The role of nutrition on effectiveness of chemotherapy

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Period:	01-02-2012 / 14-03-2012
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Abstract

Major features of cancer are weight loss and malnutrition. Prolonged malnutrition of a patient can result in cachexia. An estimated twenty percept of the cancer patients will die due to cachexia. Cachexia is a multifactorial syndrome that can develop as a result of local effects of the tumor, host responses to the tumor and anti-cancer therapies. In addition, an altered metabolism of nutrients and an increase in resting energy expenditure (REE) leads to insufficient food intake and a reduced nutritional status. During cachexia, the secretion of pro-inflammatory cytokines (e.g. IL-1β, IL-6, TNF-α and IFN-γ) play a major role in the development of cachexia. Accordingly, these cytokines are secreted as a host defence against fast proliferating tumor cells or are produced by activated tumor cells. In addition, the effect of chemotherapeutic agents could also lead to or aggravate malnutrition. Due to adverse effects of the chemotherapeutic agents, including altered taste and smell, food aversion, xerostomia and mucositis, which could negatively affect food intake.

Malnutrition can lead to a loss of lean body mass, muscle wasting, an impaired immune function and reduced quality of life. Moreover, it can result in a reduced response to chemotherapy due to chemotherapy-induced toxicity. This might be caused by changed pharmacokinetics of the drugs in cachectic patients, due to, changed body composition, altered albumin levels and CYP-450 enzyme function. In addition, increased chemotherapy-induced toxicity may lead to reduced chemotherapy dosage, treatment delays and possibly a definitive termination of treatment.

Nutritional intervention, adjusted to the patients specific needs, could be beneficial to counteract these malnutrition-related issues. Several nutrients have shown to improve the immune system of cachectic patients, including polyunsaturated fatty acids (PUFAs), galactooligosaccharide (GOS), fructooligosaccharide (FOS), branched chain amino acids (BCAAs), glutamine, arginine, vitamins A, C, and E, carotenoids, selenium, and zinc. Muscle degradation is decreased and muscle synthesis is stimulated by PUFAs, proteins and BCCAs. Antioxidative properties of some nutrients could reduce the chemotherapeutic side effects produced by reactive oxygen species (ROS). Moreover, some nutrients have shown to improve the efficacy and reduce the toxicity of chemotherapeutic agents. Glutamine for example has shown to reduce mucositis, a side effect of chemotherapeutic agents. Some nutrients even have a synergistic effect in combination with chemotherapeutics.

Novel nutritional interventions could improve the patients response to chemotherapy, improve the immune system and ultimately quality of life. However, it is important to explore the potential benefits of the combination of nutritional intervention with chemotherapy, and demonstrate clinical efficacy in preclinical and clinical studies, to improve the response to chemotherapeutic agents in cancer cachectic patients.

Contents

I.   Introduction

Cancer is a leading cause of death worldwide, with 7.6 million deaths in 2008 (1). The most common types of cancer are colorectal, breast, lung and prostate cancer, respectively (2). Most cancer deaths are caused by lung, colorectal, breast and stomach cancer (1,2).

Among these patients, a major issue during cancer is the change in body weight i.e. weight gain or weight loss (3-5). Weight gain is a common side effect in women receiving adjuvant chemotherapy for breast cancer (3-5). However, the mechanism of weight gain during cancer is not yet well understood (5). Though, weight gain is associated with adjuvant chemotherapy, including type of chemotherapy and length of the therapy, fatigue, decreased level of physical activity, increased food intake and a decreased resting energy expenditure (REE) (3,5). Weight gain is mainly caused by an increased fat mass, while the lean body mass remained unchanged. Accordingly, these cancer patients have a higher risk of recurrence and death (3,5).

In addition, weight loss is associated with progression of the disease and has a poor prognosis, as well (3,6,7). Many cancer patients suffer from weight loss and become malnourished. The incidence of malnutrition during cancer is between 30-90% and depends on localization of the tumor, tumor phenotype, stage of the disease, anti-cancer treatment, host genotype and patients characteristics, including age, gender and individual susceptibilities (6,9-11). Malnutrition is often seen in patients with cancer of the gastrointestinal (GI)-tract, pancreas or head and neck area (10,11). Malnutrition is defined as a condition in which the body does not receive enough nutrients, which leads to a deficiency of energy, protein and/or other nutrients and causes measurable adverse effects on tissue, body composition and form, and treatment outcome (6-8). Almost 50% of the patients will experience more than 10% weight loss during their disease. Prolonged weight loss by cancer-associated malnutrition can result in cachexia (10,11). Cachexia often occurs in patients with advanced diseases (6). Cachexia is a wasting syndrome including involuntary weight loss and a decreased lean body mass. Cachexia can occur even in patients eating enough, due to the presence of inflammatory processes, hypermetabolism and neurohormonal changes (7,8). Cancer-associated malnutrition and cachexia are major causes of morbidity and mortality in cancer. It is estimated that 20% of the cancer patients died due to malnutrition or cachexia (12-14).

Cachexia is a multifactorial syndrome, and is initiated due to factors from the tumor itself, the host response to the tumor, and the anti-cancer treatments (6,10,14,15). Cachexia is characterized by anorexia, early satiety, reduced food intake, metabolic abnormalities, depletion of lean body mass, muscle weakness, subcutaneous fat stores, oedema, fatigue, immune dysfunction and decreased motor and mental skills (6,10,15-17).

Cytokines, eicosanoids and hormones seems to have a significant role in the development of cancer cachexia. Pro-inflammatory cytokines including interleukin (IL)-1β, IL-6, tumor necrosis factor (TNF)-α and interferon (IFN)-γ may stimulate the occurrence of weight loss, anorexia and fatigue during cancer cachexia via several pathways. These cytokines are secreted as a host defence against fast proliferating tumor cells or are produced by activated tumor cells (6,10,18-20).

Cancer patients can receive different treatment to cure their disease or to increase quality of life in a palliative setting. One of the anti-cancer treatments is chemotherapy. Patients with cancer cachexia generally have a reduced response to chemotherapy, due to among others the presence of systemic inflammatory response. Inflammatory factors can influence the metabolism and clearance of chemotherapeutic agents. In addition, cancer patients receiving chemotherapy often have an increased risk of complications and chemotherapy-induced toxicities, which can even lead to treatment delays or

definitive termination of the treatment and consequently to a reduced quality of life and decreased survival rates (6,14,20,21).

To provide these patients with the optimal support during their treatment, nutritional support is recommended as an integral part of anti-cancer therapy. Nutritional intervention can be used as adjuvant support during chemotherapy with the aim to maintain or improve the patients nutritional status and improve immune function, therapy tolerance and quality of life of cancer patients. This thesis will give an overview of causes and mechanisms involved in cancer-related weight loss and cachexia. It is important to understand the mechanisms of cachexia to provide the optimal treatment support. Consequences of cachexia on for example efficacy and tolerance of chemotherapy will be summarised. Moreover, this thesis will outline the nutritional intervention that could be used in parallel to chemotherapy and could be beneficial for cancer patients.

II.   Cancer-associated malnutrition and cachexia

Malnutrition is progressive weight loss caused by insufficient intake of macro- and micronutrients (9,10). Macronutrients are consumed in a large amount and offers the body energy, such as carbohydrates, proteins and fats. Micronutrients are consumed in a small amount, such as vitamins, minerals and trace elements. Macro- and micronutrients are important for essential processes in the body such as growth, maintenance, protection and repair (10). Malnutrition can be caused by the presence of cancer. Some patients are not able to consume sufficient nutrients due to local effects of the tumor, while other patients suffer from systemic effects of the disease, psychological effects and/or side effects of the anti-cancer treatment (6,9,10,16). Cancer-associated malnutrition can play an important role in the development of a vicious circle (Figure 1) (10). Due to malnutrition patients encounter complications, that in turn can lead to severe illnesses. As a result of the illness, patients often have a reduced food intake that may cause a further development of malnutrition. After prolonged malnutrition during advanced

Figure 1: Malnutrition can develop to a vicious circle.
(adapted from Argiles *et al.* (10))

cancer, most patients develop cachexia (10,15). Cachexia is characterized by anorexia, early satiety, reduced food intake, metabolic abnormalities, depletion of lean body mass, muscle weakness, subcutaneous fat stores, oedema, fatigue, immune dysfunction and decreased motor and mental skills (6,10,15,16).
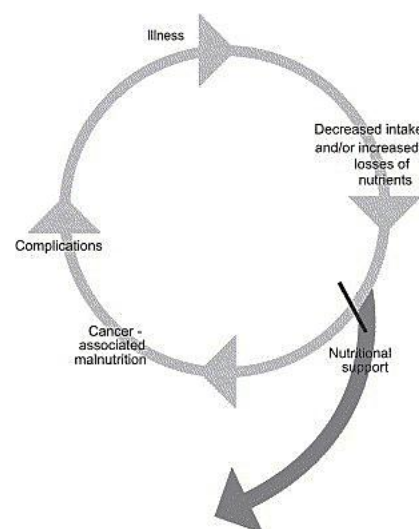
Some causes of reduced food intake during cancer are due to effects of the tumor. The tumor could be involved in the development of malnutrition due to physical obstruction of the gastrointestinal (GI)-tract, whereby the absorption of nutrients is insufficient. The tumor could also cause a reduced food intake by pain, odynophagia (painful swallowing) or dysphagia (difficulty in swallowing). Besides that, there could be a competition between the tumor and the host for the availability of nutrients. Alongside, these local effects, the tumor can play a role in systemic effects. The tumor is able to secrete cytokines, eicosanoids and hormones, which can influence the metabolism and catabolism of the patient. Accordingly, the tumor can induce early satiety, reduced appetite, anorexia, taste changes and food aversion, fatigue, nausea, and vomiting. The secreted cytokines could also have psychological effects such as depression, fear and anxiety that can influence food intake. In addition, the anti-cancer treatment (e.g. chemotherapy) could influence nutritional status. Chemotherapy can influence the taste and smell of food for a patient, which may lead to food aversion. Although, the side effect of chemotherapy such as nausea and vomiting, early satiety, constipation, diarrhoea, xerostomia (dry mouth), and mucositis (inflammation of the mucous membrane) can reduce food intake, as well (6,9,10,16,22).

