adults.

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