

Pathophysiology

Introduction

About half of all cancer patients show a cachexia syndrome, characterized by anorexia and loss of adipose tissue and skeletal muscle mass. Numerous cytokines have been postulated to play a role in the etiology of cancer cachexia. Cytokines can elicit effects that mimic leptin signaling and suppress orexigenic ghrelin and neuropeptide Y (NPY) signaling, inducing sustained anorexia and cachexia not accompanied by the usual compensatory response. Furthermore, cytokines have been implicated in the induction of cancer-related muscle wasting. In particular, tumor necrosis factor (TNF)- α , interleukin (IL)-1, IL-6, and interferon (IFN)- γ have been implicated in the induction of cancer-related muscle wasting. Cytokine-induced skeletal muscle wasting is probably a multifactorial process, which involves a protein synthesis inhibition, an increase in protein degradation, or a combination of both. In recent years, it has become evident that specific regulating molecules are upregulated (eg, members of the ubiquitin-proteasome system, myostatin, and apoptosis inducing factors), whereas other factors (eg, insulin-like growth factor 1 [IGF-1]) are down-regulated in cachexia muscle wasting.

Hormones and mediators

Leptin is a protein hormone that sends afferent signals to the brain to regulate adipose tissue mass [1–3]. The level of leptin is positively correlated with body fat mass, and dynamic changes in plasma leptin concentrations in

either direction can activate the efferent energy regulation pathways [1,4]. Leptin reduces appetite and increases energy expenditure and elicits these effects via the central nervous system [1,4]. This is due to neuropeptides downstream of leptin that regulate food intake and energy expenditure. Starvation or a loss of body fat can lead to a decrease in leptin, which in turn leads to a state of positive energy balance; conversely, food intake exceeds energy expenditure. This compensatory response is mediated by the increased production of ghrelin, NPY, and other appetite-stimulating neuropeptides, and decreased activity of anorexigenic neuropeptides such as corticotropin-releasing factor (CRF) and melanocortin (Figure 2.1A). Thus, if a disease process such as cancer was to produce factors that mimic the hypothalamic effect of excess leptin, the expected outcome would be sustained anorexia (lack of appetite) and cachexia (muscle wasting and uncontrolled weight loss), without the usual compensatory response [5,6]. In fact, in tumor-bearing states, cytokines can elicit effects that mimic leptin and suppress orexigenic ghrelin and NPY signaling, inducing anorexia and unopposed weight loss (Figure 2.1B) [6].

Serotonin may also play a role in the development of cancer-induced anorexia. This is because increased levels of plasma and brain tryptophan, the precursor of serotonin, and IL-1 may underlie the increased serotonergic activity seen in the cancer cachexia [6].

Cytokines

Cytokines are protein molecules released by lymphocytes and/or monocyte macrophages [6]. They are released into the blood stream and transported to the brain through the blood–brain barrier (BBB) and circumventricular organs (ie, ‘leaky’ areas in the BBB) [7–12]. Peripheral cytokines may influence the brain via neural pathways or second messengers such as nitric oxide and prostanoids [6]. Cytokines are also produced by neurons and glial cells within the brain, partly in response to peripheral cytokines [7–12]. Although the site of cytokine synthesis within the brain is dependent on the nature of the stimulus, systemic disease seems to predominantly influence expression in the hypothalamus, the area with the highest densities of receptors [11].

Numerous cytokines, including TNF- α , IL-1, IL-6, and IFN- γ , may play a role in the etiology of cancer cachexia [7,8,13–16]. It is not certain whether the cytokine production is primarily from tumor or host inflammatory cells. It has been hypothesized that either tumor cell production of proinflammatory cytokines or the host inflammatory cell response to tumor cells is the source of the acute phase protein response seen in many malignancies and in cachexia [17].

High serum levels of TNF- α , IL-6, and IL-1 have been found in some cancer patients and seem to correlate with the progression of certain types of tumors [18–20]. Chronic administration of these cytokines, either alone or in combination, is capable of reducing food intake and inducing cancer cachexia [6,18–21]. The role of TNF- α in mediating cachexia is supported by evidence that intraperitoneal injection of a soluble recombinant human TNF-receptor antagonist improved anorexia in tumor-bearing animals [22]. In humans, IL-1 appears to play a significant role in mediating cachexia [23].

