

Are Inflammatory Cytokines the Common Link Between Cancer-Associated Cachexia and Depression?

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A diagnosis of cancer places patients into an extremely stressful and difficult personal situation, given the current treatment options and prognoses for most tumors. The prevalence of depression among patients with cancer is estimated to be between 10% and 30%, compared with 5%–10% in the general medical population, and varies by cancer type [1–8]. Cancer-related depression is associated with faster tumor progression and shortened survival time. A causal relationship between depression and disease progression has not been established, however, and possible contributing factors are complex. Available evidence suggests a combination of potential factors, including reduced drug compliance and possible metabolic changes associated with depression, might affect the efficacy of chemotherapy [8].

In addition, causal factors associated with the onset of depression in cancer patients are difficult to assess. Multiple psychological, pathological, and pharmacological factors may lead to clinical depression in the patient with cancer. These causal mechanisms may, and often do, overlap (Figure 1) [9, 10]. The challenge of distinguishing the underlying mechanism of depression as well as differentiating clinical depression from the reactive demoralization of illness-induced physical deterioration may partly explain why cancer-associated depression remains an often unrecognized and undertreated comorbidity [11].

Cancer-related depression often coincides with uncontrolled appetite loss (anorexia) and unintentional weight loss (cachexia), especially among those patients whose disease has reached an ad-

Abstract The prevalence of depression among patients diagnosed with cancer is higher than among the general medical population and is associated with faster tumor progression and shortened survival time. Cancer-related depression often occurs in association with anorexia and cachexia, although until recently the relationship between these conditions has not been well understood. Cachexia is associated with poorer quality of life and survival outcomes and is the eventual cause of death in approximately 30% of all patients with cancer. Recent evidence has linked elevated levels of inflammatory cytokines with both depression and cachexia, and experiments have shown that introducing cytokines induces depression and cachectic symptoms in both humans and rodents, suggesting that there may be a common etiology at the molecular level. Therapeutic agents targeting specific cytokine molecules, such as interleukin-6 or tumor necrosis factor-alpha, are currently being evaluated for their potential to simultaneously treat both depression and cachexia pharmacologically. This review summarizes the available data suggesting a dual role for cytokines in the development of cancer-related depression and cachexia and describes how biologic therapies targeting specific cytokines may improve outcomes beyond depression and cachexia, such as survival and quality of life.

vanced stage or have a high symptom burden [12–14]. Cachexia is a wasting syndrome characterized by the substantial loss of adipose and muscle tissue. As many as one half of all patients with cancer demonstrate some degree of weight loss during the course of their illness. However, the etiologic relationships among depression, anorexia, and cachexia are not well defined.

Cachexia involves complex metabolic changes wherein patients typically exhibit an increased resting energy expenditure despite decreased caloric consumption. Increased caloric intake and appetite-inducing drugs have not yet demonstrated an ability to prevent the loss of lean muscle mass in cachectic patients over an extended period [15]. And although useful in treating many of the symptoms of depression in patients with cancer, antidepressants have demonstrated little

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Cytokines, Cachexia, and Depression

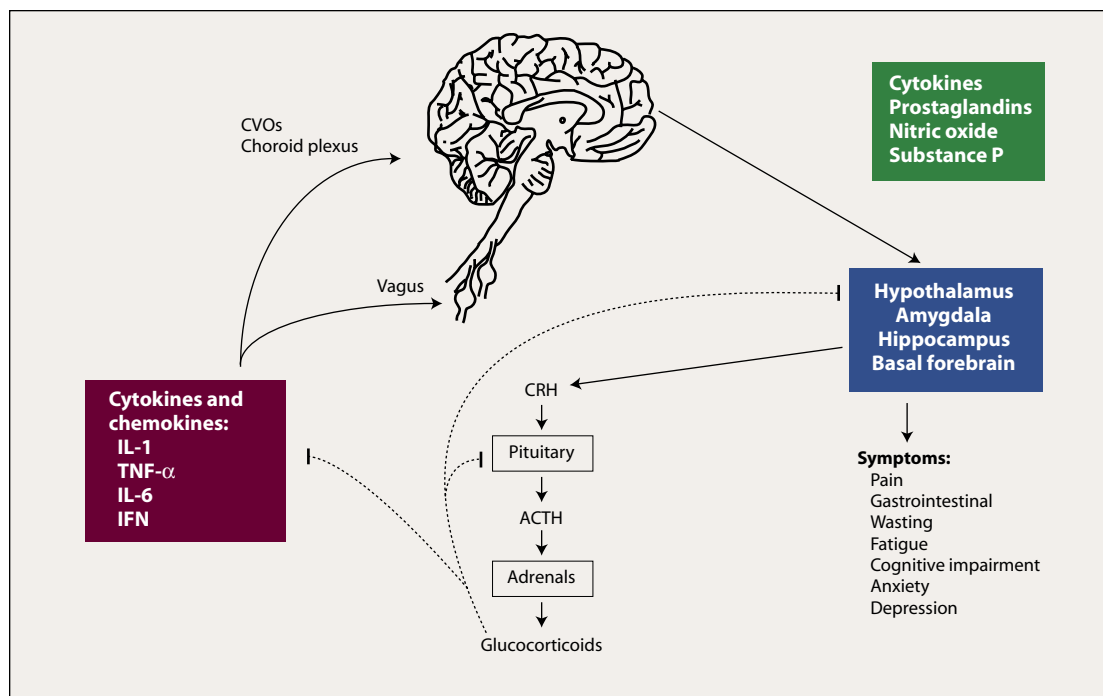


Figure 1 Biologic/Physiologic Mechanistic Framework for Cytokine-induced Sickness Behavior

In the afferent arm (solid lines), proinflammatory cytokines and chemokines (interleukin [IL]-1, tumor necrosis factor [TNF]- α , IL-6, interferon [IFN]- α , and IFN- γ) are released in the periphery by activated immunocytes. They exert their effects on peripheral nerves and directly on the brain to induce various aspects of the sickness response. These behavioral/physiologic changes are elicited by mediators acting downstream from the cytokines. Glutamate, nitric oxide, prostaglandins, and substance P act on brain regions, including the paraventricular nucleus of the hypothalamus and the amygdala. Turnover of monoamines (serotonin, dopamine, and norepinephrine) in these brain regions is affected. Availability of monoamine precursors (eg, tryptophan) may be decreased. The hypothalamic-pituitary-adrenal axis is activated, with upregulation of the plasma concentrations of corticosteroids, which in turn can provide feedback (dotted lines) to limit cytokine production. From Cleeland et al.¹⁰ Copyright © 2003 American Cancer Society. Adapted with permission from Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.

ACTH = adrenocorticotropic hormone; CRH = corticotropin-releasing hormone; CVO = circumventricular organ.

effect upon the progression of weight loss [15]. The effects of cachexia often can be more devastating and debilitating than the growth of the tumor itself. Cachectic patients live about half as long as those who do not exhibit weight loss, and approximately 30% of all patients with cancer die as the result of cachexia [15, 16]. Furthermore, the physical debilitation associated with cachexia reduces functionality and adversely impacts quality of life.

Until recently, little was known about the signaling pathways that underlie both cancer-related depression and cancer-related cachexia. The identification of elevated inflammatory cytokine levels characteristic of both depression and cachexia and the induction of depression and cachectic symptoms by the introduction of cytokines in both humans and rodents suggest that there may

be a common etiology. The prevalence and concomitant occurrence of depression and cachexia among patients with different types of cancer suggest that factors specific to particular kinds of tumors might be involved in the etiology of both depression and cachexia. The tumor, or the host, in an immunological response to the tumor, may upregulate the production of cytokines that cause both depression and cachexia (Figure 2) [10, 17].

The recent development of biologic therapies targeting specific cytokine molecules, such as interleukin (IL)-6 and tumor necrosis factor- α (TNF- α), raises the possibility of simultaneously countering the severe effects of depression and cachexia pharmacologically. Alleviating the symptoms of depression and the effects of cachexia would not only improve patient quality of life but might also improve the effectiveness of antitumor therapies.

