

Cancer Chemotherapy-Related Symptoms: Evidence to Suggest a Role for Proinflammatory Cytokines

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Purpose/Objectives: To provide an overview of the evidence that supports a role for the proinflammatory cytokines interleukin-1 β (IL-1 β), tumor necrosis factor- α (TNF- α), and interleukin-6 (IL-6) in the etiology of cancer chemotherapy-related symptoms.

Data Sources: Electronic nursing, psychology, and medicine databases; online meeting abstracts; and personal experimental observations.

Data Synthesis: Substantial evidence implicates the proinflammatory cytokines IL-1 β , TNF- α , and IL-6 in the etiology of chemotherapy-related anorexia, cachexia, anemia, pain, sleep disturbance, fatigue, and depression.

Conclusions: Further investigation into the role of these cytokines in the genesis of chemotherapy-related symptoms is warranted. The development of appropriate animal models likely will be key to understanding the relationship among cancer chemotherapy, proinflammatory cytokines, and symptoms.

Implications for Nursing: Nurses traditionally have been leaders in symptom management. The symptoms experienced by patients undergoing chemotherapy have a profound negative impact on quality of life and patients' ability to receive prescribed treatments. An understanding of potential mechanisms underlying the physiologic and behavioral consequences of chemotherapy administration will aid nurses in the development of interventions to effectively manage chemotherapy-related symptoms.

Key Points . . .

- Patients receiving chemotherapy experience a constellation of unpleasant symptoms such as fatigue, anorexia, anemia, cachexia, depression, pain, and sleep disturbance. All of the symptoms can have profoundly negative effects on quality of life and patients' ability to receive prescribed treatments.
- Clinical investigators have hypothesized that proinflammatory cytokines play a role in the genesis of chemotherapy-related symptoms.
- The idea of a common underlying mechanism for several chemotherapy-related symptoms contributed to current interest in understanding the structure of the relationships among concurrent symptoms, often referred to as symptom clusters, and also generated concern that the long-standing tradition of studying symptoms in isolation may have obscured the possibility that the symptoms might be produced by the same mechanism.

Poulter, & Hayley, 2005), which also occur in patients with cancer. Although sickness-behavior-like symptoms can exist in treatment-naïve patients, where they often are associated

Patients undergoing cancer chemotherapy with mechanistically distinct drugs display many of the classic symptoms of sickness behavior caused by the production of the proinflammatory cytokines interleukin-1 β (IL-1 β), tumor necrosis factor- α (TNF- α), and interleukin-6 (IL-6) by macrophages and other immune cells in response to an immune challenge (Bluthe, Laye, et al., 2000; Bluthe, Michaud, Poli, & Dantzer, 2000). For instance, similar to people with viral or bacterial infections, patients with cancer complain of fatigue, experience loss of appetite and pain, and suffer sleep disturbance (Lee, Dantzer, et al., 2004). Prolonged production of proinflammatory cytokines also can lead to a variety of symptoms, including anemia (Means, 2004), fat and muscle wasting (cachexia) (Argiles, Busquets, & Lopez-Soriano, 2005), and depression (Anisman, Merali,

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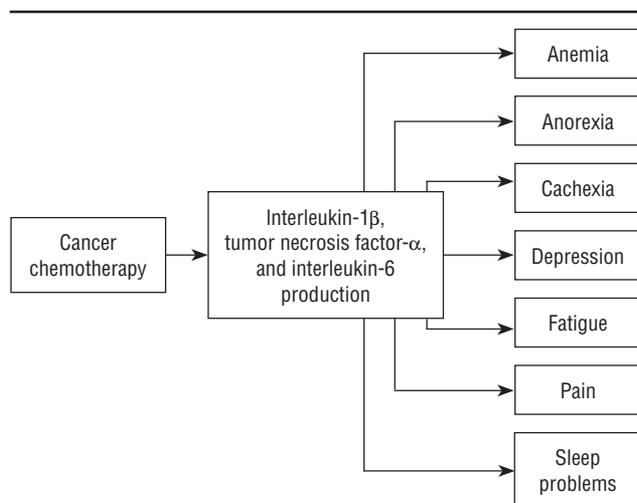
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with advanced disease, they are associated more frequently with treatment and can exist even in the absence of detectable tumor burden, as in the case of patients with breast cancer undergoing adjuvant therapy after tumor resection (Pusztai et al., 2004). Symptoms frequently begin at the onset of treatment, persist throughout treatment, and slowly decline thereafter (Curt et al., 2000; Olson et al., 2002; Schwartz, 2000; Schwartz et al., 2000) and can be so severe that they can affect patients' quality of life and their ability to adhere to treatment schedules (Bernard et al., 1991; ten Tije et al., 2004). The clinical observations suggest that, in early-stage, malignant disease, treatment rather than cancer triggers patient symptoms.

Researchers have recognized that cancer chemotherapy drugs with distinct modes of action share a common ability to activate p38 mitogen-activated protein kinase (p38 MAPK), a cellular enzyme that plays a central role in the production of proinflammatory cytokines and consequently in inducing sickness behavior (Badger et al., 1996; Branger et al., 2002). The observations led the authors of the current article to hypothesize that cancer chemotherapy drugs activate p38 MAPK in macrophages and in other cells of the innate immune system to induce IL-1 β , TNF- α , and IL-6 production and sickness behavior, hereafter referred to as chemotherapy-related symptoms. The model that guides this review is illustrated in Figure 1.