TNF- α , IL-1, IL-6, and IFN- γ have been implicated in the induction of cancer-related muscle wasting [24]. There is growing evidence that the accelerated muscle proteolysis seen during malignant tumor growth is mediated by the activation of the non-lysosomal adenosine triphosphate (ATP)-dependent ubiquitin proteasome pathway [25,26].

More direct evidence of cytokine involvement comes from experiments in which specific neutralization of cytokines can relieve anorexia and cachexia in experimental animal models [13,19,20,27]. Examples of antibodies that have been shown to successfully relieve anorexia and cachexia when administered include anti-TNF- α , anti-IL-6, anti-IL-1, and anti-IFN- γ antibodies, although no single antibody has been proven to reverse all of the features of wasting seen in cancer cachexia [19]. These studies revealed that cachexia can rarely be attributed to any one cytokine but rather is associated with a set of cytokines that work in concert [6]. Recent studies include the use of anti-IL-6 humanized monoclonal antibody, which appears to inhibit cancer cachexia in murine models [28] and may be of clinical significance in cancer patients [28].

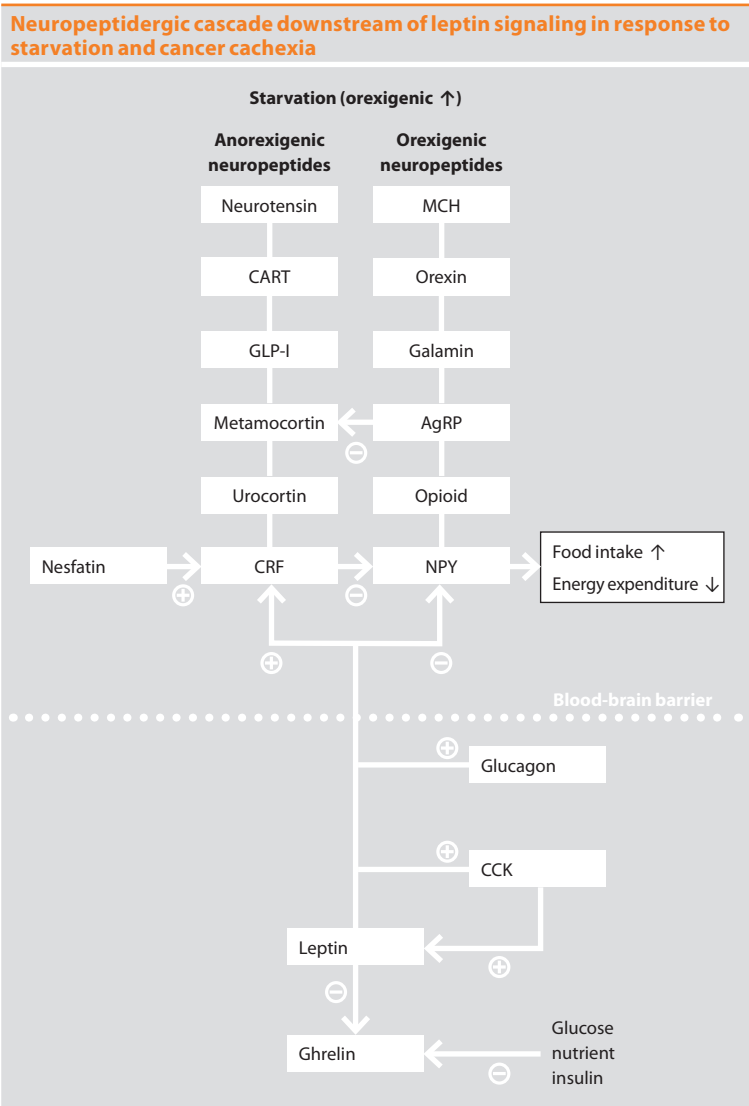


Figure 2.1 A Neuropeptidergic cascade downstream of leptin signaling in response to starvation and cancer cachexia. ACTH, adrenocorticotropic hormone; AgRP, Agouti-related peptide; BDNF, Brain-derived neurotrophic factor; CART, cocaine-amphetamine-regulated transcript; CCK, Cholecystokinin; CNS, central nervous system; CNTF, ciliary neurotrophic factor; CRF, corticotropin-releasing factor; GLP-1, glucagon-like peptide-1; IFN, interferon; IL, interleukin; LIF, leukemia inhibitory factor; MCH, mean corpuscular hemoglobin; NPY, neuropeptide Y; TNF, tumor necrosis factors. Adapted with permission from Inui et al 1999 [6].