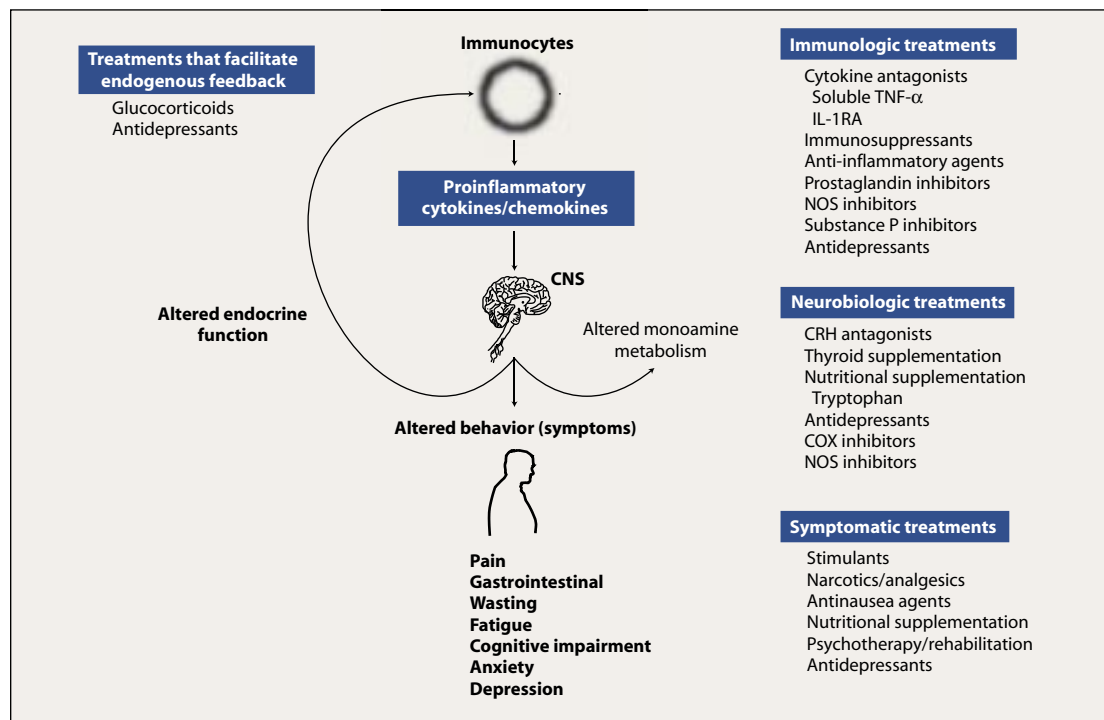


Figure 2 Treatment Strategies for Cancer-related Symptoms

The center flow diagram is a modification of the sickness response illustrated in more detail in Figure 1. Sites for the implementation of treatments directed at the sickness response circuit are shown. (1) Immunologic treatments (such as soluble receptors of tumor necrosis factor [TNF]- α and interleukin [IL]-1 receptor antagonists) that are designed to inhibit cytokine signaling directly, or treatments that block downstream mediators of inflammation, including prostaglandins, nitric oxide, and substance P; (2) neurobiologic treatments that target central nervous system (CNS) mediators of behavioral alterations including the monoamines and corticotropin-releasing hormone (CRH); (3) symptomatic treatments (such as narcotics for alleviation of pain, stimulants to combat fatigue, and antidepressants for relief from depression) that address the ultimate manifestations of upstream mediators; and (4) treatments designed to take advantage of the normal endogenous feedback circuits that limit sickness responses in settings such as viral illness. From Cleeland et al.¹⁰ Copyright © 2003 American Cancer Society. Adapted with permission from Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.

COX = cyclooxygenase; NOS = nitric oxide synthase.

In this paper, we review the role of cytokines in the development of cancer-associated depression and cachexia and suggest that these two disease syndromes may be related at the molecular level. We also discuss data that suggest possible benefits of anticytokine therapy for patients with cancer. Finally, we describe how cytokine pathway-modifying agents currently under clinical development may improve survival and quality of life for patients affected by both depression and cachexia.

The Cytokine Basis of Depression

Prevailing models of the pathophysiology of depression have focused on dysfunction of the turnover rates of monoaminergic neurotransmitters, such as serotonin and norepinephrine, and hypersensitivity of the hypothalamic-pituitary-adrenal axis. However, recent research has emphasized

the bidirectional relationships among the neural, endocrine, and immune systems, suggesting that immune-mediating molecules such as cytokines may contribute to the progression or even the etiology of depression [18–20].

Early evidence of a possible involvement of cytokines in depression arose from the presence of transiently elevated levels of circulating proinflammatory cytokines in patients experiencing physical or psychological stressors [21]. Levels of IL-6, as well as other cytokines and markers of the acute phase response, were significantly higher in patients suffering from acute depressive episodes than in normal control subjects, an effect ameliorated by successful pharmacologic treatment with the antidepressant fluoxetine [22–25]. Patients with major depression and sleep disorders demonstrated elevated serum levels of the cytokines IL-6

Peer viewpoints on this article by Dr. John A. Glaspy, Ms. Hayley Menzies, Drs. Harvey Max Chochinov and William Breitbart appear on pages 51 and 55.

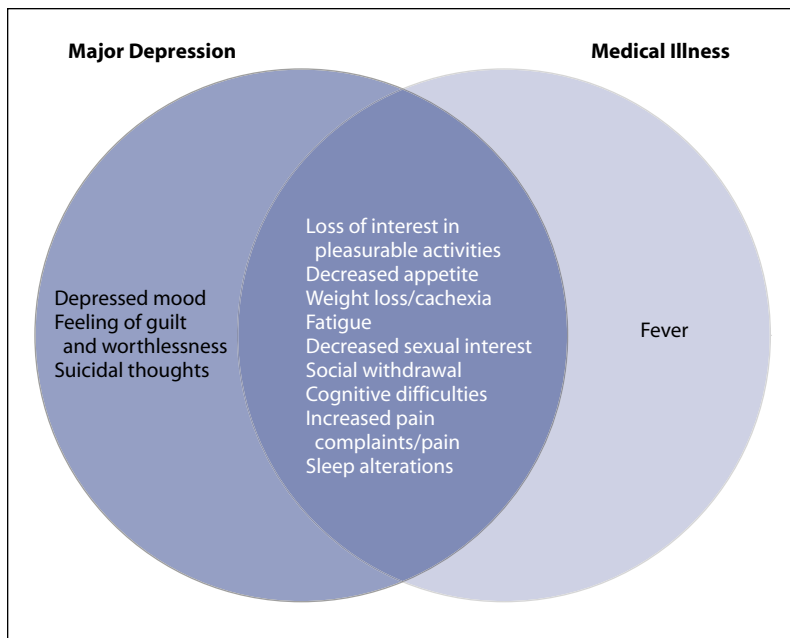


Figure 3 Relationship Between Depression and Medical Illness

Depression and sickness syndrome are characterized by many of the same symptoms, as seen in this diagram. Derived from Raison and Nemeroff.³¹

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and IL-8, along with a number of other inflammatory response molecules, compared with levels of these molecules in normal controls.

Chronic stress can lead to the overproduction of IL-6 in both humans and animals [21, 26, 27]. In a small controlled study of 24 patients with major depression, both serum TNF- α and IL-6 levels were elevated prior to antidepressant therapy, and IL-6 levels declined in patients who responded to treatment [28]. The authors of this study examined only the IL-6 and TNF- α cytokines, as well as C-reactive protein (CRP). Sample size prevented individual symptom analyses. At a population level, the clinical threshold for all symptoms determined the response to antidepressant treatment and its relationship to cytokine production.

Evidence from human patients and animal models suggests a causative role of cytokines in the etiology of many classic symptoms of major depression, particularly those associated with psychomotor retardation, fatigue, and anorexia [29]. The administration of exogenous cytokines can trigger “sickness syndrome”—metabolic and behavioral changes in the body that typically occur in response to pathogenic challenges. Sickness syndrome involves many of the physiologic manifestations characteristic of major depression, including anorexia, weight loss, anhedonia (an in-

ability to enjoy previously pleasurable activities), social isolation, fatigue, sleep disturbance, cognitive disturbance, decreased libido, and psychomotor retardation (Figure 3) [1, 8, 30, 31].

Symptoms reminiscent of sickness syndrome, such as decreased food consumption, lethargy, and impaired learning and memory, can be rapidly induced in normal mice by the systemic administration of the cytokines IL-1, IL-2, interferon-alpha (IFN- α), or TNF- α , as well as lipopolysaccharide, an active fragment of a bacterial endotoxin known to induce the synthesis of endogenous cytokines [10]. Similarly, human patients receiving cytokine therapy such as IL-2 (aldesleukin [Proleukin]) or IFN- α (Intron A, Roferon-A) for a variety of diseases (eg, hepatitis C, HIV infection, or cancer) display symptoms of sickness syndrome almost immediately after cytokine administration, and the symptoms usually disappear soon after treatment cessation [10, 32].

Finally, the rate of depression in patients undergoing cytokine therapy is high—nearly 50% for patients treated with chronic, high-dose, IFN- α [33]. Not much is known about the exact mechanism by which cytokines induce the symptoms of sickness syndrome. There is considerable bidirectional “cross-talk” among the immune, endocrine, and neural systems in which proinflammatory cytokines appear to function as both immunoregulators and neuromodulators [18, 34, 35]. A number of cytokines, including IL-1, IL-2, IL-6, IL-12, TNF- α , IFN- γ , and macrophage inflammatory protein-1-alpha (MIP-1 α), have been implicated in triggering the peripheral nervous system and central nervous system (CNS) to release neurotransmitters such as norepinephrine, epinephrine, and dopamine [34, 36].

Cytokines could affect the CNS either directly by acting on nerve cells in the CNS or indirectly by impacting other neuroendocrine pathways. Extensive evidence shows that cytokines, including members of the IL-1 family, IL-6, IFN- α , TNF- α , and transforming growth factor-beta (TGF- β), are produced by neuronal and glial cells in the brain and are active within the CNS [18, 37, 38]. Peripheral cytokines, whether endogenously produced or exogenously introduced, can also directly influence neuron behavior by entering the CNS at the circumventricular organs, sites lacking an effective blood-brain barrier [34].