Cachectic patient suffer from a deficiency of macro- and micronutrients. Deficiently of macronutrients can lead to reduced energy and protein synthesis. Carbohydrates are body's preferred energy source. Carbohydrates are a fuel for the muscles, brain and other tissues. Deficiency of carbohydrates will affect, among others, activity level. In addition, fats are a rich energy source and essential for the absorption of fat soluble vitamins. Insufficient intake of fats could lead to vitamin deficiencies. Due to decreased protein intake, the concentration of amino acids will reduce. Deficiency of amino acids could cause reduced muscle synthesis, increased fatigue, and it will affect multiple organ systems and the immune system. Moreover, when carbohydrates and fats are unavailable, proteins will be used as an energy source (10). Cachectic cancer patients might also have a deficiency of micronutrients, including vitamin A, B, C and E, selenium and zinc. Micronutrients are essential for several processes in the body such as growth, maintenance, protection and repair, as well (9,10,23). Moreover, micronutrients are also

involved in the response of the immune system. Deficiency of vitamins and minerals (especially zinc, selenium, vitamin E and C) in cancer patients has a negative effect on the immune defence. During cancer there is an increased need for micronutrients due to the increased amount of immune cells. The immune response is activated as a host defence against tumor cells or it is activated by the tumor to stimulate among others tumorgenesis (9). In addition, deficiency of some of the vitamins B can cause depressive symptoms. Deficiency of some micronutrients, among others vitamin A, C and E and zinc can cause a high risk of complications after surgical interventions due to a less sufficient wound healing (9).

The inflammatory environment plays a role as a contributor to the development of the tumor. In addition, inflammatory cytokines are activated as a host defence against the tumor cells. As contributor to de development of cancer, inflammation is involved in the continuous production of cytokines, chemokines, reactive oxygen species (ROS), nitrogen species, and in the activation of nuclear factor-κB (NF-κB). NF-κB is activated during infection and inflammation. Activated NF-κB is involved in cell survival, proliferation, and angiogenesis, but also regulates expression of inflammatory cytokines (10,20).

Pro-inflammatory cytokines are secreted either by the tumor or by the host in response to the presence of fast proliferating tumor cells (18,20,24). Cytokines released by tumor cells probably act only locally to promote inflammation and activate cytokine release by the host (18,20,24). Pro-inflammatory cytokines such as interleukin (IL)-1β, IL-6, tumor necrosis factor (TNF)-α and interferon (IFN)-γ, play a major role in the development of cachexia. These cytokines are involved in systemic inflammation, the control of central energy balance, the control of metabolism of muscle and adipose tissue and in the modulation of appetite (6,10,18,24).

Food intake is affected by these cytokines, through their effects on, among others, the central nervous system (CNS). They could affect taste and food aversion, hypogeusia (reduce ability to taste) and hyposmia (reduce ability to smell), early satiety, anorexia, pain, depression and anxiety (25).

Anorexia

Anorexia is defined as the decreased desire to eat and is a common issue during cancer (11,12). Anorexia is involved in disruption of central en peripheral signals that regulate eating behaviour (12). Anorexia can be caused by the release of tumor factors or host factors. Appetite is affected by many cytokines such as IL-1β, IL-6 and TNF-α. These cytokines can have an effect on the hypothalamus of the brain, that is involved in the regulation of food intake. Anorexia is associated with increased levels of IL-1β, which induces the production of hormones such as leptin and this may lead to an early satiety (6,11,25). In addition, cytokines affect neuropeptide Y (NPY) during anorexia. Inhibition of the NPY-cascade leads to a reduced appetite and food intake (25). Moreover, the cytokines, IL-6 and TNF-α can play a role in the inhibition of the NPY-cascade and stimulation of proopiomelonocortin (POMC) (9). The POMC neurons are affected by IL-1β, as well. IL-1β binds surface receptors of POMC neurons, to inhibit food intake (26). POMC is a polypeptide hormone precursor that can be cleaved to peptides, which are involved in energy homeostatis, melanocyte stimulation and immune modulation. During anorexia there is an imbalance between NPY and POMC. This imbalance affects, among others, resting energy expenditure (REE). NPY decreases REE, while POMC stimulates REE (11). Anorexia may also be aggravated by taste and food aversions, depression or anxiety (25).

Taste changes

Taste changes might cause food aversion and reduction of food intake. Aversions of food containing high amount of proteins, coffee, tea, citrus fruit and chocolate are frequently observed in cancer patients (22). These taste change during cancer cachexia is suggested to be caused by a zinc deficiency or by amino-like substances secreted by tumor cells. In addition, taste changes are often caused by the chemotherapeutic treatment of the patients, this will be explained later (22). Moreover, changes of taste negatively affect quality of life (QoL), probably due to the lack of interest and pleasure during dining, since food plays a major role in social activities (22).

Depression and anxiety

Patients reporting taste changes and anorexia have a higher change of depression (22,27,28). Depression leads to among others, alterations in appetite, sleep and fatigue. Moreover, 85% of the patients with depression exhibit symptoms of anxiety (28). Depression is caused by a decreased circulation of monoamine (e.g. noradrenaline, dopamine and serotonin) concentrations (29). Increased expression of IL-1 is associated with depression in cancer patients and this correlates with changed serotonin concentrations and difference in metabolism (25).

Neuroendocrine factors

Neuroendocrine factors are also affected by malnutrition and cachexia. An alteration in the ratio of catabolic and anabolic hormones may influence the development of malnutrition. An increase in this ratio can induce an elevated catabolisc state and a failure to accumulate lean body mass (10). Mediators involved in anabolism of skeletal muscles are insulin, glucagon, growth hormone and testosterone. Mediators involved in catabolism are cortisol and myostatin (6). Cancer patients often have insulin-resistance, growth hormone resistance, and increased expression of cortisol en myostatin (18). There is a link between systemic inflammation and insulin resistance. IL-6 expression is associated with insulin resistance, and TNF-α causes phosphorylation of the insulin-receptor substrate in skeletal muscle that alters insulin signal transduction (18). Furthermore, in 50% of the cachectic patients, insulin-like growth factor 1 (IGF-1) is downregulated in the muscles. IGF-1 can have effects on muscle anabolism (26). IGF-1 is also able to stimulate cell proliferation and differentiation and inhibits apoptosis (3).

Chemotherapy

Anti-cancer therapies could affect the food intake of patients. Actually, it were the adverse effects of chemotherapeutic agents causing the reduced food intake. Most common adverse effects of chemotherapy are anorexia, early satiety, altered taste and smell, food aversions, xerostomia (dry mouth), nausea and vomiting, mucositis, constipation, and diarrhoea but it can also cause abdominal cramping and bloating (swelling), paralytic ileus and malabsorption (22).

Food taste and smell are affected by chemotherapy, since it affects fast proliferating cells. Taste receptors located in the tongue, have a life span of approximately 10 days (22), hence these receptors will be destroyed by chemotherapy and this will lead to changes of taste. Alterations of taste includes, metallic food taste, food taste like cardboard or sandpaper, food is too salty, sweet, sour or bitter, or patients encounter loss of taste (22). Taste changes occur during chemotherapy administration and can least for a few hours to several days, weeks or months (6,22). Chemotherapeutic agents such as carboplatin, cisplatin, cyclophosphamide, doxorubicin, 5-fluorouracil, levamisole, methotrexate and paclitaxel are most commonly associated with taste alterations (22). Due to the altered taste patient can develop food aversion which lead to a reduced food intake and a decreased QoL (6,22).

Lean body mass

Cytokines induce the release of hormones that regulates early satiety such as cholecystokinin, glucagon, insulin and leptin. Alongside, cytokines are involved in metabolic changes including alteration in lipid, carbohydrate and amino-acid metabolism (e.g. lipolysis and skeletal muscle protein breakdown). These changes are associated with anorexia and are also contributors for the development of cachexia (25).

Cachexia is characterized by progressive loss of body weight. Loss of weight during cachexia is due to depletion of both adipose tissue and skeletal muscle mass. Total body mass is the lean body mass together with adipose tissue (Figure 2). Lean body mass is the fat-free mass in the body and contains total body protein, including skeletal muscles and organs (e.g. metabolic tissue such as liver and kidney), intracellular water, extracellular water, bone tissue and skin (8,17,30). So depletion of skeletal muscles will cause depletion of lean body mass (21).
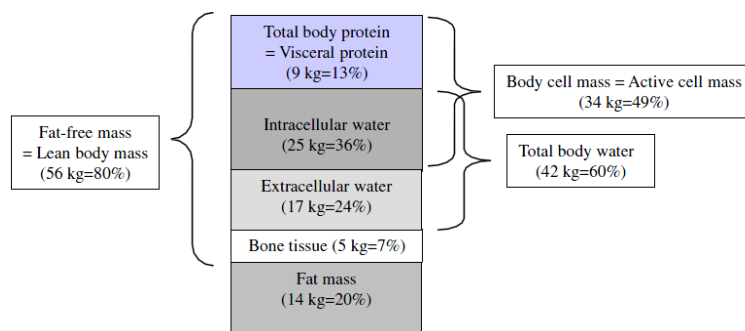

Figure 2: The total body mass is consists of the lean body mass and the fat mass.