Neuropeptidergic cascade downstream of leptin signaling in response to starvation and cancer cachexia

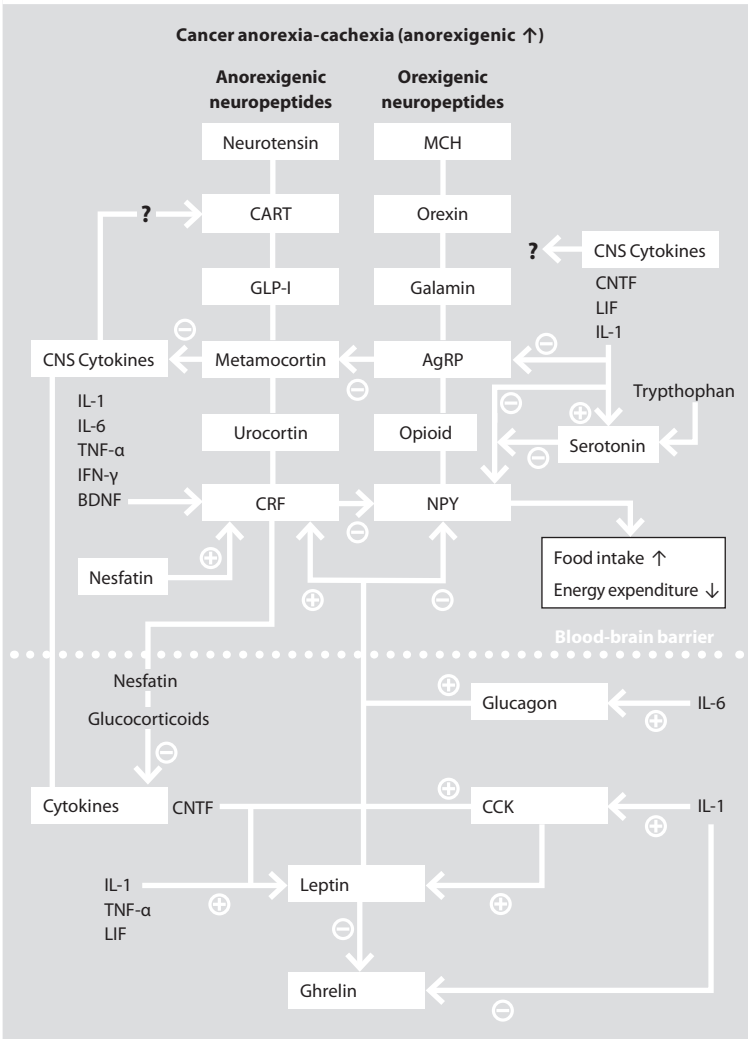


Figure 2.1 B Neuropeptidergic cascade downstream of leptin signaling in response to starvation and cancer cachexia. ACTH, adrenocorticotrophic hormone; AgRP, Agouti-related peptide; BDNF, Brain-derived neurotrophic factor; CART, cocaine-amphetamine-regulated transcript; CCK, Cholecystokinin; CNS, central nervous system; CNTF, ciliary neurotrophic factor; CRF, corticotropin-releasing factor; GLP-1, glucagon-like peptide-1; IFN, interferon; IL, interleukin; LIF, leukemia inhibitory factor; MCH, mean corpuscular hemoglobin; NPY, neuropeptide Y; TNF, tumor necrosis factors. Adapted with permission from Inui et al 1999 [6].

The problem with ascribing specific tissue responses to individual cytokines is that considerable overlap and redundancy exists in the cytokine network [9–12,16]. Administration of either TNF- α or IL-1 will induce the synthesis of a variety of other pro-inflammatory cytokines such as IL-6 [6]. Thus, studies that use pharmacological administration of recombinant cytokines may not discriminate between biological responses induced directly by the administered cytokine and those induced secondarily by other stimulated cytokines [6]. Systemic diseases such as cancer and chronic inflammation may elicit a cytokine cascade in which several cytokines are induced simultaneously [16].

Systemic changes in response to inflammation are referred to as the acute-phase response [29], and up to 50% of patients with solid epithelial cancers may have an elevated acute-phase protein response (APPR) [30]. APPR is correlated with elevated resting energy expenditure and reduced energy intake [31] and longitudinal studies have found a poorer prognosis in patients displaying this response, independent of weight loss [32].