Cytokines may indirectly affect neuroendocrine systems associated with the etiology of depression

by contributing to the breakdown of the serotonergic system and by stimulating the hypothalamic-pituitary-adrenal axis. IL-1 and IL-6 induce production of acute phase proteins and are associated with a decrease in the plasma level of tryptophan, the precursor to serotonin. In addition, IL-1 can activate the serotonergic transporter, thus increasing the reuptake of serotonin from the synaptic cleft [20, 26]. IL-6 has been shown to trigger the production of corticotropin-releasing hormone, which can elevate circulating levels of adrenocorticotropic hormone and, ultimately, endogenous cortisol levels [39]. Glucocorticoid hypersecretion can lead to further tryptophan suppression, trigger the breakdown of fat stores, and reduce glucose uptake by skeletal muscle [40]. In this way, proinflammatory cytokines may produce the physiologic effects of depression and progressive weight loss, providing a possible molecular basis for a link between physical and mental illness [21].

Cytokines in Cancer-related Depression

A number of recent studies link elevated cytokine levels to depression in patients with cancer, suggesting that inflammatory cytokines may be responsible for the relatively high rate of major depression observed in these patients (Table 1) [1, 41, 42]. Early clinical studies of patients with untreated myelodysplastic syndrome and acute leukemia correlated depression symptoms such as fatigue, cognitive impairment, and reduced quality of life with increased levels of the cytokines IL-1 receptor antagonist (IL-1RA), TNF- α , IL-6, IL-8, and epidermal growth factor (EGF). Additional evidence linked IL-1 and various interferons to cancer-related fatigue [10].

In a small study of patients with pancreatic, esophageal, and breast cancers, elevated plasma levels of IL-6 were identified among patients who also suffered from major depression, compared with IL-6 levels in non-depressed cancer patients and healthy control subjects [24]. The same study showed a correlation between cancer-related depression and a reduced ability to suppress cortisol levels after dexamethasone administration, further suggesting a connection among inflammatory cytokines, hyperactivity of the hypothalamic-pituitary-adrenal axis, and depression.

Considering the prevalence of cancer-related depression, one could speculate that the depressive symptoms might be physiologically related to either the presence of the tumor, as a result

Table 1

Prevalence of Depression in Various Cancer Types Correlates Inversely With Mean Length of Survival and Directly with Serum Cytokine Levels

CANCER TYPE	PREVALENCE OF DEPRESSION ¹⁻⁸	5-YEAR RELATIVE SURVIVAL RATE ¹	SERUM IL-6 LEVELS (PG/ML) ^{40,41}
Pancreatic	50%	4.4%	Not determined
Gastric	11%	22.5% (stomach)	10.0–12.5
Oropharynx	22%–40%	37.3%	79.6
Colon	13%–25%	62.3%	35.7
Lymphoma	17%	70.6%	2.0–4.6 (median)
Acute leukemia	1.5%	46.3% (all leukemia)	Not determined
Gynecologic	23%	71.4%	55.6 (median, ovarian)
Breast	10%–26%	86.6%	6.0–86.0
General medical population	5%–10%	≈100%	Varies by condition

Values shown are means, unless otherwise indicated. IL = interleukin

of cytokine secretion by the tumor itself, or its treatment. Secretion of cytokines by tumors has been demonstrated, and cytokines have been implicated in promoting cancer progression in at least some types of cancer. A number of prostate cancer cell lines, for example, have been shown to express IL-6 receptor and secrete IL-6, suggesting that cytokine production might be a key component of the neoplastic process [43]. Although IL-6 plays a paracrine growth inhibitory function in hormone-dependent prostate cancer cell lines, IL-6 has demonstrated the ability to act as both an autocrine and paracrine growth factor for hormone-refractory cell lines, thus implicating this cytokine in prostate cancer progression.

In a study of 120 patients who underwent radical prostatectomy for localized prostate cancer, preoperative levels of IL-6 and its soluble receptor (sIL-6R) correlated with preoperative prostate-specific antigen (PSA) levels and tumor volumes. IL-6 and sIL-6R levels were predictive of cancer progression after surgery; patients with bone metastases exhibited exceptionally high levels of both molecules [44]. Moreover, a number of cytokines, including TNF- α , IL-1, and IL-6, are induced by hypoxia, which is typically present within the core of solid tumors [45, 46].

In addition to tumor-produced cytokines, host immune responses to the tumor may also elevate cytokine levels. The destruction of neoplastic cells, as a result of tumor pathology or cancer therapy, leads to the accumulation of necrotic tissue and, consequently, to the release of cytokines and the

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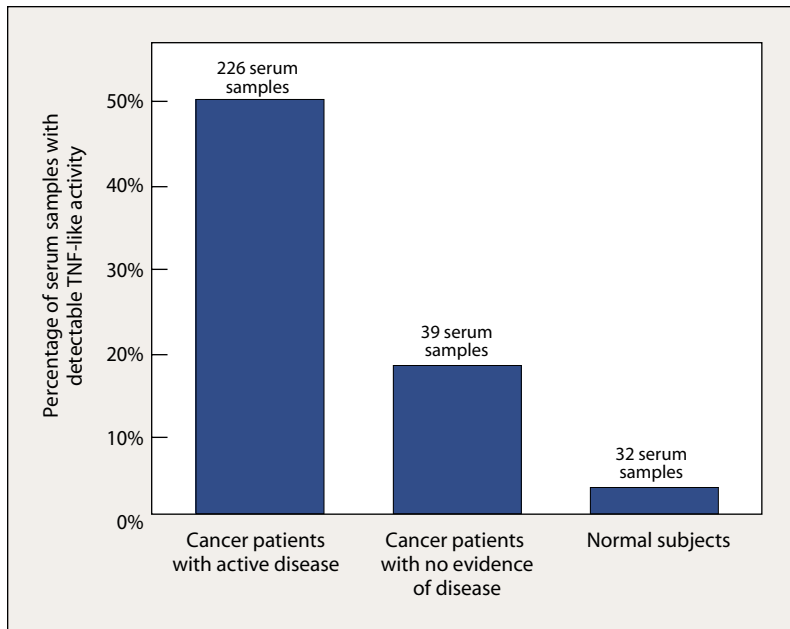


Figure 4 Serum Tumor Necrosis Factor Levels in Cancer Patients

The chart shows a correlation between serum tumor necrosis factor (TNF)-like activity and active cancer progression. Adapted with permission from Balkwill et al.⁴⁹

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recruitment of phagocytic cells. For example, serum TNF- α and IL-6 levels rose in lymphoma patients within 90 minutes of infusion of anti-CD20 antibody [47]. Anti-CD20 produces a rapid lysis of neoplastic cells, suggesting that the clinical symptoms associated with anti-CD20 antibody infusion, including fever, chills, nausea, vomiting, hypotension, and dyspnea, may result from the release of cytokines from lysed tumor cells.

Consistent with this hypothesis is the clinical evidence that cytokine-based antitumor therapies such as IL-2 and IFN- α , which are used to treat renal cell carcinoma, chronic myelogenous leukemia, and melanoma, are associated with a high incidence of depression [32]. This theory may help explain the accumulating evidence of a relationship among chemotherapy, irradiation, and surgery and the development of depression in patients with cancer [1].

The Cytokine Basis of Cancer-related Cachexia

With some frequency in cancer, but rarely in major depression, weight loss can progress to the severe wasting of cachexia, a condition known to contribute to immobility, propensity to infection, shortened duration of survival, and overall decreased quality of life. Although anorexia may

be present in the cancer patient with cachexia, cachexia cannot be explained by inadequate caloric and nutritional intake alone, since nutritional supplements do not usually stop the progressive wasting [14]. Instead, cachexia reflects substantial metabolic changes in patients with cancer, which, like cancer-related depression, may stem from the pathophysiology of the tumor, the body's immunologic response to that tumor, or the therapy selected to combat tumor progression and metastasis.

A significant body of evidence indicates that proinflammatory cytokines play a central role in the etiology and pathology of cachexia. TNF was originally identified as a circulating factor involved in cachexia and was called cachectin [48]. A study that examined serum TNF levels in cancer patients found that 50% of 226 patients with active cancer showed detectable TNF-like activity, compared with 18% of 39 patients with regressed cancer and 3% of 32 normal subjects (Figure 4) [49]. Cachectic symptoms in adenocarcinoma-bearing mice are paralleled by increased levels of IL-6 [50]. Both the elevated levels of IL-6 and the cachexia can be relieved by administration of anti-IL-6 antibodies, the cytokine-blocking drug suramin, or the cytokine modulator IL-12 [51, 52].

Furthermore, tumor-induced cachexia and the hypercalcemia caused by bone resorption are not observed in IL-6 knockout mice [53]. Recently, a monoclonal antibody directed against IL-6, CNTO 328 (previously known as cCLB8), was shown to inhibit human tumor-induced body weight loss in nude mice, providing further evidence that IL-6 released by tumor cells induces cachexia and that direct inhibition of IL-6 by a monoclonal antibody can prevent loss of body weight [54].