Resting energy expenditure

Besides a reduced food intake (i.e. anorexia), altered metabolism is also a contributor for the development of cachexia. In most cancer patients the resting energy expenditure (REE) is increased, whereas the total energy expenditure (TEE) remains unchanged or is decreased (6,10,18). A stable energy balance indicates that the energy intake is equal to the TEE. The energy intake is characterised by the macronutrient composition. TEE is divided into REE; this is the amount of energy expenditure needed to support basic physiological processes, thermic effect of food (TEF), and activity energy expenditure (AEE) (31). REE is determined by the type of tumor and patient characteristics (10,11,18). Long-term hypermetabolism during cachexia negatively effects the energy balance and induces wasting, when it is not compensated by increased energy intake. A negative energy balance leads to progressive weight loss (31). Most likely REE increases due to an imbalance between the pro-inflammatory cytokines (e.g. IL-1β, IL-6, TNF-α and IFN-γ) and the anti-inflammatory cytokines (e.g. IL-4, IL-12 and IL-15) (14). REE is associated with a changed carbohydrate metabolism. In cancer patients, turnover and production of glucose by the liver is increased (gluconeogenesis), this is caused by hypoxia, which is a common feature during cancer. However, this activates an energy-inefficient process (anaerobe glycolysis) that converts glucose into pyruvate when oxygen is limited. This process needs approximately 40 times more glucose than the tricarboxylic acid cycle (11). Moreover, due to insulin-resistance, the uptake of glucose by the muscles is decreased. Lack of glucose in the muscles will lead to oxidation of amino acids and will then lead to loss of lean body mass (11,18). Accordingly, the amino acid levels present in plasma will decrease. Generally, the amount of arginine, valine and leucine are decreased, while the amount of tryptophan is even increased (15).

Skeletal muscle mass

Proteins are needed for structural and functional properties in the body. In healthy persons, during fasting, muscle amino acids and some visceral proteins are used for neo-glycogenesis, while the protein catabolism is slowly decreased and lean body mass is preserved. However, during cancer, proteins for the synthesis of skeletal muscles and internal organs are used as energy source, leading to muscle atrophy and depletion of lean body mass (6,10,11). This process includes an increased protein turnover, reduction in muscle protein synthesis and an increase in hepatic protein synthesis (6).

Proteolysis-inducing factor

Increased protein turnover, skeletal muscle wasting and weight loss might be induced by proteolysis-inducing factor (PIF) (9,10). PIF is a glycoprotein, which binds to specific membrane receptors on skeletal muscles and liver, while these receptors are absent in kidney and adipose tissues (32). In addition, PIF is able to activate the enzyme phospholipase A_2 in muscle cells, which leads to increased levels of arachidonic acid (AA) in the cell membrane. Transformation of AA to 15-hydroxyeicosatetraenic acid by 15-lipogenase causes the formation of reactive oxygen species (ROS). ROS induces NF-κB expression that leads to the activation of the ubiquitin-proteasome system (9). Multiple ubiquitin molecules are covalently attached to the proteins in muscle cells. These tagged proteins are recognised and degraded by attachment of a polyubiquitin chain (14,18). A correlation can be observed between the amount of PIF secreted in the urine and the amount of weight loss, because PIF is produced by tumor cells and is rapidly eliminated in the urine (6,10,32). In addition, PIF also activates NF-κB that results in production of IL-6 and TNF-α. These cytokines induce also the ubiquitin-proteasome system (32).

Acute phase protein - response

The proteolysis of proteins to amino acids and small peptides by the ubiquitin-proteasome system is a rapid and effective method. The amino acids are converted by the liver to acute phase proteins (APPs) (33). The APP-response is an important factor in the process of cancer cachexia. During cachexia, APP-response is associated with hypermetabolism, anorexia, accelerated weight loss and poor survival (10,18). APPs are blood proteins that are synthesised in the liver after stimulation of inflammatory cytokines, such as IL-1β, IL-8 and TNF-α, but the APP-response is primarily activated by IL-6 (11,18). An APP-response comprise a complex series of reactions induced to prevent tissue damage (6,18,34), however, the precise mechanism is unknown yet. It may be that there is an mismatch in the amino acid composition between proteins synthesized in the liver and those broken down in muscles, which leads to further depletion of amino acid reserves and skeletal muscles (18).

Positive APPs such as C-reactive protein (CRP) and mannose-binding protein are increased after inflammatory stimuli (6,11,18). CRP is related to bacterial opsonisation and a correlation is found between IL-6 and CRP concentrations (18). Circulating concentrations of CRP are associated with progressive nutritional decline, systemic inflammation and can be used as a prognostic factor. Therefore, in a clinical setting CRP levels are often used to measure inflammation and for predicting survival of a patient and predicting response to chemotherapy (18,20,34). Presence of inflammation is often indicated with CRP levels above 10 mg/L.

The APP-response during cachexia, changes the protein synthesis of the liver. Because of this the synthesis of albumin is shifted to APPs such as CRP. Albumin is a negative APP. Albumin is a blood protein and plays a role in binding and transporting of hormones, fatty acids, ions and drugs in the bloodstream. Decreased synthesis of albumin could develop hypoalbuminaemia (levels below 35 g/L) (11,18). Hypoalbuminaemia is associated with increased mortality and morbidity. Drugs normally bound to albumin, will be free in the plasma during hypoalbuminaemia, which will lead to higher drug levels. Accordingly,

chemotherapeutic agents which are meanly bound to albumin might have a greater risk of severe toxicity during hypoalbuminaemia.

The Glasgow Prognostic Score (GPS) is an inflammation-based score, using CRP and albumin levels. Patients with elevated CRP levels (>10 mg/L) and/or hypoalbuminaemia (<35 g/L) have high GPS scores. Patients with high score have a significantly greater risk of reduced survival in comparison with patients with lower scores (20). Furthermore, GPS could reflect nutritional status of patients.

Adipose tissue

Lipid-mobilising factor

During cachexia loss of adipose tissue is caused due to an increased lipolysis, turnover of glycerol and free fatty acid, oxidation of fatty acids, mobilisation of peripheral fat, decreased lipogenesis and depletion of fat stores (6,10,11,14,32). Lipid-mobilising factor (LMF) is secreted by cachexia-inducing tumors (9,18) and causes increased lipid mobilisation and stimulates loss of body fat by an increased metabolism (10,18). LMF together with zinc α-glycoprotein (ZAG) activate the hormone-sensitive lipase, which leads to hydrolytic release of fatty acids from the adipocytes (9). LMF also upregulates uncoupling proteins (UCP) in adipose tissue, skeletal muscle and liver. UCPs are mitochondrial membrane proteins that medicate proton leakage and stimulation of heat instead of ATP (14,18). Lipolysis is also stimulated by TNF-α by activation of NF-κB which stimulates the lipoprotein lipase activity (32).

Leptin

Factors derived from adipose tissue are adipokines. Adipokines have humoral functions and regulates, among others, metabolism, food intake, and inflammation. Due to the inflammation related to cachexia, expression of among others leptin and adiponectin are impaired (24). Leptin is an adipocytokine because it is produced by adipose tissue and acts like a cytokine (26). When adipose tissue is decreased, the concentration of leptin is decreased, as well (10,11). Leptin is associated with cachexia by the induction of anorexia and wasting. Moreover, leptin induces muscle catabolism. In addition, leptin acts on a hormone in the hypothalamus of the brain and inhibits appetite by inhibiting NPY and anandamide and stimulates the synthesis of hypothalamic melanocortin (α-MSH; a product of POMC) (11,26). α-MSH induce anorexia by activating two melanocortin receptors, Mc3r and Mc4r. Increased melanocortin signalling has been associated with anorexia (11).

III. Effect of malnutrition on chemotherapy tolerance and efficacy

It was found that weight loss due to malnutrition affected the outcome of chemotherapy in cancer patients. Dewys *et al.* investigated the prognostic effect of weight loss on response to chemotherapy and survival for several tumor types. The study described that for each tumor type, survival was shorter in patients with weight loss compared to patients without weight loss (35). Ross *et al.* investigated malnutrition in non-small-cell lung carcinoma (NSCLC) patients. They found an association with weight loss in these patients and an increased toxicity (e.g. anaemia). Fewer cycles of chemotherapy were delivered and more treatment delays were reported. Patients with weight stabilisation during treatment had a better progression-free and overall survival (36).

Most chemotherapies have a very narrow therapeutic window. The therapeutic window is the range of drug dosages between drug toxicity and suboptimal therapy. In addition, chemotherapy is used long-term and often in combination with other cytotoxic drugs. Therefore, a change in pharmacokinetics can cause inefficacy or severe toxicity of the chemotherapy (37-39). Moreover, pharmacokinetics of chemotherapies are affected by malnutrition or cachexia. On that account it is important to investigate patients characteristics, for example the state of malnutrition, the amount of weight loss, amount of lean body mass and concentration CRP. These characteristics might be used to adjust, among others, the dose of chemotherapy for these patients (30).