C-reactive protein

C-reactive protein (CRP) is the most common method used to assess the magnitude of the systemic inflammatory response [29]. The modified Glasgow prognostic score combines CRP and plasma albumin concentrations to create a simple scoring system that serves as a prognostic factor that is independent of stage and treatment and that predicts survival [33,34] (Table 2.1).

Raised CRP concentrations at the time of admission to hospital is indicative of an increased risk for all-cause mortality; there is a 22.8-fold increase in cancer mortality in patients with highly-elevated CRP

Modified Glasgow prognostic score	
Biochemical measure	Score
C-reactive protein $\leq 10\text{mg/L}$ + albumin $\geq 35\text{g/L}$	0
C-reactive protein $\leq 10\text{mg/L}$ + albumin $< 35\text{g/L}$	0
C-reactive protein $> 10\text{mg/L}$	1
C-reactive protein $> 10\text{mg/L}$ + albumin $< 35\text{g/L}$	2

Table 2.1 Modified Glasgow prognostic score. Combines C-reactive protein and plasma albumin concentrations to create a scoring system to predict survival.

concentrations (>80 mg/L) [35]. In a study of patients with inoperable non-small cell lung cancer who had at least 5% weight loss, almost 80% had elevated CRP levels [36]. In patients without weight loss, those who displayed evidence of a systemic inflammatory response reported more fatigue ($P<0.05$) [36]. In another study of patients with gastroesophageal cancer, the rate of weight loss was also correlated with elevated CRP serum concentrations [37].

Negative nitrogen balance

In adults, muscle mass remains fairly constant in the absence of stimuli (eg, exercise) and thus protein synthesis and degradation generally remain in balance [38]. However, in cachexia, muscle atrophy occurs, which results from a decrease in protein synthesis, an increase in protein degradation, or a combination of both [39]. In recent years, it has become evident that specific regulating molecules are upregulated (eg, members of the ubiquitin-proteasome system, myostatin, and apoptosis-inducing factors), whereas other factors (eg, IGF-1) are downregulated in cachexia [24].

A major barrier to the effective management of skeletal muscle wasting is the inadequate understanding of its underlying biological mechanisms [24]. The most evident metabolic explanation for muscle decline is an imbalance between protein catabolism and anabolism [24]. In addition to an increase in catabolism, a reduction in anabolism has been shown to occur in cancer cachexia [24]. Skeletal muscle wasting can be mediated by multiple factors derived from tumor and host cells [39].

At least four major proteolytic pathways (lysosomal, calcium-dependent, caspase-dependent, and ubiquitin-proteasome-dependent) operate in skeletal muscle and may be altered during cachexia [24]. Aside from these four distinct pathways, the autophagic/lysosomal pathway must also be considered [24]. In this pathway, portions of the cytoplasm and cell organelles are sequestered into autophagosomes, which subsequently fuse with lysosomes, where the proteins are digested [40].

When dissecting the molecular regulation of the ubiquitin-proteasome-dependent system (UPS) and autophagy, it became evident that forkhead box O (FoxO) transcription factors play a central role [24]. The UPS is a major intracellular system that regulates skeletal muscle wasting in

response to tumor factors and inflammatory cytokines [39]. In cancer cachexia, the decrease in skeletal muscle protein synthesis is partly related to the increased serum levels of proteolysis-inducing factor (PIF) [24]. Recent evidence suggests that PIF decreases protein synthesis by inhibiting protein translation initiation through phosphorylation of the eukaryotic initiation factor 2 [24,41,42].

Myostatin

Myostatin is an extracellular cytokine that is mostly expressed in skeletal muscles and is known to play a crucial role in the negative regulation of muscle mass [43]. Upon binding to the activin type IIB receptor, myostatin can initiate several different signaling cascades, resulting in decreased muscle growth and differentiation [43]. Muscle size is regulated via a complex interplay of myostatin signaling with the IGF-1/phosphoinositide 3-kinase (PI3K)/Akt pathway, which is responsible for increased protein synthesis in muscle [43]. Therefore, the regulation of muscle weight is a process in which myostatin plays a central role, but the mechanism of its action and the role of the signaling cascades involved are not fully understood [43]. Myostatin upregulation was observed in the pathogenesis of muscle wasting during cancer cachexia [43].