Evidence suggests that the mechanism of cytokine involvement in cachexia is through induction of hepatic synthesis of acute phase response proteins (eg, complement proteins, coagulation proteins, and proteinase inhibitors) and their consequent effect on the neuroendocrine system. Cytokines stimulate hepatocytes and other cells in the liver, such as monocytes, endothelial cells, fibroblasts, and adipocytes, to synthesize and secrete higher than normal levels of proteins involved in the acute phase response.

Often observed in instances of trauma, inflammation, and infection, acute phase response proteins are involved in a wide range of activities, including neutralization of inflammatory agents,

minimization of local tissue damage, and participation in tissue repair and regeneration. CRP, for example, is an IL-6–induced acute phase protein frequently used as a marker for inflammation [55].

Elevated levels of acute phase response proteins are observed in a significant proportion of patients with cancer, particularly those with pancreatic, lung, kidney, or esophageal cancer, and that proportion increases with advanced disease progression [56]. The presence of an acute phase response has also been linked to increased weight loss in patients with lung or pancreatic cancer and in patients with melanoma [57–60]. Moreover, a substantial acute phase response tightly correlates with reduced survival rates in patients with renal, colorectal, or pancreatic cancer [61–63]. These data suggest that the cytokine-triggered acute phase response may lie at the root of cancer-related cachexia.

Proinflammatory cytokines may also induce cancer-related cachexia through their influence on the neuroendocrine system. Elevated levels of both cortisol and glucagons have been observed in patients with cancer [64, 65]. Cytokines can induce hyperactivity of the hypothalamic-pituitary-adrenal axis, leading to increased release of cortisol, which can produce muscle protein loss, increased energy expenditure, and glucose intolerance in humans [66, 67]. In addition, expression of leptin, an adipose tissue–derived hormone that helps maintain stable body weight by reducing appetite and increasing energy expenditure, has been linked to cytokine production in some models of inflammation.

The administration of TNF has been shown to increase leptin production [68, 69]. However, the involvement of leptin in cachectic patients with cancer remains unclear [70]. Cytokine production may be the molecular underpinning of both cancer-related depression and cancer-associated cachexia since proinflammatory cytokines actively induce the acute phase response and are known to affect neuroendocrine pathways that influence metabolism.

There are sufficient data demonstrating that cachexia is more than a secondary comorbidity to cancer and suggesting that the same might be true for depression. Depression reduces compliance with cancer treatments, decreases cancer drug effectiveness, and, in some studies, shortens overall survival, which may partly be due to the development of cachexia [8]. Cachexia may be responsible for nearly one third of cancer deaths, independent

of tumor burden or metastases [16].

The critical contribution of depression and cachexia to cancer mortality highlights the need for improved screening procedures to identify patients suffering with symptoms of depression and wasting, as well as the development of new therapeutics or treatment regimens to counter them. Inhibiting cytokine activity has the potential to alleviate symptoms of depression and the immobility and weakness characteristic of cachexia. The consequent improvement in patient constitution would allow more aggressive anticancer treatments, extend patient survival, and improve patient quality of life. A number of treatment options are already available or being developed that may repress the proinflammatory cytokine cascade and prove beneficial if incorporated into current antitumor treatment regimens.

ANTIDEPRESSANTS

If tumor biology can affect one's mental state, the opposite might also be true. Some psychosocial group intervention studies have highlighted the potential for psychological intervention to significantly improve survival in patients with breast cancer or melanoma [71–73], indicating that mental health treatment could improve cancer treatment and outcomes. However, not all studies in this area are positive [74].

The effect of antidepressant therapy on cancer survival has not been well studied. The bidirectional signaling of the immune and neuroendocrine systems allows both serotonin and noradrenaline to function as immunomodulators. Thus, an effective increase in noradrenergic and serotonergic activity mediated by antidepressant treatment could further influence the immune system [20]. Improved quality of life was found in one study of antidepressants in advanced solid tumor patients, but no difference in median survival was seen [75].

Antidepressant medications that attenuate serotonin reabsorption exert their effects at least in part by suppressing proinflammatory cytokine activity and therefore blunt the acute phase response [20]. Chronic treatment with the tricyclic antidepressant imipramine or the selective serotonin-reuptake inhibitor fluoxetine can alleviate lipopolysaccharide-induced anhedonia in rats by inhibiting proinflammatory cytokine production by monocytes and macrophages [37, 38].

In vitro research also supports a cytokine inhibitory effect for some antidepressants. The synthesis and release of IL-6, TNF- α , and IL-1 by human

monocytes are significantly inhibited when the cells are incubated with various antidepressants and lipopolysaccharide [20, 76]. In addition, elevation in the concentration of serotonin in vitro resulting from the introduction of a selective serotonin-reuptake inhibitor leads to an increase in production of the anti-inflammatory cytokine IL-10 and a decrease in the synthesis of IFN- γ [77]. The administration of desipramine, a metabolite of imipramine, to mice increases the capacity of splenocytes to produce IL-10 [78]. Normalization of previously elevated circulating levels of IL-6 and CRP was reported after fluoxetine was administered to 22 depressed patients [23], and serum TNF- α and IL-6 levels dropped in patients responding to amitriptyline in a controlled study of 24 patients suffering major depression [28].

Although many of the symptoms of depression can be successfully treated with antidepressant medications in patients with cancer, the symptoms of cachexia have proven more resistant to these same drugs. In a large, placebo-controlled clinical trial of 704 patients with cancer reporting fatigue related to antitumor therapy, patients treated with paroxetine experienced significant improvement in the mean level of depression compared with placebo-treated patients, but there was no difference between the two groups in the alleviation of fatigue [79]. Both anorexia and weight loss in lipopolysaccharide-challenged rats could be reversed by chronic treatment with the tricyclic antidepressants desipramine or imipramine, but not with the more selective drugs venlafaxine (Effexor) or paroxetine, suggesting that tricyclics might possess anticachectic properties [80, 81]. However, extended treatment with desipramine produced an anhedonic response, suggesting that long-term treatment might not alleviate depressive and cachectic symptoms.

An increase in body mass index (BMI) was demonstrated following 6 weeks' administration of the tricyclic agents amitriptyline and nortriptyline, but not in paroxetine-treated patients or placebo-treated control subjects [82]. Interestingly, the increase in BMI was preceded by a significant increase in circulating levels of soluble TNF- α receptor p75, suggesting early involvement of the TNF- α signaling pathway in the weight-control process.

Although the utility of antidepressants in treating cachectic symptoms in patients with cancer remains to be fully determined, the connection between the symptoms of cancer-related depression and the initiation of cachexia warrants further ex-

ploration of prophylactic antidepressant use. This is particularly so for patients suffering from cancers with a high susceptibility to depression, such as pancreatic cancer.

A randomized, double-blind, placebo-controlled clinical study has examined the benefit of paroxetine administration prior to the initiation of IFN- α therapy in 40 patients with malignant melanoma [33]. Patients in the paroxetine treatment group received the drug 2 weeks before IFN- α therapy was started and continued to receive paroxetine during the first 12 weeks of interferon treatment. Of the 18 patients who received paroxetine, 11% developed signs of major depression, compared with 45% of placebo-treated patients ($n = 20$). Severe depression led to the discontinuation of IFN- α therapy in just one patient (6%) in the paroxetine group, versus seven patients (35%) in the placebo group. For patients about to undergo cytokine-based cancer treatments, reducing the risk of depression by prophylactic antidepressant treatment appears to improve treatment compliance and tolerability and may thereby improve patient outcomes [35].

PROGESTATIONAL AGENTS

The synthetic progestins megestrol and medroxyprogesterone have drawn significant interest in attempts to manage cancer-related cachexia. Although their mechanisms of action in alleviating cachexia have yet to be determined, megestrol and medroxyprogesterone may act through steroid hormone-like effects that include reducing serum levels of the proinflammatory cytokines IL-1, IL-6, and TNF- α [83]. A number of placebo-controlled clinical trials provide evidence that these drugs can stimulate appetite, reverse weight loss, and improve quality of life in cachectic patients with cancer [56, 84]. However, the weight gain realized through megestrol treatment tends to consist mostly of fat accumulation and water retention, rather than an increase in lean tissue mass.