The distribution of anti-cancer drugs depends on absorption, distribution, metabolism and elimination. These four pharmacokinetic processes are essential for the dose calculation. Absorption is important for oral drugs, intravenously administrated drugs have a complete bioavailability. The bioavailability of oral drugs is affected by the absorption of the intestinal and the first-pass effect (39,40). Distribution is depending of the drug-drug and drug-protein interaction in the body. Drug can bind to plasma proteins such as albumin and α1-acid glycoprotein. These plasma proteins transport the drug to their targets (37,39). Most anticancer drugs are metabolized in the liver, by for example cytochrome P450 (CYP-450) enzymes (38,39,41). CYP-450 enzymes comprising a large family of related but distinct enzymes. These enzymes differ from each other, in for example, amino acid sequence and in the specificity of the reactions that they catalyse. CYP-450 enzymes can catalyse oxidation, reduction or hydrolysis of drugs. The oxidation-reaction requires molecular oxygen and nicotinamide-adenine-dinucleotide-phosphate (NADPH). After this reaction, the drug is more susceptible for conjugation with a substituent group. This conjugate is mostly pharmacologically inactive and less lipid-soluble. However, some oral administrated drugs are prodrugs, CYP-450 enzymes metabolise these compounds for activation of these drugs (38). The drugs are mainly excreted through the biliary tract and the kidneys. Anthracyclines, taxanes and vinca alkaloids are mainly excreted through the biliary tract, while methotrexate, carboplatin, bleomycin, etoposide and capecitabine are mainly excreted by renal filtration (39,40).

Absorption

Absorption of some orally administrated drugs is affected in presence or absence of food in the GI-tract. Food intake slows gastric emptying, raises the pH, increases hepatic blood flow, decreases surface area available for absorption and prolongs GI-transit times (37,38). Some anti-neoplastic drugs (e.g. methotrexate and 6-mercaptopurine) should be given in a fasting state, since the absorption of these drugs is better (37). Moreover, absorption can also be affected by the tumor in the GI-tract or anticancer therapy of the GI-tract. The tumor can cause obstruction of the GI-tract, while chemotherapy could cause, for example, esophagitis (dumping syndrome) or mucositis (inflammation of mucous membranes in the GI-tract) (42,43).

Distribution

Distribution of the chemotherapy is also affected by malnutrition. Malnutrition causes reduced hepatic protein synthesis (40). Inflammation during cachexia activates APP-response, this causes increased production of CRP, lactate dehydrogenase and α1-acid glycoprotein and decreased levels of albumin (i.e. hypoalbuminemia). Low albumin levels correlates with higher toxicity of the drugs, due to more unbounded drugs in the plasma (20,37,39-41,44). Patients that were malnourished and had hypoalbuminemia developed more chemotherapy-induced toxicity. Hypoalbuminemia was associated with anemia, fatigue and appetite loss (45). The chemotherapeutic agents, including prednisolone, etoposide, teniposide, cisplatin, and paclitaxel, have a very high drug-protein binding. Due to low albumin levels, these therapies can be more toxic because more unbound cytotoxic drugs is present in the circulation (37,45).

The size of lean and fat compartments is related to the pharmacokinetic properties of a drug (30,46). The volume of distribution is the ratio between the amount of drug in the body and the concentration of the drug measured in blood or plasma. Higher volume distribution indicates extensive distribution and tissue binding (40). Hydrophilic drugs, are mainly distributed to lean body masses. While, lipophilic drugs are mainly distributed to adipose tissue (21,30,46). During cancer-associated malnutrition the body composition may be changed by for instance, decreased skeletal muscle mass and lean body mass (40). Since dose of most chemotherapeutic agents is based on body surface area (BSA; depending on height and weight), the changed body composition is not taken into account. Most of the chemotherapeutics are distributed to the lean body mass, therefore, changes of body composition a factor of concern (21,30,47). Patients with the same BSA could have a different lean body mass (21). Decreased lean body mass could indicate a smaller volume of distribution of hydrophilic chemotherapeutics, lower capacity for metabolism and clearance that leads to enhanced toxicity. Patients with a decreased lean body mass behave as if overdosed (21). Effects of dose-limiting toxicity include treatment delays and definitive termination of treatment (21). There is a growing evidence to suggest that lean body mass may be a better factor for normalizing doses of anti-cancer drugs that are distributed and metabolized in the lean body mass compartment (30,46). Prado *et al.* investigated the relation between lean body mass, liver size, and liver function and the drug epirubicin. They found that decreased lean body mass could be associated with greater incidence of toxicity (46). Furthermore, 5-fluorouracl is relatively hydrophilic and is distributed and metabolized in the lean body mass compartment. Patients experienced more toxicity of 5-fluorouracl when lean body mass was decreased relative to BSA (30).

Metabolism

The liver is responsible for the metabolism of most of the chemotherapeutics. Each drug has a specific biotransformation pathway with membrane-bound enzymes. Liver metabolism is related to organ size/volume, drug-metabolizing enzyme activity and liver blood flow. The liver size is influenced by variety of factors in patients with cancer including, age, chronic malnutrition, liver disease, liver dysfunction (i.e. steatosis), surgical resection and hepatomegaly caused by infection, inflammation or metastases (46). Nutritional status can influence the hepatic blood flow and hepatic metabolism (37,39,40). The CYP-450 enzymes, present in the liver could affected by nutritional status. Some CYP-450 enzymes are suppressed by depletion of NADPH reserves that may occur during malnutrition. Thus the activity of some CYP-450 enzymes is decreased, which could lead to decreased metabolism and clearance of drugs that in turn may lead to increased toxicities or drug inactivity. Moreover, patients with high levels of CRP (level: >10 mg/l), are associated with a decreased metabolic activity (20,41). When clearance is decreased, half-life of a drug is increased. This will lead to high concentrations of the drug, which will affect efficacy and toxicity (37). Examples of drugs mainly cleared by hepatic elimination are vinorelbine and fluorouracil (39).

Excretion

Not only the liver is affected by cachexia but also the kidneys, resulting for example in a reduced glomerular filtration rate (GFR). This affects especially the clearance of carboplatin and methotrexate, because these drugs are mainly eliminated by the kidneys. Due to reduced GFR the half-life of the drugs will increase, and this will lead to longer exposure of the body to the drugs and may cause more toxicity (37,40).

IV.   Reduced drug dosage versus nutritional intervention

Patients with cancer often encounter weight loss at the time of diagnosis and during chemotherapy. The adherence of these patients to chemotherapy treatment might be affected, due to chemo-induced toxicity, which can lead to reduced chemotherapeutic dosage (36,48), treatment delays and possibly a definitive termination of treatment (21,46).

It is important to avoid dose-limiting-toxicity of chemotherapy, because delay or termination of the treatment can give the tumor a new opportunity to grow, which might lead to an increased mortality. Side effects of chemotherapy, such as toxicity can cause symptoms such as nausea, vomiting and diarrhoea. This affects the mucous membrane (e.g. stomatitis and enteritis) and central nervous system (e.g. anorexia) (13). These side effects can lead to a reduced food intake and further weight loss, as well as to a reduced tolerance to chemotherapy.

As mentioned previously, the dosage of chemotherapy could be decreased to reduce toxicity. The dose should be adjusted in accordance to several factors, including systemic inflammation (CRP and albumin levels) and body composition (30). However, due to the narrow therapeutic window of chemotherapeutic agents, a decreased dosage could reduce the effectiveness of the chemotherapy. Therefore, nutritional intervention, to improve nutritional status and reduce systemic inflammation in patients, may be a better approach to support optimal treatment and reduce toxicity.

In cachectic patients an altered liver function may affect the chemotherapy-induced toxicity. Some drugs need to be metabolized in the liver to become active, less toxic or cleared. Due to malnutrition CYP-450 enzymes can be suppressed, slowing the metabolism of cytotoxic drugs and increasing the half-life of these drugs (20,41). This may lead to toxicity or ineffectiveness of the chemotherapeutic agent. To speculate on this matter, it is unlikely that lowering chemotherapeutic dosage will affect the function of the CYP-450 enzymes. Therefore, metabolism of the drugs would not be affected. In addition, by lowering chemotherapeutic dosage, toxicity might reduce but it could also negatively affect effectiveness of these drugs. However, with nutritional support it could be possible to improve liver function and improve CYP-450 function, which may lead to improved effectiveness of the chemotherapy and reduced toxicity.

Besides decreased CYP-450 enzyme function, albumin concentrations can also be decreased during malnutrition. Due to increased APP synthesis during cachexia, albumin synthesis is reduced (20,39,40). Speculatively, nutritional support may inhibit the APP-response whereby the albumin synthesis could be increased. Some nutrients have already shown to improve albumin levels, this will be explained later in this thesis. Increased albumin leads to more albumin-drug interactions and less unbound drugs, which may reduce the toxicity of the unbound drugs. Reducing the chemotherapeutic dosage may reduce toxicity of the unbound drugs, but the transport to the target cells is still reduced, whereby the efficacy of the chemotherapy is not improved. As well, reducing the chemotherapeutic dosage may negatively affect efficacy of the therapy due to the small therapeutic window.