Data are available that demonstrate a beneficial effect of myostatin inhibition in cancer cachexia [44], but conflicting study results have also been reported [45]. With respect to apoptosis, several reports demonstrated an increase in apoptosis or apoptosis-related proteins in skeletal muscle after the induction of cachexia [24]. The skeletal muscle of cachectic tumor-bearing animals reveals the presence of DNA fragmentation, a hallmark of apoptosis [46].

Insulin-like growth factor-1

One of the main positive regulators of muscle growth is IGF-1 [43]. Under normal conditions, IGF-1 signaling blocks the myostatin pathway [47], and an inhibition of IGF-1 can occur when myostatin is overexpressed [48,49]. The mechanism by which IGF-1 regulates myostatin signaling includes the inhibition of transcription factors responsible for the induction of atrogenes via phosphorylation through the PI3K/Akt pathway [43].

Akt plays a significant role in different metabolic processes in the cell, particularly in the hypertrophic response to insulin and IGF-1 [50,51] and is the 'crossing point' between the IGF-1 and myostatin pathways [43]. It is likely that under conditions of muscle wasting, myostatin can reverse the Akt/mammalian target of rapamycin (mTOR) pathway, which is normally responsible for protein synthesis, to inhibit protein synthesis (eg, via FoxO, GSK-3 β), leading to loss of muscle mass [43] (Figure 2.2).

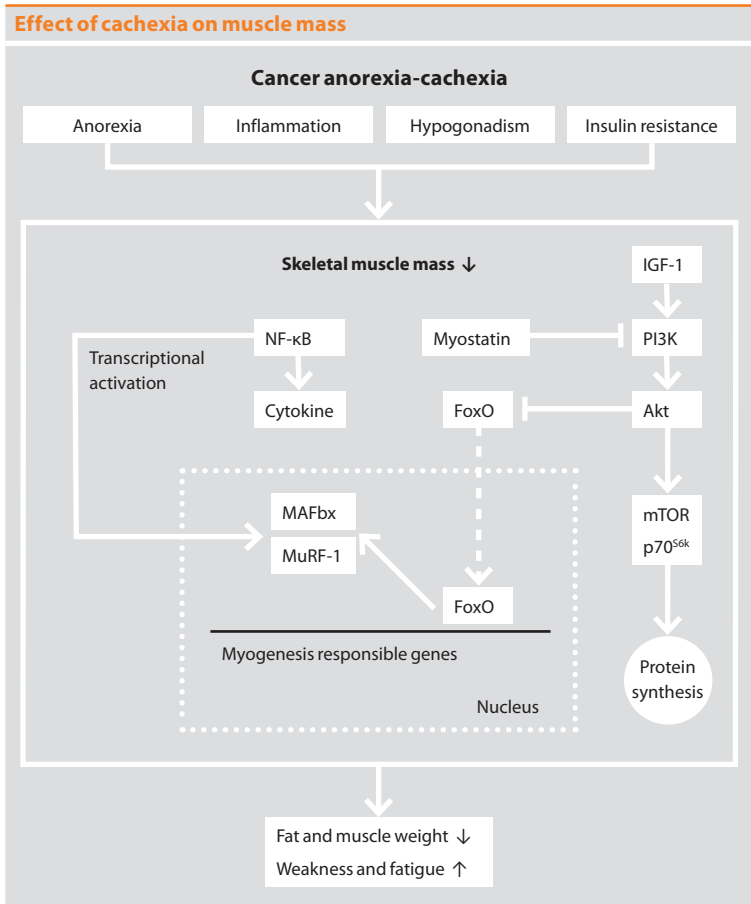


Figure 2.2 Effect of cachexia on muscle mass. FoxO, forkhead box transcription factor; IGF-1, insulin-like growth factor-1; MAFbx, muscle-specific RING finger; mTOR, mammalian target of rapamycin; MuRF-1, muscle RING-finger protein-1; NF- κ B, Nuclear factor-kappa B; PI3k, phosphatidylinositol 3-kinase.

Another factor that may contribute to decreased anabolism is angiotensin II [24]. In an animal model of continuously administered angiotensin II, markedly reduced plasma IGF-1 levels occurred [52] and angiotensin II-infused hypertensive rats lost 18–26% of their body weight within a week, an effect that was completely reversed by losartan (an angiotensin II receptor type 1 receptor antagonist) [52].

Experimental data suggest that local IGF-1 may act as a regenerative agent, promoting the recruitment of stem cells to sites of muscle injury [53]. Because IGF-1 is reduced in experimental models of cachexia [54], it is reasonable to assume that under conditions of cachexia, the function of satellite cells is impaired.