Thus, megestrol does not appear to fundamentally affect the cachectic process [85]. Further, results of a randomized, double-blind, placebo-controlled clinical trial in 243 patients with small cell lung cancer demonstrated a reduced response to chemotherapy among those treated with megestrol versus patients receiving placebo (68% vs 80%; $P = 0.03$). The megestrol arm also trended toward poorer median survival (8.2 months vs 10.0 months, respectively; $P = 0.49$) [86]. Considering

the modest benefits and the adverse effects of progestational drugs, such as venous thrombosis and peripheral edema, enthusiasm for megestrol and medroxyprogesterone in the treatment of cancer-related cachexia has been justifiably limited. Currently, the administration of megestrol alone or in combination with omega-3 fatty acid dietary supplementation as a means of improving patient outcomes by countering cancer-related cachexia is being evaluated in patients receiving radiation therapy for lung, head, neck, and oropharyngeal cancers.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit prostaglandin synthesis through the cyclooxygenase enzymes COX-1 and COX-2 and are frequently used to treat the symptoms of fever and pain in patients with cancer. An ibuprofen dose of 400 mg 3 times daily has been shown to decrease circulating levels of IL-6 and cortisol in a small study of cachectic patients with colorectal cancer [87]. This effect was associated with diminished serum concentrations of acute phase response proteins and improvement in whole-body protein metabolism [88]. A placebo-controlled study of 16 cachectic patients with pancreatic cancer demonstrated that ibuprofen administration also significantly reduced resting energy expenditure [89].

These results suggest that NSAIDs may improve patient outcome when combined with antitumor therapies. This suggestion is supported by results of a study of 135 patients with cancer suffering from substantial weight loss who were randomly assigned to treatment with the NSAID indomethacin (50 mg twice daily), a corticosteroid, or placebo [90]. Mean survival for the indomethacin-treated patients was more than double that of placebo-treated patients ($P < 0.03$).

Whereas the gastrointestinal toxicity associated with extended use of NSAIDs remains a concern, the newer generation of COX-2-specific inhibitors may help mitigate the gastrointestinal side effects of these agents. Overall, NSAIDs may offer a promising option for treating cachexia in patients with advanced cancer, and more clinical studies are warranted.

MELATONIN

Melatonin is a neuroendocrine-regulating hormone that has a demonstrated ability to reduce

serum TNF- α levels in patients with advanced cancer. In a placebo-controlled clinical study of 86 evaluable patients with advanced metastatic solid tumors, melatonin (20 mg/day) significantly reduced circulating TNF- α levels; substantially fewer patients receiving melatonin than those who received placebo lost more than 10% of their total body weight, suggesting that melatonin might suppress some of the symptoms of cytokine-induced cachexia [91]. Small cell lung cancer patients receiving melatonin in addition to chemotherapy ($n = 34$) demonstrated a significant improvement in 1-year survival compared with those receiving chemotherapy alone ($n = 36$; $P < 0.05$) [92]. Further studies are required, however, to determine what role melatonin supplementation might play in the treatment of cancer-related cachexia.

THALIDOMIDE

The anti-inflammatory agent thalidomide (Thalomid) has been shown to inhibit TNF- α activity in patients suffering from a number of disease states, including cancer. Thalidomide-treated AIDS patients with comorbid tuberculosis gain weight and report significantly improved quality of life, suggesting that thalidomide might also have a role in treating cachectic patients with cancer [93]. Indeed, patients with advanced cancer treated with thalidomide have reported improvements in insomnia, restlessness, nausea, and appetite, resulting in improved patient well-being for a majority of patients [94]. Interest in thalidomide as an antitumor agent has increased after recent evidence suggested that thalidomide also has antiangiogenic properties and that it exhibits antitumor activity in several types of cancer [95–97].

EICOSAPENTAENOIC ACID

Although caloric supplementation has not proven effective at stemming cachectic wasting in patients with cancer [14], one nutritional additive, eicosapentaenoic acid, a major component of fish oil, has shown potential in modulating cytokine and acute phase response protein production. Evidence suggests that eicosapentaenoic acid can suppress IL-6 production by peripheral blood mononuclear cells isolated from cachectic patients with cancer, and supernatants derived from lipopolysaccharide-stimulated mononuclear cells were no longer capable of promoting hepatocyte CRP production after eicosapentaenoic acid treatment [98]. In vivo, oral supplementation with eicosapentaenoic acid

significantly reduced CRP levels in cachectic patients with cancer, although serum IL-6 levels were unaffected in these patients.

A study of 20 patients with advanced pancreatic cancer who were administered fish oil-containing dietary supplements showed significant improvements in appetite and performance status, including a reduction in resting energy expenditure [99]. These results indicate that further clinical study into the efficacy of eicosapentaenoic acid supplementation for the treatment of cancer-associated cachexia is warranted.

ANTICYTOKINE-TARGETED BIOLOGICS

The identification of a cytokine basis for both cancer-related depression and cancer-related cachexia combined with recombinant technologies has allowed for the development of new biologic agents that can target signaling pathway components with a high degree of specificity. The application of such drugs to cytokine signaling in patients with cancer represents a promising new direction that may strike directly at the pathophysiology of cancer-related depression and cachexia.

The injection of TNF- α or the implantation of TNF- α -secreting transformed cells into rodents induces hypophagia and weight loss and activates muscle protein degradation through the ubiquitin pathway [100, 101]. These findings, in addition to the observation of elevated TNF- α levels in patients with cancer-related cachexia, have prompted interest in the potential therapeutic benefits of inhibiting TNF signaling. Indeed, the administration of a soluble TNF type I receptor construct to tumor-bearing rats resulted in significantly increased food consumption and weight gain in comparison with control animals, suggesting that TNF inhibitors may be worthy of study in cachectic patients with cancer [102].

ETANERCEPT

Etanercept (Enbrel) is a receptor-antibody fusion protein that combines the human TNF type II receptor with the human IgG₁ Fc region. Etanercept binds membrane-bound TNF- α and is currently used as a treatment for various arthritic conditions. There are indications from a controlled clinical trial with 234 rheumatoid arthritis patients that etanercept administration can yield significant quality-of-life improvement, as assessed by multiple patient-reported indices, including the energy and mental health mea-

asures on the Medical Outcomes Study questionnaire and a fatigue scale originally developed and validated to measure cancer-related fatigue [103]. Although this report cannot distinguish if the benefits of etanercept are due to alleviation of arthritic symptoms, it raises the question as to whether targeted cytokine modulation may alleviate depression and fatigue in patients with conditions other than rheumatoid arthritis.

In a rodent model of heart failure, anhedonia in rats was relieved by treatment with etanercept [104]. Since anhedonia is relatively common in depression and cachexia, it is plausible that TNF antagonism may reduce the risk of depression and cachexia in vulnerable humans. A small clinical study of patients with myeloid metaplasia reported that 12 of 20 patients receiving etanercept experienced improvement in debilitating constitutional symptoms, such as night sweats, severe fatigue, fever, and weight loss [105].

In addition, a phase I clinical trial examined the use of etanercept to reduce the adverse effects of IL-2 therapy in 24 patients with advanced cancer [106]. Patients receiving etanercept in addition to IL-2 had lower TNF bioactivity and exhibited partial suppression of the typical increases in IL-1, IL-6, IL-8, and CRP levels induced by IL-2 administration. A phase III placebo-controlled, double-blind study is currently examining the efficacy of etanercept to treat cancer-related cachexia. Details of this trial are available online at <http://cancer.gov/clinicaltrials/NCCTG-N00C1>.

INFLIXIMAB

Another biologic of interest for its ability to block TNF- α signaling is infliximab (Remicade), a chimeric IgG₁ monoclonal antibody that inhibits both membrane-bound and soluble forms of TNF- α . Infliximab has been approved by the US Food and Drug Administration for the treatment of rheumatoid arthritis, Crohn's disease, and ankylosing spondylitis. The utility of an antibody treatment for cachectic symptoms was first demonstrated in tumor-bearing mice, in which treatment with a rabbit antibody raised against murine TNF- α was shown to reduce cancer-associated anorexia and loss of body fat and protein [107].

In another study, transgenic mice that constitutively express human TNF- α exhibited anorexia, severe weight loss, and rapid death [108]. Administration of infliximab to these transgenic mice reversed their weight loss and prevented the

high rate of mortality. Currently, a phase II randomized, double-blind, placebo-controlled clinical trial is under way to evaluate the efficacy of infliximab in combination with chemotherapy as a treatment for cancer-related cachexia in patients with pancreatic cancer. Details of this trial are available online at <http://cancer.gov/clinicaltrials/CO168T60>.

IL-6 ANTIBODIES

A cytokine target of great interest is IL-6, which is a key inducer of acute phase response protein production and has been linked to both cancer-related depression and cancer-related cachexia in preclinical and clinical studies. Elevated levels of IL-6 and symptoms of cachexia evident in a mouse adenocarcinoma model were alleviated by the administration of an anti-IL-6 antibody [50]. Antibodies to IL-6 were also capable of relieving the cachectic condition in mice with cervical cancer and substantially prolonging the survival of human tumor-bearing mice [109, 110]. Antibodies to the IL-6 receptor attenuated muscle atrophy in IL-6 transgenic mice [111]. These results strongly support a clinical examination of IL-6 blockade for the treatment of cancer-related cachexia.

In a small study, multiple myeloma patients receiving BE-8, a murine monoclonal antibody to IL-6, demonstrated a low daily production of IL-6 and a complete inhibition of CRP synthesis [112, 113]. The patients also exhibited a decrease in hypercalcemia from bone resorption, a reduction in fever, and reduced tumor mass. Eleven HIV-positive patients with lymphoma were treated daily with BE-8 for 21 days in an open-label study [113]. BE-8 treatment improved lymphoma-associated fever and cachexia. Mean body weight increased by 1.4 kg between day 1 and day 21 and reached 12 kg over 120 days in one patient who received three courses of treatment. In a dose-escalation study of CNTO 328, CRP levels fell below detection levels in 11 of 12 patients with multiple myeloma [114].