In these examples decreasing the dosage of chemotherapeutic agents will not improve effectiveness of these agents. Thus, reducing the total dose of chemotherapy is not always the best solution to increase chemotherapy tolerance of patients. For cachectic patients it is important to reduce further weight loss and decrease inflammation. To reduce the inflammation and the APP-response, patients could be treated with nonsteroidal anti-inflammatory drugs (NSAIDs). The three main therapeutic effects of NSAIDs are anti-inflammatory, analgesic (reduction of mild or morderate pain) and antipyretic (lowering body temperature). Besides these effects NSAIDs could induce side

effects such as gastric irritation, effect on renal blood flow and prolonged bleeding by inhibition of platelet function. Nevertheless, the use of NSAIDs is out of the scope of this thesis.

Moreover, nutritional support may additionally improve nutritional status, reduce systemic inflammation, improve liver and kidney function (e.g. higher albumin levels and improved CYP-450 enzyme function) and may stabilize or increase the lean body mass and/or body weight (10,44). Due to among others an improved liver and kidney function, toxicity of chemotherapy might be reduced while effectiveness of chemotherapy could be increased. For that reason, nutritional support should be part of the routine treatment of cancer patients with malnutrition. The anti-cancer therapy together with nutritional support might reduce tumor growth and improve clinical outcomes, decrease complications of the disease and the treatment and increase the quality of life of the patient (15,42). The aim of nutritional support should be the prevention or reversal of malnutrition, thereby improving the adherence of the treatment, eventually leading to reduced progression of the disease and finally improving quality of life for the patient (15).

V. Nutritional intervention

Options for nutritional support

There are different possibilities to improve nutritional status. Firstly, dietetic advice should be considered as long as oral feeding is possible. When patients cannot meet their nutritional requirements with normal food alone, oral nutritional supplements can increase nutrient intake of the patients. Enteral tube feeding is for patients who are unable to meet their nutrients requirements with oral intake. Finally, a more rarely applied intervention is parenteral nutrition for patients who are not able to meet their nutrient requirements with oral nutritional supplements or enteral tube feeding (13,15,42).

Dietetic advice

Dietary counselling is aimed to improve the food intake of patients with cancer via normal foods, to circumvent that patients become malnourished. Therefore, early nutritional intervention is necessary (15). For cachectic cancer patients, it is important to take frequent and small meals and to avoid negative consequences of anorexia. Then nutritional intake should be increased to slow down the muscle and fat wasting (33). Even when no nutritional problems are identified in patients with cancer, it is important to have a good nutritional status, for example to undergo anti-cancer therapies (15). Late intervention in malnourished patients may only prevent further decline of nutritional status rather than reverse malnutrition (10).

Oral nutritional supplementation

Oral nutritional supplements (ONS) are applied to avoid nutrient deficiency when patients are not able to meet their nutritional requirements despite dietetic advice (15). ONS enhances the nutritional intake of the patients and may have benefits such as increased appetite and weight gain, increased energy and protein intake, decreased GI-toxicity, increased immune response and improved performance status, depending on the specific nutrients that were added (13,15). ONS should contain adequate amounts of all nutrients including, protein, energy, vitamins, and minerals but also fibres. Effectiveness of ONS depends on sufficient intake by the patient over an extended period of time. Patient intake is affected by the flavour, texture and volume of the ONS (15). ONS are often ready to use products with a high caloric density, small volume and optimized taste in order to support patient compliance (13).

Enteral tube feeding

Patients who are unable to meet their nutrient requirements with dietetic advice and ONS can choose for enteral tube feeding (15), but the GI-tract function should still be adequate (10). Reasons for the use of tube feeding could be the incapacity or limited ability to swallow or ingest food, due to dysphagia, upper GI-tract obstruction or central nervous system pathology. Enteral tube feeding is also used when patients suffer from increased nutritional losses due to impaired digestion or absorption (15). Patients often suffer from stomatis or vomiting, whereby patients are unable to meet their nutritional needs via oral food intake (33). During enteral tube feeding, intake of nutrients and calories is occurs via a tube, that can be is placed in the stomach or duodenum. Obviously, this is only feasible if the GI-tract function is adequate (10,13). Enteral tube feeding can lead to an increased appetite, increased energy and protein intake, improved nutritional status, but also reduced GI-toxicity during chemotherapy, improved treatment tolerance and immune function, as well as an increased quality of life (13,15).

Parenteral nutrition

Parenteral nutrition is rarely used in cancer patients, because it negatively affects clinical outcome, and may cause other problems such as infectious complications and sepsis. However, parenteral nutrition is indicated when oral intake and enteral tube feeding is physically impossible. This may occur in case of stomach or bowel dysfunction or after surgery when parts of the GI-tract are removed. During parenteral nutrition administration of nutrients is applied via an intravenous catheter (13,15,33).

Specific ingredients for nutritional support

The energy requirements differ per patient. They depend on the degree of malnutrition and metabolic stress, energy losses and the level of physical activity. Therefore, nutritional support should be determined on individual needs (15). Nutritional support should be personalised to individual nutrition requirements. For this the nutritional status, dietary restrictions, GI-function, tolerance and feasibility, and medical conditions, expected treatment and side effect are to be taken into account (15).

Individual nutritional requirements can be calculated using for example the Harris-Benedict (Equation 1) or Schofield equation (Equation 2) (15). Overall nutrient intake should include 20% protein (1.2-2 g/kg/day), 20% fats and 50-60% carbohydrates (13). Malnutrition causes an increased body protein turnover, increased skeletal muscle breakdown and decreased synthesis, which leads to muscle wasting. Adequate dietary intake of proteins is necessary. The same applies for carbohydrates and fat that are important sources of energy. Fat is a concentrated form of energy, containing among others essential fatty acids and fat soluble vitamins (15).

Equation 1: Harris and Benedict equation (15)
$$Males\ BMR\ (kJ/Day) = (57.5 \times W) + (20.9 \times H) - (28.3 \times A) + 278$$
$$Females\ BMR\ (kJ/Day) = (40.0 \times W) + (7.7 \times H) - (19.6 \times A) + 2.741$$
BMR= Basal metabolic rate; W = Body Weight (kg); H= Height (cm); A= Age (years); kJ= Kilojoules

Equation 2: Schofield equation (15)
$$Males\ (30-60\ years)\ BMR\ (MJ/Day) = (0.048 \times W) + 3.653$$
$$Males\ (over\ 60\ years)\ BMR\ (MJ/Day) = (0.034 \times W) + 3.538$$
$$Females\ (30-60\ years)\ BMR\ (MJ/Day) = (0.049 \times W) + 2.459$$
$$Females\ (over\ 60\ years)\ BMR\ (MJ/Day) = (0.038 \times W) + 2.755$$
BMR= Basal metabolic rate; W = Body Weight (kg); H= Height (cm); A= Age (years); mJ= Megajoules

Inflammation is a key component for the development of cachexia and negatively affects the survival of patients. Therefore it is important to use anti-inflammatory nutrients to reduce the cancer cachexia syndrome (42,44,49). In addition, it is important to support the immune system with nutrients that provide specific benefits (49). Relevant nutrients in this regard are polyunsaturated fatty acids (PUFA), galactooligosaccharide (GOS) and fructooligosaccharide (FOS), glutamine, arginine, nucleotides, and micronutrients such as vitamin E, vitamin C and β-carotene, zinc and selenium (42,49,50). Potential targets for these nutrients are the mucosal barrier function, cellular defence and/or the local or systemic inflammatory response (49,50). The mucosal barrier function is the first line of defence against pathogens. During the disease it is important to maintain the structure and functionality of the mucosal barrier. Cellular defence is the second line defence against pathogens, consisting of granulocytes, macrophages, lymphocytes and plasma cells. Activation of these effector cells is coordinated by the release of cytokines and other mediators. The third target is the systemic inflammatory response. During systemic inflammation, inflammatory mediators, such as pro-inflammatory cytokines (e.g. IL-1β, IL-6, TNF-α and IFN-γ), APPs (e.g. CRP), blood leucocytes and neutrophils are released in the circulation. Besides the blood flow is increased and the vascular permeability is

induced, therefore the migration of molecules from the circulation to the tissue can increased. This affects the endothelium, the smooth vascular and bronchial muscles, and platelet aggregation, and therefore it may affect organ function (50).

Polyunsaturated fatty acids

Polyunsaturated fatty acids (PUFAs) are described to be potent modulators of the immune system (13,19,51,52). Two relevant types of PUFAs are omega (ω)-3 fatty acids and ω-6 fatty acid, with eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) as the main ω-3 fatty acids. An essential ω-3 fatty acid is α-linolenic acid, because humans cannot synthesise this fatty acid it must be obtained by their diets. EPA and DHA can be synthesised in the body, by chain extension and desaturation of α-linolenic acid (51). However, this process is insufficient and slow, therefore, it could be beneficial to obtain EPA and DHA directly from the diet. High amounts of ω-3 fatty acids can be found in fish (e.g. sardines, salmon, mackerel, and herring) and fish oils (53,54). Both EPA and DHA can have beneficial effects on the immune system and on the inflammatory response (13,19).