Oxidative stress

There is a wealth of evidence suggesting that oxidative stress is associated with chronic diseases and it is assumed that an increase in reactive oxygen species (ROS) directs muscle cells into a catabolic state that leads to muscle wasting [24,55,56]. In cachexia, ROS are regarded as crucial players for muscle protein catabolism via their stimulation of the UPS [24]. In addition, experimental cancer cachexia appears to be mediated by increased nitrosative stress secondary to increased nitric oxide formation [57,58]. Indeed, protein tyrosine nitration is markedly increased in the muscles of tumor-bearing rats with advanced cachexia, due to lower levels of antioxidant enzymes [57,58].

Anabolic hormones

There is a relative deficiency or resistance to anabolic hormones in cachectic states. Up to 50% of men with metastatic cancer present with low concentrations of testosterone prior to chemotherapy [59]. A reduction in testosterone might lead to reduced bone mass, muscle strength, and sexual function in both men and women [60,61] and low concentrations of testosterone and other anabolic hormones are major contributors to cachexia-related wasting of skeletal muscle [62]. However, with respect to a correlation between body composition (including muscle mass) and the concentration of anabolic hormones, conflicting results have been reported in the current literature [24,59,63,64].

Effects on antineoplastic therapy

Catabolic drivers

Antineoplastic therapies such as surgery, radiotherapy, and chemotherapy are known to have a negative impact on a patient’s nutritional intake through the development of systemic inflammation, exacerbation of already-reduced energy, and, particularly, on swallowing difficulties and anorexia due to nausea [17,65]. Additionally, surgical patients may be fasted for prolonged periods perioperatively and both chemotherapy and radiotherapy can induce side effects such as anorexia, nausea, vomiting, mucositis, taste change, or lethargy [65,66] (Table 2.2, Table 2.3, and Table 2.4).

Nutritional consequences of cachexia	
Tongue or pharynx	Need for nutrition by tube (dysphagia)
Thoracic oesophagus	Gastric stasis or malabsorption of fats (due to vagotomy)
Stomach	Dumping syndrome, anaemia, malabsorption of fats, iron, calcium and vitamins
Duodenum	Biliary-pancreatic deficiency
Jejunum	Reduced absorption of glucose, fats, protein, folic acid, vitamin B12
Ileum or ileocaecal valve	Malabsorption of vitamin B12, biliary salts and fats
Small intestine	Malabsorption of fats, glucose, protein, folic acid, vitamin B12 diarrhea
Jejunum and ileum	Complete malabsorption
Colon (subtotal or total resection)	Water and electrolyte loss
Pancreas	Malabsorption and diabetes
Liver	Transient hypoalbuminaemia

Table 2.2 Nutritional consequences of cachexia.

Effects of radiation therapy in cancer treatment		
Region irradiated	Early effects	Late effects
Head and neck	Odynophagia, xerostomia, mucositis, anorexia, dysosmia, hypogeusia	Ulceration, xerostomia, dental caries, osteoradionecrosis, trismus, hypogeusia
Thorax	Dysphagia	Fibrosis, stenosis, fistula
Abdomen and pelvis	Anorexia, nausea, vomiting, diarrhea, acute enteritis, acute colitis	Ulceration, malabsorption, diarrhea, chronic enteritis, chronic colitis

Table 2.3 Effects of radiation therapy in cancer treatment.

Gastrointestinal side effects of chemotherapeutic drugs	
Drug	Severity and duration
Chemotherapeutic drugs commonly associated with severe nausea and vomiting	
Nitrogen mustard (mustine hydrochloride; mechlorethamine hydrochloride)	Occurs in virtually all patients. May be severe, but usually subsides within 24 hours
Chloroethyl nitrosoureas, Streptozotocin (streptozocin)	Variable, but may be severe. Occurs in nearly all patients. Tolerance improves with each successive dose given on a 5-day schedule
Cis-platinum (cisplatin)	May be very severe. Tolerance improves with intravenous hydration and continuous 5-day infusion. Nausea may persist for several days
Imidazole carboxamide (dacarbazine)	Occurs in virtually all patients. Tolerance improves with each successive dose given on a 5-day schedule
Chemotherapeutic drugs commonly associated with mucositis	
Methotrexate	May be quite severe with prolonged infusions or if renal function is compromised. Severity is enhanced by irradiation. May be prevented with administration of adequate citrovorum rescue factor (folinic acid; leucovorin)
5-Fluorouracil (fluorouracil)	Severity increases with higher doses, frequency of cycles, and arterial infusions
Actinomycin D (dactinomycin)	Very common; may prevent oral alimentation. Severity enhanced by irradiation
Adriamycin (doxorubicin)	May be severe and ulcerative. Increased in presence of liver disease. Severity enhanced by irradiation
Bleomycin	May be severe and ulcerative
Vinblastine	Frequently ulcerative

Table 2.4 Gastrointestinal side effects of chemotherapeutic drugs.