Similarly, in a phase II trial, all 16 patients with multiple myeloma receiving BE-8 in addition to chemotherapy demonstrated reduced CRP levels, and the reduction correlated with a high rate of complete response [115]. Daily BE-8 administration for 15 days normalized previously elevated CRP levels in 9 of 10 patients with B-lymphopro-

liferative disorder who completed the treatment schedule, and the reduction in CRP levels again correlated with a high remission rate [116]. Finally, BE-8 treatment reduced CRP levels in three patients with metastatic renal cell carcinoma and, by repressing toxicities related to IL-6 overproduction, improved quality of life for six patients with renal cell carcinoma patients previously treated with IFN- α or IL-2 [117, 118]. A phase I/II clinical trial examining CNTO 328 therapy in renal cell carcinoma is currently under way. On the basis of these early reports, anti-IL-6 antibodies may prove to be a promising therapeutic approach for combating the symptoms of depression and cachexia in patients with cancer.

Conclusion

A significant overlap exists between the vegetative symptoms of major depression and cancer-related cachexia, and these symptoms may be related to cytokine activity, patient quality of life, and survival from disease. Ample evidence suggests a relationship between the appearance of depression-like symptoms and cachexia and the production of proinflammatory cytokines in patients with cancer. The release of cytokines induced by the presence of tumor can influence multiple neuroendocrine pathways, altering mood severe enough to cause clinical depression and weight loss; the consequent depression and severe wasting of cachexia are linked to poor compliance with cancer treatments and decreased survival.

Major depression in patients with cancer is treatable with available antidepressant medications. However, to date, cancer-related cachexia is less amenable to treatment. Recently developed biologic therapies that specifically target cytokine signaling pathways, such as anti-TNF- α and anti-IL-6 molecules, hold promise as more effective therapeutics that may simultaneously alleviate anorexia and depression. By alleviating the symptoms of both depression and cachexia, particularly in combination with existing anti-tumor regimens, these drugs may improve cancer patient survival and enhance quality of life. Further research into possible mechanisms of action, therapeutic targets, and optimal patient selection is warranted to improve the management of depression and cachexia in patients with advanced cancers.

Peer viewpoints on this article by Dr. John A. Glaspy, Ms. Hayley Menzies, Drs. Harvey Max Chochinov and William Breitbart appear on pages 51 and 55.

References

1. Demetrashvili M, Raison CL, Miller AH. Depression in at-risk populations. *Cent Nerv Syst News* 2002;4:9–12.
2. Hirschfeld RM. The comorbidity of major depression and anxiety disorders: recognition and management in primary care. *Prim Care Companion J Clin Psychiatry* 2001;3:244–254.
3. Wittchen HU, Kessler RC, Beesdo K, et al. Generalized anxiety and depression in primary care: prevalence, recognition and management. *J Clin Psychiatry* 2002;63(suppl 8):24–34.
4. Skaer TL, Sclar DA, Robison LM, Galin RS. Trends in the rate of depressive illness and use of antidepressant pharmacotherapy by ethnicity/race: an assessment of office-based visits in the United States, 1992–1997. *Clin Ther* 2000;22:1575–1589.
5. Sharpe M, Strong V, Allen K, et al. Major depression in outpatients attending a regional cancer centre: screening and unmet treatment needs. *Br J Cancer* 2004;90:314–320.
6. Patrick DL, Ferketich SL, Frame PS, et al. National Institute of Health state-of-the-science conference statement: symptom management in cancer: pain, depression and fatigue. July 15–17, 2002. *J Natl Cancer Inst* 2003;95:1110–1117.
7. Carr D, Goudas L, Lawrence D, et al. Management of cancer symptoms: pain depression and fatigue. Evidence Report/Technology Assessment No. 61. AHRQ Publication No. 02-E032. Agency for Healthcare Research and Quality. July 2002.
8. McDaniel JS, Musselman DL, Porter MR, Reed DA, Nemeroff CB. Depression in patients with cancer: diagnosis, biology, and treatment. *Arch Gen Psychiatry* 1995;52:89–99.
9. Chochinov HM. Depression in cancer patients. *Lancet Oncol* 2001;2:499–505.
10. Cleeland CS, Bennett GJ, Dantzer R, et al. Are the symptoms of cancer and cancer treatment due to a shared biologic mechanism? A cytokine-immunologic model of cancer symptoms. *Cancer* 2003;97:2919–2925.
11. Ballenger JC, Davidson JR, Lecrubier Y, et al. Consensus statement on depression, anxiety, and oncology. *J Clin Psychiatry* 2001;62(suppl 8):64–67.
12. Walsh D, Doona M, Molnar M, Lipnickey V. Symptom control in advanced cancer: important drugs and routes of administration. *Semin Oncol* 2000;27:69–83.
13. Stone P, Richardson A, Ream E, et al. Cancer-related fatigue: inevitable, unimportant and untreatable? Results of a multi-centre patient survey. *Cancer Fatigue Forum. Ann Oncol* 2000;11:971–975.
14. Chang VT, Hwang SS, Feuerman M, Kasimis BS. Symptom and quality of life survey of medical oncology patients at a veterans affairs medical center: a role for symptom assessment. *Cancer* 2000;88:1175–1183.
15. Tisdale MJ. Biology of cachexia. *J Natl Cancer Inst* 1997;89:1763–1773.
16. Pirisi A. US researchers find key link in muscle-wasting syndrome. *Lancet* 2000;356:1249.
17. Lee BN, Dantzer R, Langley KE, et al. A cytokine-based neuroimmunologic mechanism of cancer related symptoms. *Neuroimmunomodulation* 2004;11:279–292.
18. Maier SF, Watkins LR. Cytokines for psychologists: implications of bidirectional immune-to-brain communication for understanding behavior, mood, and cognition. *Psychol Rev* 1998;105:83–107.
19. van West D, Maes M. Activation of the inflammatory response system: a new look at the etiopathogenesis of major depression. *Neuro Endocrinol Lett* 1999;20:11–17.
20. Leonard BE. The immune system, depression and the action of antidepressants. *Prog Neuropsychopharmacol Biol Psychiatry* 2001;25:767–780.
21. Kiecolt-Glaser JK, Glaser R. Depression and immune function: central pathways to morbidity and mortality. *J Psychosom Res* 2002;53:873–876.
22. Maes M, Meltzer HY, Bosmans E, et al. Increased plasma concentrations of interleukin-6, soluble interleukin-6, soluble interleukin-2 and transferrin receptor in major depression. *J Affect Disord* 1995;34:301–309.
23. Sluzewska A, Rybakowski JK, Laciak M, et al. Interleukin-6 serum levels in depressed patients before and after treatment with fluoxetine. *Ann N Y Acad Sci* 1995;762:474–476.
24. Musselman DL, Miller AH, Porter MR, et al. Higher than normal plasma interleukin-6 concentrations in cancer patients with depression: preliminary findings. *Am J Psychiatry* 2001;158:1252–1257.
25. Sluzewska A, Rybakowski J, Bosmans E, et al. Indicators of immune activation in major depression. *Psychiatry Res* 1996;64:161–167.
26. Song C, Lin A, Bonaccorso S, et al. The inflammatory response system and the availability of plasma tryptophan in patients with primary sleep disorders and major depression. *J Affect Disord* 1998;49:211–219.
27. Kiecolt-Glaser JK, Preacher KJ, MacCallum RC, et al. Chronic stress and age-related increases in the proinflammatory cytokine IL-6. *Proc Natl Acad Sci U S A* 2003;100:9090–9095.
28. Lanquillon S, Krieg JC, Bening-Abu-Shach U, Vedder H. Cytokine production and treatment response in major depressive disorder. *Neuropsychopharmacology* 2000;25:370–379.
29. Capuron L, Dantzer R. Cytokines and depression: the need for a new paradigm. *Brain Behav Immun* 2003;17(suppl 1):S119–S124.
30. Tchekmedyian NS, Kallich J, McDermott A, Fayers P, Erder MH. The relationship between psychologic distress and cancer-related fatigue. *Cancer* 2003;98:198–203.
31. Raison CL, Nemeroff CB. Cancer and depression: prevalence, diagnosis, and treatment. *Home Health Consultant* 2000;7:34–41.
32. Capuron L, Ravaut A, Gualde N, et al. Association between immune activation and early depressive symptoms in cancer patients treated with interleukin-2-based therapy. *Psychoneuroendocrinology* 2001;26:797–808.
33. Musselman DL, Lawson DH, Gumnick JF, et al. Paroxetine for the prevention of depression induced by high-dose interferon alfa. *N Engl J Med* 2001;344:961–966.
34. Szelényi J. Cytokines and the central nervous system. *Brain Res Bull* 2001;54:329–338.
35. Raison CL, Miller AH. Depression in cancer: new developments regarding diagnosis and treatment. *Biol Psychiatry* 2003;54:283–294.
36. Akiyoshi M, Shimizu Y, Saito M. Interleukin-1 increases norepinephrine turnover in the spleen and lung in rats. *Biochem Biophys Res Commun* 1990;173:1266–1270.
37. Dantzer R, Aubert A, Bluthé R-M, et al. Mechanisms of the behavioural effects of cytokines. In: Dantzer R, Wollman EE, Yirmiya R, eds. *Cytokines, Stress and Depression*. New York, NY: Kluwer Academic/Plenum Publishers; 1999:83–106.
38. Yirmiya R, Pollak Y, Morag M, et al. Illness, cytokines, and depression. *Ann NY Acad Sci* 2000;917:478–487.
39. Dentino AN, Pieper CF, Rao MK, et al. Association of interleukin-6 and other biologic variables with depression in older people living in the community. *J Am Geriatr Soc* 1999;47:6–11.
40. Menkes DB, MacDonald JA. Interferons, serotonin and neurotoxicity. *Psychol Med* 2000;30:259–268.
41. SEER Cancer Statistics Database 1975–2000, National Cancer Institute.
42. Trikha M, Corringham R, Klein B, Rossi JF. Targeted anti-interleukin-6 monoclonal antibody therapy for cancer: a review of the rationale and clinical evidence. *Clin Cancer Res* 2003;9:4653–4665.
43. Smith PC, Hobisch A, Lin DL, Culig Z, Keller ET. Interleukin-6 and prostate cancer progression. *Cytokine Growth Factor Rev* 2001;12:33–40.
44. Shariat SF, Andrews B, Kattan MW, et al. Plasma levels of interleukin-6 and its soluble receptor are associated with prostate cancer progression and metastasis. *Urology* 2001;58:1008–1015.
45. Brown JM. Exploiting the hypoxic cancer cell: mechanisms and therapeutic strategies. *Mol Med Today* 2000;6:157–162.
46. Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow? *Lancet* 2001;357:539–545.
47. Winkler U, Jensen M, Mancke O, et al. Cytokine-release syndrome in patients with B-cell chronic lymphocytic leukemia and high lymphocyte counts after treatment with an anti-CD20 monoclonal antibody (rituximab, IDEC-C2B8). *Blood* 1999;94:2217–2224.
48. Beutler B, Cerami A. Cachectin: more than a tumor necrosis factor. *N Engl J Med* 1987;316:379–385.
49. Balkwill F, Osborne R, Burke F, et al. Evidence for tumour necrosis factor/cachectin production in cancer. *Lancet* 1987;2:1229–1232.
50. Strassmann G, Fong M, Kenney JS, Jacob CO. Evidence for the involvement of interleukin 6 in experimental cancer cachexia. *J Clin Invest* 1992;89:1681–1684.
51. Strassmann G, Fong M, Freter CE, et al. Suramin interferes with interleukin-6 receptor binding in vitro and inhibits colon-26-mediated experimental cancer cachexia in vivo. *J Clin Invest* 1993;92:2152–2159.
52. Mori K, Fujimoto-Ouchi K, Ishikawa T, et al. Murine interleukin-12 prevents the development of cancer cachexia in a murine model. *Int J Cancer* 1996;67:849–855.
53. Cahlin C, Korner A, Axelsson H, et al. Experimental cancer cachexia: the role of host-derived cytokines interleukin (IL)-6, IL-12, interferon-gamma,