Anti-inflammatory properties of EPA are related to down-regulation of pro-inflammatory cytokines such as IL-1β, IL-6 and TNF-α (10,13,15,50). Because of a decreased IL-6 production, EPA might lead to a decreased APP-response (55). EPA has an anti-inflammatory effect via several pathways, including inhibition of cyclooxygenase (COX) activity, production of novel anti-inflammatory lipid mediators (including, resolvins, protectins and maresins), alteration of membrane dynamics and increased cellular oxidative stress (19,51). Dietary fatty acids can incorporate into the phospholipid of the cell membrane and alter the activity and affinity of receptors, membrane fluidity and transport properties (19,50,53). Changes of fluidity of the cell membrane and binding of cytokines and cytokine-inducing agonist to receptors can be changed by altering the membrane PUFA composition. In addition, incorporation of ω-3 fatty acids into cell phospholipid membranes, influences the synthesis of lipid-derived mediators such as eicosanoids, phosphatidic acid, and platelet-activating factor. The enzyme phospholipase A_2 releases PUFAs from the membrane phospholipids and these can act as precursor for the COX-pathway (50). ω-3 fatty acids are substrates for the synthesis of prostaglandin (PG)-E3, an anti-tumorigenic PG, instead of the pro-tumorigenic and pro-inflammatory PG, PG-E2 (51,53,56). Besides, ω-3 fatty acids can have anti-tumor effects by inhibition of tumor cell proliferation, increasing tumor cell apoptosis, stimulating cell differentiation, reducing tumor angiogenesis and modulating tumor-extracellular matrix interaction (53).

Besides the anti-inflammatory properties, is EPA involved in reduced weight and protein loss. EPA administration is associated with an increased lean body mass. EPA reduces the effects of LMF and PIF. In addition EPA prevents NF-κB accumulation and reduced ubiquitin-proteasome system. Due to this muscle wasting is reduced (10,13,15,50,55,57).

Branched amino acids

Cachectic cancer patients who experience weight loss can benefit from high-energy and high-protein supplements. An example is a combination of the ω-3 fatty acid (e.g. EPA), and amino acids, including branched amino acids (BCAAs) (11,23,33). This combination may reduce muscle wasting and stimulate the synthesis of new muscles. EPA does not affects the decreased synthesis of muscles and for that reason BCAA can be added (11). BCAAs (leucine, isoleucine and valine) are precursors of glutamine and alanine and are regulators of protein synthesis and degradation, and a source of energy for muscles and other tissues (13). BCAAs are also able to improve albumin synthesis and they may also reduce anorexia, by inhibiting the transport of tryptophan across the blood-brain barrier (23). Catabolism of leucine, one of the BCAAs, generate β-hydroxy-β-methyl butyrate, which may reduce cachexia by modifying NF-κB expression. Leucine in combination with high protein stimulate muscle protein synthesis (23).

Galactooligosaccharide/Fructooligosaccharide

Prebiotic oligosaccharides such as galactooligosaccharide (GOS) and fructooligosaccharide (FOS) have shown to have immune-modulating activities . These oligosaccharides have been associated with improved gut barrier function. It stimulates bifidobactera, lactobacilli and other healthy bacteria, while it reduces harmful bacteria in the gut. In addition, the oligosaccharides are fermented by colonic microbiota and during this process intestinal lactate and short-chain fatty acids (SCFA; e.g. butyrate, acetate and propionate) are formed. Because of this pH is reduced in the intestinal lumen, which may lead to inhibition of pathogen growth and adhesion (53,58,59). Thus GOS/FOS could have a beneficial effect in cancer patients by stimulating the growth of beneficial bacteria, including bifidobactera and lactobacilli, and reducing the pH in the intestinal lumen and therefore the immune response may be improve. Moreover, these oligosaccharides may block or activate specific receptors on immune cells leading to improve immune responses that may lead to enhanced resistance to systemic infection (58). Supplements containing GOS/FOS could be beneficial for patients treated with chemotherapy, this will be explained in more detail later in this thesis.

Glutamine

BCCAs are essential donors of nitrogen needed for the synthesis of glutamine and alanine in skeletal muscles. Glutamine is an important nutrient for many cell types, and is a precursor for the synthesis of other amino acids, such as purines, pyrimidines and glutathione (GSH). Glutamine is a non-essential amino acid. Glutamine is released from the muscle cells during stress and injury to provide energy to the host organism. However, it is a source of energy and nitrogen for rapidly dividing cells of for example the immune system (49,50). Glutamine is released to increase T and B cell function, and protects cells against apoptosis (49). In addition glutamine is the primary fuel for the GI-epithelium and it is essential for maintenance of the gut mucosal structure (60). Therefore, this could be an essential nutrient during chemotherapy, as explained later in this thesis.

During among others cancer a deficiency of this amino acid can occur, which leads to reduced immune function of the host, affects intestinal mucous membrane and protein-energy metabolism (13,23,49,50,60).

Supplementation of glutamine in cancer patients showed to induce the cytotoxic activity of natural killer cells and lymphocyte-activated killer cells and the proliferation and function of lymphocyte and macrophages. Lymphocytes use glutamine as a primary fuel source. Natural killer cells optimal function is depending on adequate supplies of glutamine and GSH. During cancer, glutamine supplementation may cause storages of GSH in the hepatic and intestinal mucosal. GSH in the gut is involved in the detoxification of reactive oxygen species (ROS) and pro-oxidative nutrients (50,60). During cachexia, supplementation of glutamine can improve protein metabolism by decreasing the protein breakdown and increasing protein synthesis in gut mucosa and skeletal muscles (60). Due to improved immune function, GSH production and stimulated protein synthesis in cachectic cancer patients, tumor growth and further weights loss are inhibited.

Arginine

Arginine is a semi-essential amino acid, obtain from the diet and by synthesis via the urea cycle. Arginine is metabolized via the arginase-pathway to ornithine and urea (50). Arginine stimulates release of growth hormone, prolactin, insulin and anti-insulinaemic hormones (50). Moreover, it functions as a precursor for nitric oxide (NO). NO is an ubiquitous cellular messenger and is important for immune function, blood flow, platelet aggregation and memory. T-lymphocytes depend on arginine in several processes, including proliferation and expression of the TCR complex (50,61). In addition arginine may enhance natural killer activity, which inhibits tumor growth. Higher arginine levels are essential during stress, illness and malnutrition, among others to enhance the immune function by stimulation the thymus and synthesis of t-lymphocytes. Therefore,

supplementation with arginine in cancer patients could be beneficial. Arginine could potentially improve immune function, reduce infectious complication, improve wound healing and reduce tumor growth, and thereby decrease mortality (49,62).

Nucleotide

Nucleotides are necessary for the synthesis of DNA and RNA and are incorporated into important cofactors (e.g. coenzyme A and NADPH). Nucleotides are important for cells with a high turnover rate such as immune cells and cells of the GI-tract. Nucleotide synthesis needs purines and pyrimidines. Purines and pyrimidines are efficiently absorbed from the diet or generated by RNA turnover in healthy persons. In addition, glutamine is a major source of nitrogen, necessary for *de novo* synthesis of nucleotides. Insufficient dietary intake of nucleotides (e.g. purines and pyrimidines) results in suppression of IL-2 production and selective loss of T-helper lymphocyte, this leads to impaired T-cell function, weakened natural killer cell activity and suppressed lymphocyte proliferation. Moreover, insufficient nucleotides leads to genomic instability. Nucleotide intake during cancer could be beneficial, by improving immune cell function and gut microbiota, which may lead to improved digestion and absorption of food in the GI-tract (50).

Antioxidants

Some vitamins, including vitamin A, C and E, have shown to have antioxidant properties. Carotenoid such as α-, and β-carotene, lycopene, lutein, zeaxanthin and cryptoxanthin have antioxidant activities (63). These carotenoid are found in plants and are responsible for colours. Some carotenoids function as a provitamin A, when they are converted to retinal (52). Carotenoids are lipophilic because of long hydrocarbon chains with conjugated double bonds. Antioxidant activity of β-carotene is by reducing the forming of singlet oxygen and it can inhibit peroxidation of membrane lipids (52). Vitamin C (ascorbic acid) is a water soluble vitamin. Administration of vitamin C can decrease markers of oxidative stress, by scavenge radicals (63). Ascorbic acid also inhibits lipid peroxidation (52). Vitamin E is a lipid-soluble compound. The function of vitamin E is reduce lipid peroxidation and prevent oxidative damage of the DNA (63). Vitamin E is highly present in α-toxopherol. α-toxopherol protects membrane lipids by reduction of lipid peroxidation (52). These aforementioned antioxidants, reduce ROS and oxidative stress, which is beneficial for cachectic cancer patients because excess of ROS can damage cell lipids, proteins and DNA, inhibit there normal function and resulting in apoptosis. Moreover, ROS and oxidative stress induce the development of cachexia. These actions are counteracted by these antioxidants (64). Antioxidants could influence the effectiveness of chemotherapeutic agents, by scavenge ROS, as well as it could protect healthy cells against ROS, this will be explained in more detail later in this thesis.

Cysteine

During cancer cachexia glutathione levels are decreased by increased cysteine degradation. In addition, glycolytic activity and lactate production is increased during cachexia, which causes acidification of muscle cells and impaired glutathione metabolism. Administration of N-acetyl-cysteine can increase the availability of cysteine during cachexia (23). This is important to maintain the glutathione levels and the antioxidant potential of glutathione and thereby reducing oxidative activity of ROS (64). This may reduce inflammation and thus reduce synthesis of pro-inflammatory cytokine in cachectic cancer patients. Moreover, n-acetyl-cysteine may normalize the redox state and increase plasma albumin levels. Accordingly, it can improve quality of life in cancer patients (19).