Symptoms will depend on the nature and course of the chemotherapeutic drugs being used and the location, volume, and dose of radiotherapy [65]. Some cytotoxic drugs may even generate their own cachexia-like side effects [67]. For example, treatment with antitubulin taxanes reduces body weight in tumor-bearing mice more than healthy mice, even when the agents significantly reduce tumor growth [67]. However, the complex relationship between cancer cachexia and the effects of antineoplastic drugs remains to be fully elucidated [67].

C-reactive protein

A key (but often variable) component of cachexia is hypercatabolism that is directly caused by tumor metabolism, systemic inflammation, or

other tumor-mediated effects. The most widely accepted index of systemic inflammation is serum CRP [68]. CRP plasma values are positively correlated with weight loss, the occurrence of cachexia, and recurrence in advanced cancer [69]. Its role as a predictor of survival has been shown in multiple myeloma, melanoma, lymphoma, ovarian, renal, pancreatic, and gastrointestinal tumors [69,70].

Recent studies suggest that CRP is much more than a mere marker of the body's inflammatory load [71,72]. In cultured human umbilical vein endothelial cells, CRP was shown to activate endothelial cells, which, in turn, express intracellular adhesion molecule-1 [73], as well as vascular-cell adhesion molecule-1 and E-selectin, which are involved in leukocyte-binding to the endothelial layer. CRP also activates the expression of monocyte chemoattractant protein-1 [72]. In addition, circulating factors, such as lipid-mobilizing factors and PIF may play a role in the development of cancer anorexia and cachexia [73]. These are tumor-derived catabolic factors acting directly on adipose tissue and skeletal muscle, without affecting food intake [73].

However, cachexia can exist without overt systemic inflammation, and thus indirect indices reflecting the catabolic drive such as responsiveness to chemotherapy and the rate of progression should also be assessed [68]. These include insulin resistance, prolonged high-dose corticosteroid therapy, hypogonadism, and increased resting energy expenditure [68].

Increased nuclear factor- κ B activity

NF- κ B, a nuclear transcription activator factor, plays a major role in upregulating inflammatory gene expression, including expression of cyclooxygenase 2 inhibitors (COX-2), nitric oxide synthase, TNF- α , IL-1, and IL-6 [74]. The proinflammatory response occurs particularly with the formation of p65-p50 dimers, which act as the central control to an inflammatory response. NF- κ B is one of the principal transcription factors to transduce TNF- α signals into the cells. Moreover, it also activates gene transcription of other cytokines, acute-phase response proteins, and cell adhesion molecules [75].

Activation of NF- κ B accelerates inflammation, increases cellular proliferation of tumors, and prevents apoptosis [76]. Inhibition of NF- κ B

therefore is both antineoplastic and can reduce cachexia. Inhibition of NF- κ B also sensitizes tumors to chemotherapy and radiation, something that is the subject of multiple research trials [77].

In fact, genetic overexpression of nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor (I κ B) blocks NF- κ B-dependent processes. Two studies have shown that glucocorticoid administration induces transcription of the *I κ B* gene [78,79]. Increased levels of *I κ B* gene trap NF- κ B in inactive cytoplasmic complexes, hence inhibiting its ability to induce transcription of inflammatory cytokines. Moreover, fumaric acid, which blocks the nuclear translocation of NF- κ B, has a high anti-inflammatory capacity [78]. More recently, activation of NF- κ B by overexpression of a I κ B phosphorylating kinase was sufficient to block myogenesis, thus illustrating the link between NF- κ B and cachexia development [79]. However, complete inhibition of NF- κ B has proven detrimental; knockout studies targeting the major subunits of NF- κ B show severe immunodeficiency in mice, which was lethal in some cases [80]. Resolution of inflammation also requires NF- κ B expression and complete inhibition of NF- κ B can lead to severe cellular apoptotic damage in critical illness [81].

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