and tumor necrosis factor alpha evaluated in gene knockout, tumor-bearing mice on C57 Bl background and eicosanoid-dependent cachexia. *Cancer Res* 2000;60:5488–5493.

54. Zaki MH, Nemeth JA, Trikha M. CNTO 328, a monoclonal antibody to IL-6, inhibits human tumor-induced cachexia in nude mice. *Int J Cancer* 2004;111:592–595.

55. Husain TM, Kim DH. C-reactive protein and erythrocyte sedimentation rate in orthopaedics. *Univ Pa Orthop J* 2002;15:13–16.

56. Fearon KC, Moses AG. Cancer cachexia. *Int J Cardiol* 2002;85:73–81.

57. Staal-van den Brekel AJ, Dentener MA, Schols AM, Buurman WA, Wouters EF. Increased resting energy expenditure and weight loss are related to a systemic inflammatory response in lung cancer patients. *J Clin Oncol* 1995;13:2600–2605.

58. Scott HR, McMillan DC, Crilly A, McArdle CS, Milroy R. The relationship between weight loss and interleukin 6 in non-small-cell lung cancer. *Br J Cancer* 1996;73:1560–1562.

59. Wigmore SJ, Fearon KC, Maingay JP, Lai PB, Ross JA. Interleukin-8 can mediate acute-phase protein production by isolated human hepatocytes. *Am J Physiol* 1997;273:E720–E726.

60. Harvie MN, Campbell IT, Howell A, et al. The influence of the acute-phase response on energy balance in advanced cancer patients. *Proc Nutr Soc* 1998;57:103a.

61. Blay JY, Negrier S, Combaret V, et al. Serum level of interleukin 6 as a prognosis factor in metastatic renal cell carcinoma. *Cancer Res* 1992;52:3317–3322.

62. Falconer JS, Fearon KC, Ross JA, et al. Acute-phase protein response and survival duration of patients with pancreatic cancer. *Cancer* 1995;75:2077–2082.

63. Nielsen HJ, Pappot H, Christensen IJ, et al. Association between plasma concentrations of plasminogen activator inhibitor-1 and survival in patients with colorectal cancer. *BMJ* 1998;316:829–830.

64. Schaur RJ, Semmelrock HJ, Schauenstein E, Kronberger L. Tumor host relations. II: influence of tumor extent and tumor site on plasma cortisol of patients with malignant diseases. *J Cancer Res Clin Oncol* 1979;93:287–292.

65. Knapp ML, al-Sheibani S, Riches PG, Hanham IW, Phillips RH. Hormonal factors associated with weight loss in patients with advanced breast cancer. *Ann Clin Biochem* 1991;28:480–486.

66. Bessey PQ, Watters JM, Aoki TT, Wilmore DW. Combined hormonal infusion simulates the metabolic response to injury. *Ann Surg* 1984;200:264–281.

67. Watters JM, Bessey PQ, Dinarello CA, Wolff SM, Wilmore DW. Both inflammatory and endocrine mediators stimulate host responses to sepsis. *Arch Surg* 1986;121:179–190.

68. Grunfeld C, Zhao C, Fuller J, et al. Endotoxin and cytokines induce expression of leptin, the ob gene product, in hamsters. *J Clin Invest* 1996;97:2152–2157.

69. Zumbach MS, Boehme MW, Wahl P, et al. Tumor necrosis factor increases serum leptin levels in humans. *J Clin Endocrinol Metab* 1997;82:4080–4082.

70. Simons JP, Schols AM, Campfield LA, Wouters EF, Saris WH. Plasma concentration of total leptin and human lung-cancer-associated cachexia. *Clin Sci (Lond)* 1997;93:273–277.

71. Spiegel D, Bloom JR, Kraemer HC, Gotthel

E. Effect of psychosocial treatment on survival of patients with metastatic breast cancer. *Lancet* 1989;2:888–891.

72. Fawzy FI, Fawzy NW, Hyun CS, et al. Malignant melanoma: effects of an early structured psychiatric intervention, coping, and affective state on recurrence and survival 6 years later. *Arch Gen Psychiatry* 1993;50:681–689.

73. Ross L, Boesen EH, Dalton SO, Johansen C. Mind and cancer: does psychosocial intervention improve survival and psychological well-being? *Eur J Cancer* 2002;38:1447–1457.

74. Goodwin PJ, Leszcz M, Ennis M, et al. The effect of group psychosocial support on survival in metastatic breast cancer. *N Engl J Med* 2001;345:1719–1726.

75. Fisch MJ, Loehrer PJ, Kristeller J, et al. Fluoxetine versus placebo in advanced cancer outpatients: a double blind trial of the Hoosier Oncology Group. *J Clin Oncol* 2003;21:1937–1943.

76. Xia Z, DePierre JW, Nassberger L. Tricyclic antidepressants inhibit IL-6, IL-1 beta and TNF-alpha release in human blood monocytes and IL-2 and interferon-gamma in T cells. *Immunopharmacology* 1996;34:27–37.

77. Kubera M, Kenis G, Bosmans E, Scharpe S, Maes M. Effects of serotonin and serotonergic agonists and antagonists on the production of interferon-gamma and interleukin-10. *Neuropsychopharmacology* 2000;23:89–98.

78. Kubera M, Holan V, Basta-Kaim A, et al. Effect of desipramine on immunological parameters in mice, and their reversal by stress. *Int J Immunopharmacol* 1998;20:429–438.

79. Morrow GR, Hickok JT, Roscoe JA, et al. Differential effects of paroxetine on fatigue and depression: a randomized, double-blind trial from the University of Rochester Cancer Center Community Clinical Oncology Program. *J Clin Oncol* 2003;21:4635–4641.