Zinc

Zinc has several functions, including regulation of neurotransmitter systems, antioxidant mechanisms, neurotropic factors and neuronal precursor cells (28). Low serum zinc levels correlates with mood disorders, e.g. depression (28). Human with depression are often associated with changed food intake, and this can lead to anorexia. Zinc is also an antioxidant affecting immune function. Zinc can increase glutathione levels (28), it functions as a cofactor for the thymus hormone thymulin, which stimulates differentiation of thymocytes into active t-lymphocytes, and influence the proliferation rate of t-lymphocytes. This might improve immune system (52). In cachectic patients, supplementation of zinc could be beneficial, because of the anti-depressant activity and stimulating food intake, thereby it could reduce malnutrition (28). Moreover, stimulation of the immune system by zinc, it might reduce inflammation associated with cachexia.

Selenium

Selenium is an essential micronutrient for humans. Selenium has antioxidant activity and has the possibility to enhance immune response, suppress cell proliferation, alter metabolism of carcinogens, and induce apoptosis (65). Deficiency of selenium in the body is associated with an increased risk of several cancers, due to the effect of selenium on genomic stability (66). Selenium is mainly absorbed in the upper small intestine via active transport. Selenium is found in tissues such as muscles, liver, kidneys and spleen (52). Selenium is a component of the selenoprotein selenocysteine (SE-Cys) and seleomethionine (Se-Met) (52,63,66,67).

Selenium and selenoproteins play a role in antioxidant protection system of the human body (52,66). Because selenium is important for the formation of antioxidant enzymes, including glutathione peroxidase (GSH-Px) and thioredoxin reductase (TRs) (52,63,65-67). Due to this, selenium has the ability to scavenge ROS, while GSH-Px removes ROS (66). Moreover, selenium is necessary for TR activation. TR reduces oxidized thioredoxin, which reduces disulphide binding of several proteins such as NF-κB (65). In addition, selenium also have some anti-cancer properties, including inhibition of DNA synthesis, altering DNA methylation, inducing DNA strand breakage and inducing apoptosis (65,67). Selenium can induce apoptosis independent of DNA damage, probably by activation of p53-homologs p73 and p63 (65,66). For these reasons selenium supplementation in cachectic patients could be beneficial. Selenium can decrease tumor growth by inducing apoptosis and improve immune function by the antioxidant properties. Thereby reducing inflammation by inhibition of NF-κB and the formation of antioxidant enzymes to reduce ROS.

VI. Interactions between nutritional intervention and chemotherapy

The aforementioned nutrients are often used in nutritional intervention for cachectic patients. Since these nutrients are used in combination with chemotherapy, it is important that this combination is safe and have a possibly beneficial effect on chemotherapeutic effectiveness. Some nutrients can improve the adherence and efficacy, while others can reduce the toxicity of chemotherapeutic agents in cachectic patients. Moreover, some of these nutrients might even have a synergistic effect in combination with chemotherapy.

Polyunsaturated fatty acids

ω-3 fatty acids may have a beneficial effect in patients treated for cachexia, since they are able to inhibit the wasting of muscle cells and improves the nutritional status of the patients. In animal studies is shown that supplementation of ω-3 fatty acids before or during chemotherapy can be beneficial in decreasing tumor size, reducing side effects and prolonging survival (54).

Potential mechanisms of PUFAs to modulate the tumor cell response to chemotherapeutic agents might be the alteration of the membrane fluidity of the cells and the high susceptibility of ω-3 fatty acids to oxidation. Due to the incorporation of ω-3 fatty acids into the phospholipids of the cell membrane, the membrane fluidity of the cells is affected. These changes in the cell membranes may affect the susceptibility of tumor cells to chemotherapy. Due to the incorporation of ω-3 fatty acids, cell membranes may become more susceptible to chemotherapeutic agents, which may lead to an improved anti-tumor response (54,68). Due to increased lipid peroxidation, ω-3 fatty acids may cause irreversible tumor cell damage. Exposure of ω-3 fatty acids to free radical attack, leads to formation of lipid hydroperoxidedes. Lipid peroxidation is induced by the reaction of lipid radicals and oxygen to form a fatty acid peroxyl radical. This peroxyl radical may attack fatty acid chains in cell membranes. Thereby, inhibiting DNA synthesis, cell division and tumor growth. Some chemotherapeutic agents (e.g. doxorubicin and epirubicin) induce tumor cell death by the formation of oxygen free radicals and thereby causing irreversible cell damage. ω-3 fatty acids may have synergistic effects with these drugs, due to the peroxidizing effects (54,68).

Murphy *et al.* investigated the effect of fish oil (EPA and DHA) supplementation on chemotherapy efficacy and treatment-related toxicity. Patients with NSCLC receiving (platinum based) chemotherapy and fish oil had a significant increased response rate compared to patients receiving only chemotherapy (69). Bougnoux *et al.* investigated the efficacy, safety and anti-tumor activity of the combination DHA and ROS-generating chemotherapy regimen in breast cancer patients. They show that adverse side effects are reduced and the efficacy of chemotherapy is improved by supplementation with DHA (70).

Nevertheless, not all the studies have shown these beneficial effects. For example Miyata *et al*. concluded that nutritional intervention of ω-3 fatty acids-rich nutritional supplement via enteral nutrition during chemotherapy in esophageal cancer patients could reduce chemotherapy-related adverse events, although this combination did not improve tumor response and body weight during chemotherapy (71).

Galactooligosaccharide/Fructooligosaccharide

Faber *et al.* investigated a specific nutritional supplement, including GOS/FOS in a mouse-model of chemotherapy-induced neutropenia, colonized with *Pseudomonas aeruginosa*. Chemotherapy could suppress the immune function of a patient, which could result in higher risk of bacterial infections. Faber *et al.* found that mice with nutritional intervention, including GOS/FOS, had a significant reduction of bacterial translocation.

GOS/FOS might have played a role in modulation of the intestinal microbiota, gut barrier function, immune function and a reduced inflammatory state. The reduction of translocation of *P. aeruginosa* could indicate that GOS/FOS are beneficial for the intestinal mucosa and improving immune cell function (58). GOS/FOS have shown to stimulate the growth of beneficial bacteria such as bifidobacteria and lactobacilli, which could inhibit pathogens in the GI-tract and probably inhibit the translocation of the pathogens. Accordingly, improving patient's immune system during chemotherapy.

Glutamine

Glutamine supplementation have shown to protect the GI-tract of cancer patients against chemotherapeutic agents. Therefore, supplementation of glutamine might be beneficial during chemotherapy. Chemotherapeutic agents affect rapidly proliferating cells of the GI-tract and therefore could induce severe mucositis (i.e. intestinal mucosal damage). Accordingly, mucositis occurs, in particular, in rapidly dividing mucosal cells of the GI-tract, mouth, throat, stomach and intestines. Cells of the GI-tract have a short life span and use glutamine as an oxidative fuel source. For this reason glutamine protects rapidly proliferating cells against chemotherapeutic agents by providing energy (53,60). The use of oral glutamine was investigated by Noe *et al.* in a setup to prevent chemotherapy-induced mucositis. It was shown that mucositis was less severe in patients receiving glutamine-supplementation (60). In addition, glutamine induces the production and/or preservation of the antioxidant GSH in normal tissues, while the level of GSH in tumor cells is reduced, thereby increasing the anti-tumor effect of the chemotherapy and reducing chemotherapy-induced gut injury. It appears that glutamine makes tumor cells more sensitive for chemotherapeutic agents and enhance the selectivity of these drugs, while it also protects normal cells in healthy tissues (50,53,60).

Antioxidant

Some researchers stated that antioxidant supplementation should be avoided during chemotherapy, while others stated that under controlled circumstances antioxidant supplementation may enhance the therapeutic efficacy of chemotherapeutic agents (72). Some chemotherapeutics (e.g., taxol, cisplatin, gemcitabine, bleomycin, mitomycin C, and chloropromazin) produce free radicals (ROS). These free radicals are responsible for cellular damage and killing of malignant cells. Unfortunately, due to this fact, ROS can cause severe side effects. Antioxidants are able to neutralize these free radicals. Some known nutrients have antioxidative capacities, including vitamins A, C, and E, carotenoids, selenium and glutathione. But also enzymes could have antioxidant properties, including glutathione peroxidase (72,73). In this way, antioxidants could protect normal cells for the actions of the chemotherapy, but for the same reason, antioxidants are also able to protect tumor cells for the actions of the chemotherapy. However, most chemotherapeutic agents have elucidated mechanisms of action that are not based on the generation of free radicals. These chemotherapeutics have the ability to interrupt cell cycle progression and disrupt programmed cell death of mostly fast proliferating cells. Therefore, antioxidants could enhance anticancer activity of chemotherapeutics by reducing the toxic side effects produced by the free radicals (72,73).

Selenium

Besides the antioxidant and anti-tumor properties of selenium, it can increase the efficiency of anti-tumor drugs, as well (67,74). Although the precise mechanism is unknown, evidence might suggest that a selenium species (i.e. methylseleninic acid; MSA) induces DNA strand breaks and decreases NF-κB activity (67,74). Tumor cells stimulate the expression of NF-κB, which plays a major role in cancer development and tumor cell protection for apoptosis. Moreover, it is associated with decreased cytotoxic drug activity. Selenium in combination with a chemotherapeutic agent showed a decreased NF-κB expression, and cells were more susceptible for cytotoxic agents. In

addition, the induction of DNA damage, can lead to increased cell death (74). Because of this selenium may have a synergistic interaction with chemotherapy activity.

Branched amino acids

Due to improved nutritional status of patients receiving nutritional support, side effects of chemotherapy could be decreased, due to protection of healthy cells by the antioxidants and the increased fluidity of tumor cell membranes by PUFAs. Besides this, the distribution and clearance of the chemotherapy could be improved, due to the influence of nutritional support on hepatic protein synthesis. BCAAs supplementation may improve liver function by increased skeletal muscle synthesis and reduced protein catabolism. When proteins are insufficient available, skeletal muscles proteins are used as energy source and as amino acids for hepatic protein synthesis, thereby decreasing the amount of muscles and increased synthesis of hepatic proteins. Accordingly, supplementation of high level of proteins, such as BCCAs, provide sufficient amount of proteins for the synthesis of skeletal muscles and these BCAA can be used for the synthesis of liver proteins such as albumin. Improving skeletal muscles might improve physical activity and eventually improve quality of life of patients.

In addition, BCAA stimulates recovery of serum albumin levels. Because BCAAs are amino acids used for muscle protein metabolism and albumin synthesis (23). Albumin synthesis is also stimulated due to reduced inflammation, particularly reduction of IL-6, leading to a reduced APP-response, then the protein synthesis is shifted back for proteins such as CRP to albumin. Albumin is a transport protein for chemotherapeutics and many other factors. By increasing albumin, less free-drug is available in the body, which reduces the toxic side effect of the chemotherapy and increased the transport to target cells (37,39). Due to improved liver function, metabolism of chemotherapeutic agents will improve, which leads to reduced toxicity and/or improved response of chemotherapeutics (37,39). More studies are required to investigate potential benefits of chemotherapy in combination with nutritional intervention to improve the response to therapy in cancer patients.

VII. Discussion

Malnutrition and progressive weight loss are common features of most cancers types. Malnutrition can be caused by factors of the tumor, host response to the tumor and anti-cancer therapies. Cachexia can occur after prolonged malnutrition. It is characterized by systemic inflammation, anorexia and progressive weight loss. Synthesis of inflammatory cytokines is stimulated by the tumor but also by the host response to tumor cells. Cytokines (such as IL-1β, IL-6, TNF-α and IFN-γ) play a major role in the pathogenesis of cachexia. Several pathways are affected by cachexia, which can influence patient's response to chemotherapy. Chemotherapeutic agents might become ineffective or toxic for these patients. Nutritional intervention can improve the nutritional status of the patient. In addition, nutritional support with specific ingredients may improve immune function of the body and reduce chemotherapy-induced toxicity.

The European society for clinical nutrition and metabolism (ESPEN) and American society for parenteral and enteral nutrition (ASPEN) have made guidelines for nutritional intervention (75,76). According to the ESPEN guidelines on Enteral nutrition: Non-surgical oncology (76) and the ESPEN guidelines on Parenteral nutrition: Non-surgical oncology (75), nutrition with oral nutritional supplements and tube feeding is preferred when normal food intake is insufficient. This offers the possibility to increase or ensure nutrient intake (76). Parenteral nutrition can be used when normal food intake is insufficient and/or enteral nutrition is not possible (75). Cancer enteral nutrition by means of oral nutritional supplements (ONS) and tube feeding has been shown to reduce weight loss. A combination of anti-tumor therapy and nutritional support can therefore be beneficial for patients with advanced cancers. However, the enteral nutrition guideline does not give an indication whether nutritional intervention via enteral nutrition is beneficial to improve the tumor response to chemotherapy, due to lack of evidence (76). Parental nutrition is not recommended during chemotherapy. However, in some cases parental nutrition is better tolerated than enteral nutrition and it is recommended when gastrointestinal toxicity from chemotherapy occurs and/or enteral nutrition is not feasible. Evidence is lacking about the benefits of parental intervention in patients during chemotherapy (75).

The efficacy of nutritional intervention has been examined in systemic reviews, but benefits of nutritional intervention on clinical outcome and quality of life of cancer patients remains unclear (7). Potential reasons for the lack of evidence may be the heterogeneity of the patients during the study, high dropout rates at the end of studies, lack of patient compliance or subclinical toxicity (7,77).

Cachexia is characterized by many factors, including anorexia and inflammation, which are involved in progressive loss of body weight, loss of skeletal muscle mass and muscle weakness. The cachexia-syndrome is an important factor for morbidity and mortality during cancer. The effect of chemotherapeutic agents could also lead to or aggravate malnutrition. Despite of the current lack of evidence to reduce cancer cachexia and/or improve effectiveness of anti-cancer therapies by nutritional intervention, novel concepts of, nutritional support, e.g. combined with chemotherapeutic agents could be beneficial and may improve quality of life (6,7,10,13).

Inflammation is an important factor in cancer-cachectic patients and chemotherapeutic agents may be involved in this, as well. In addition, inflammation leads to a reduced immune function and the production of intrinsic antioxidants. Therefore, it is important to improve food intake and enhance the antioxidant levels in the body before, during and after chemotherapy (72). Inflammation can be reduced by nutrients with anti-inflammatory and anti-oxidant properties. Nutrients, including polyunsaturated ω-3 fatty acids, glutamine, arginine, vitamins A, C, and E, carotenoids, selenium, and zinc have shown to have antioxidant properties (42,49,50). In addition, ω-3 fatty acids also have shown to have anti-inflammatory properties including, down-regulation of pro-inflammatory cytokines (e.g. IL-1β, IL-6 and TNF-α), inhibition of COX-activity, production of novel anti-inflammatory lipid mediators (e.g. resolvins, protectins and

maresins), alteration of membrane dynamics and increased cellular oxidative stress (19,51). These nutrients possess several actions to improve the immune system of cancer patients and protect cells from inflammation and infections.

The dosage of the nutrients can be based on the recommended dietary allowance (RDA) of a patient. This dosages is a useful and safe measure according to Ströhle *et al.*. However, the daily food intake of the patient should be taken into account, to avoid overnutrition of some compounds (9,76). Nutritional support might improve nutritional status when compliance is sufficient. Compliance of these interventions depends on the flavour, texture and volume. Nutritional intervention could be started when a patient is undernourished or the patients will be unable to eat for more than seven days in the near future (75). However, nutritional support should start as early as possible, for example at the time of the cancer diagnosis. Early interventions might avoid further weight loss and possible prevent the onset of or slow down the cachexia–syndrome. In addition, it could improve prognosis and outcome, and finally improve quality of life of a patient.

It is often shown that combinations of nutrients have more benefit than one component of an intervention. For example Faber *et al*. investigated in a cancer-cachexia mouse-model the effect on cachexia of nutritional ingredients, including fish oil, specific oligosaccharide mixture, high protein content and leucine, alone or a mixture of these nutrients. They concluded that individual ingredients showed no effect on body weight, carcass weight and skeletal muscles, which might indicate that individual ingredients do not reduce the cachectic state. However, a mixture of ingredients showed to increase body weight, carcass weight, skeletal muscle weight. In addition, cachectic state of the mice was reduced (23,78).

A nutritional supplement may therefore contain a combination of different nutrients, including proteins, amino acids (BCCAs), carbohydrates, fats such as PUFAs (e.g. EPA and DHA), GOS/FOS, antioxidants (vitamin A, C, and E), and micronutrients (zinc and selenium). A combination of these nutrients could by beneficial because several pathways could be affected, which could lead to a synergistic effect of the different nutrients. In addition, a combination of nutritional intervention with chemotherapy could be beneficial. Some nutrients, such as PUFAs, glutamine, selenium, BCCAs, and antioxidants have shown to have synergistic effect on chemotherapy (39,54,60,70,72,74). Because of this, effectiveness is improved and toxicity is reduced of chemotherapeutic agents. This results in reduced treatment delays and decreased termination of treatment. Moreover, this may reduce tumor growth, improve nutritional status, it may stabilize or increase the lean body mass and/or body weight, reduce systemic inflammation, reduced (infectious) complications, improve liver and kidney function, increase physical activity and improve clinical outcomes, decrease complications of the disease and the treatment and finally increase the quality of life of patients.

Nevertheless, more studies are required to investigate effectiveness of nutritional intervention in patients with cachexia. For example, dose adjustments, contraindications and starting point of the intervention should be investigated, to avoid overnutrition of some components, but also to avoid ineffectiveness of some components. Moreover, it is important to investigate the combination of the nutritional intervention with chemotherapeutic agents in cancer-cachectic patients. Currently, the evidence available on this topic is inconsistent due to conflicting results in the studies described in literature. Therefore, it is important to know the pharmacokinetics of chemotherapeutic agents in cancer-cachectic patients, with and without nutritional intervention, to adjust the dosages of the drug. Moreover it is crucial to know which pathways are affected by the nutrients to improve effectiveness of chemotherapy, to avoid that further stimulation of these pathways, which could lead to toxicity. In addition, pre-clinical and clinical studies have to be performed to investigate nutritional intervention in combination with chemotherapy. Thereby investigating nutritional status, immune function, but also treatment adherence, occurrence of chemotherapeutic-toxicities, incidence of toxicities, effectiveness of the chemotherapy, and ultimately the survival of the patients.

VIII.   References

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