80. Shen Y, Connor TJ, Nolan Y, Kelly JP, Leonard BE. Differential effect of chronic antidepressant treatments on lipopolysaccharide-induced depressive-like behavioural symptoms in the rat. *Life Sci* 1999;65:1773–1786.

81. Yirmiya R. Endotoxin produces a depressive-like episode in rats. *Brain Res* 1996;711:163–174.

82. Hinze-Selch D, Schulz A, Kraus T, et al. Effects of antidepressants on weight and on the plasma levels of leptin, TNF-alpha and soluble TNF receptors: a longitudinal study in patients treated with amitriptyline or paroxetine. *Neuropsychopharmacology* 2000;23:13–19.

83. Inui A. Cancer anorexia-cachexia syndrome: current issues in research and management. *CA Cancer J Clin* 2002;52:72–91.

84. Maltoni M, Nanni O, Scarpi E, et al. High-dose progestins for the treatment of cancer anorexia-cachexia syndrome: a systematic review of randomised clinical trials. *Ann Oncol* 2001;12:289–300.

85. Loprinzi CL, Schaid DJ, Dose AM, Burnham NL, Jensen MD. Body-composition changes in patients who gain weight while receiving megestrol acetate. *J Clin Oncol* 1993;11:152–154.

86. Rowland KM Jr, Loprinzi CL, Shaw EG, et al. Randomized double-blind placebo-controlled trial of cisplatin and etoposide plus megestrol acetate/ placebo in extensive-stage small-cell lung cancer: a

North Central Cancer Treatment Group study. *J Clin Oncol* 1996;14:135–141.

87. McMillan DC, Leen E, Smith J, et al. Effect of extended ibuprofen administration on the acute phase protein response in colorectal cancer patients. *Eur J Surg Oncol* 1995;21:531–534.

88. Preston T, Fearon KC, McMillan DC, et al. Effect of ibuprofen on the acute-phase response and protein metabolism in patients with cancer and weight loss. *Br J Surg* 1995;82:229–234.

89. Wigmore SJ, Falconer JS, Plester CE, et al. Ibuprofen reduces energy expenditure and acute-phase protein production compared with placebo in pancreatic cancer patients. *Br J Cancer* 1995;72:185–188.

90. Lundholm K, Gelin J, Hyltander A, et al. Anti-inflammatory treatment may prolong survival in undernourished patients with metastatic solid tumors. *Cancer Res* 1994;54:5602–5606.

91. Lissoni P, Paolorossi F, Tancini G, et al. Is there a role for melatonin in the treatment of neoplastic cachexia? *Eur J Cancer* 1996;32A:1340–1343.

92. Lissoni P, Paolorossi F, Ardzioia A, et al. A randomized study of chemotherapy with cisplatin plus etoposide versus chemoendocrine therapy with cisplatin, etoposide and the pineal hormone melatonin as a first-line treatment of advanced non-small-cell lung cancer patients in a poor clinical state. *J Pineal Res* 1997;23:15–19.

93. Klausner JD, Makonkawkeyoon S, Akarasewi P, et al. The effect of thalidomide on the pathogenesis of human immunodeficiency virus type 1 and M tuberculosis infection. *J Acquir Immune Defic Syndr Hum Retrovirology* 1996;11:247–257.

94. Bruera E, Neumann CM, Pituskin E, et al. Thalidomide in patients with cachexia due to terminal cancer: preliminary report. *Ann Oncol* 1999;10:857–859.

95. Strupp C, Germing U, Aivado M, et al. Thalidomide for the treatment of patients with myelodysplastic syndromes. *Leukemia* 2002;16:1–6.

96. Rajkumar SV. Thalidomide in newly diagnosed multiple myeloma and overview of experience in smoldering/indolent disease. *Semin Hematol* 2003;40(4 suppl):17–22.

97. Amato RJ. Thalidomide therapy for renal cell carcinoma. *Crit Rev Oncol Hematol* 2003;46(suppl):S59–S65.

98. Wigmore SJ, Fearon KC, Maingay JP, Ross JA. Down-regulation of the acute-phase response in patients with pancreatic cancer cachexia receiving oral eicosapentaenoic acid is mediated via suppression of interleukin-6. *Clin Sci (Lond)* 1997;92:215–221.

99. Barber MD, Ross JA, Voss AC, Tisdale MJ, Fearon KC. The effect of an oral nutritional supplement enriched with fish oil on weight-loss in patients with pancreatic cancer. *Br J Cancer* 1999;81:80–86.

100. Tracey KJ, Morgello S, Koplin B, et al. Metabolic effects of cachectin/tumor necrosis factor are modified by site of production: cachectin/tumor necrosis factor-secreting tumor in skeletal muscle induces chronic cachexia, while implantation in brain induces predominantly acute anorexia. *J Clin Invest* 1990;86:2014–2024.

101. Llovera M, Garcia-Martinez C, Agell N, Lopez-Soriano FJ, Argiles JM. TNF can directly induce the expression of ubiquitin-dependent proteolytic system

in rat soleus muscles. *Biochem Biophys Res Commun* 1997;230:238–241.

102. Torelli GF, Meguid MM, Moldawer LL, et al. Use of recombinant human soluble TNF receptor in anorectic tumor-bearing rats. *Am J Physiol* 1999;277:R850–R855.

103. Mathias SD, Colwell HH, Miller DP, et al. Health-related quality of life and functional status of patients with rheumatoid arthritis randomly assigned to receive etanercept or placebo. *Clin Ther* 2000;22:128–139.

104. Grippo AJ, Francis J, Weiss RM, Felder RB, Johnson AK. Cytokine mediation of experimental heart failure-induced anhedonia. *Am J Physiol Regul Integr Comp Physiol* 2003;284:R666–R673.

105. Steensma DP, Mesa RA, Li CY, Gray L, Tefferi A. Etanercept, a soluble tumor necrosis factor receptor, palliates constitutional symptoms in patients with myelofibrosis with myeloid metaplasia: results of a pilot study. *Blood* 2002;99:2252–2254.

106. Trehu EG, Mier JW, Dubois JS, et al. Phase I trial of interleukin 2 in combination with the soluble tumor necrosis factor receptor p75 IgG chimera. *Clin Cancer Res* 1996;2:1341–1351.

107. Sherry BA, Gelin J, Fong Y, et al. Anticachectin/tumor necrosis factor- α antibodies attenuate

development of cachexia in tumor models. *FASEB J* 1989;3:1956–1962.

108. Siegel SA, Shealy DJ, Nakada MT, et al. The mouse/human chimeric monoclonal antibody cA2 neutralizes TNF in vitro and protects transgenic mice from cachexia and TNF lethality in vivo. *Cytokine* 1995;7:15–25.

109. Tamura S, Ouchi KF, Mori K, et al. Involvement of human interleukin 6 in experimental cachexia induced by a human uterine cervical carcinoma xenograft. *Clin Cancer Res* 1995;1:1353–1358.

110. Mauray S, Fuzzati-Armentero MT, Trouillet P, et al. Epstein-Barr virus-dependent lymphoproliferative disease: critical role of IL-6. *Eur J Immunol* 2000;30:2065–2073.

111. Tsujinaka T, Fujita J, Ebisui C, et al. Interleukin 6 receptor antibody inhibits muscle atrophy and modulates proteolytic systems in interleukin 6 transgenic mice. *J Clin Invest* 1996;97:244–249.

112. Bataille R, Barlogie B, Lu ZY, et al. Biologic effects of anti-interleukin-6 murine monoclonal antibody in advanced multiple myeloma. *Blood* 1995;86:685–691.

113. Emilie D, Wijdenes J, Gisselbrecht C, et al. Administration of an anti-interleukin-6 monoclonal antibody to patients with acquired immunodeficiency syndrome and lymphoma: effect on lym-

phoma growth and on B clinical symptoms. *Blood* 1994;84:2472–2479.

114. van Zaanen HC, Lokhorst HM, Aarden LA, et al. Chimaeric anti-interleukin 6 monoclonal antibodies in the treatment of advanced multiple myeloma: a phase I dose-escalating study. *Br J Haematol* 1998;102:783–790.

115. Moreau P, Harousseau JL, Wijdenes J, et al. A combination of anti-interleukin 6 murine monoclonal antibody with dexamethasone and high-dose melphalan induces high complete response rates in advanced multiple myeloma. *Br J Haematol* 2000;109:661–664.

116. Haddad E, Paczesny S, Leblond V, et al. Treatment of B-lymphoproliferative disorder with a monoclonal anti-interleukin-6 antibody in 12 patients: a multicenter phase 1-2 clinical trial. *Blood* 2001;97:1590–1597.

117. Blay JY, Rossi JF, Wijdenes J, et al. Role of interleukin-6 in the paraneoplastic inflammatory syndrome associated with renal-cell carcinoma. *Int J Cancer* 1997;72:424–430.

118. Legouffe E, Liautard J, Gaillard JP, et al. Human anti-mouse antibody response to the injection of murine monoclonal antibodies against IL-6. *Clin Exp Immunol* 1994;98:323–329.