Chemotherapy, p38 Mitogen-Activated Protein Kinase, Interleukin-1 β , Tumor Necrosis Factor- α , and Interleukin-6

The p38 MAPK is activated in response to a number of stimuli, including pathogens, cytokines, growth factors, and



Note. The authors hypothesize that chemotherapeutic drugs activate p38 mitogen-activated protein kinase in macrophages and in other cells of the innate immune system to induce interleukin-1 β , tumor necrosis factor- α , and interleukin-6 production and sickness behavior, referred to as chemotherapy-related symptoms.

Figure 1. The Proposed Relationship Between Cancer Chemotherapy, Interleukin-1 β , Tumor Necrosis Factor- α , and Interleukin-6 Production and Chemotherapy-Related Symptoms

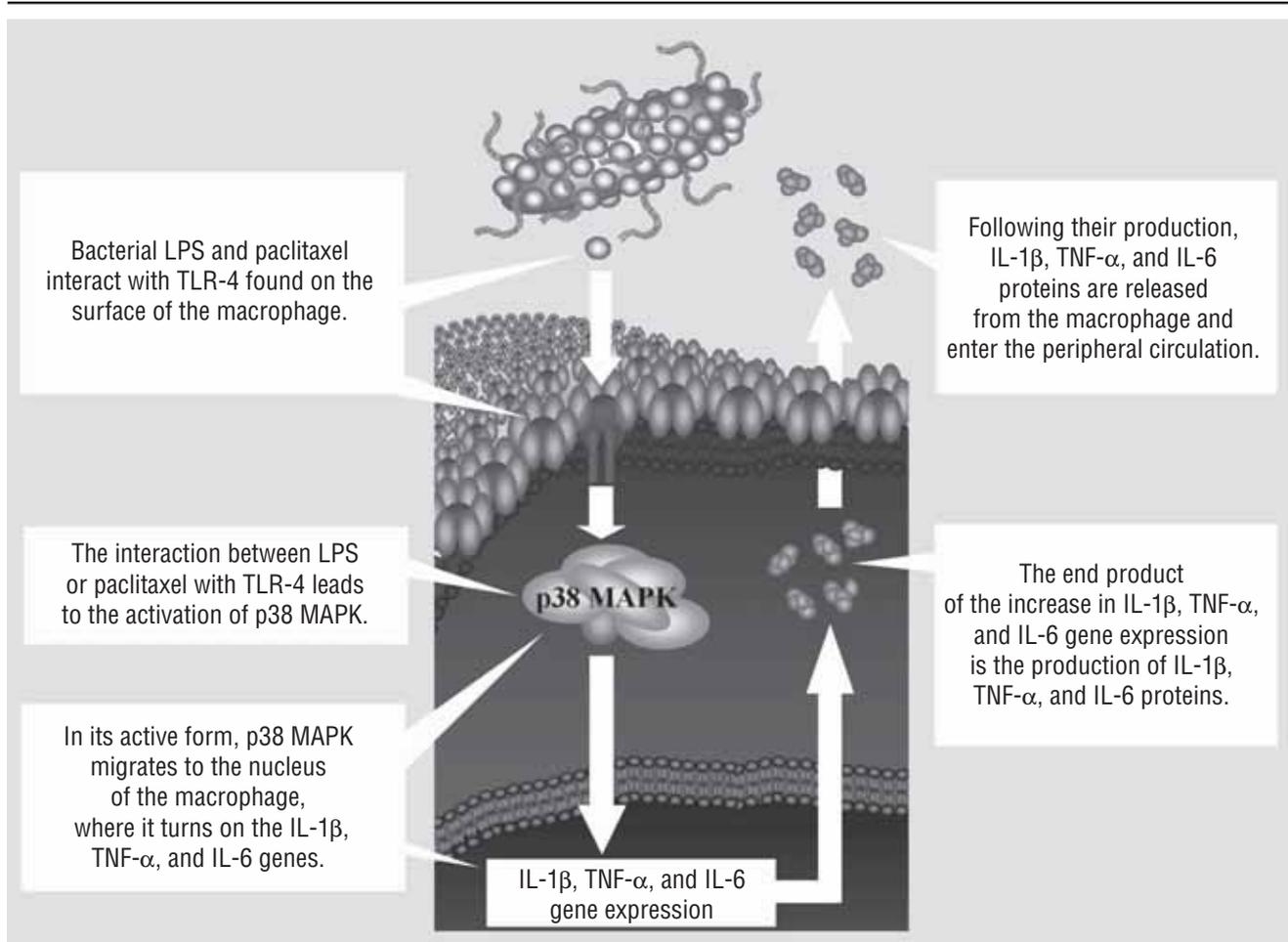
environmental stressors (Roux & Blenis, 2004). The activity of the enzyme is central to the production of proinflammatory cytokines in response to an immune challenge. Several cancer chemotherapy drugs have been shown to increase the activity of the enzyme in a variety of cancer cell cultures grown in laboratories (Olson & Hallahan, 2004). However, whether the drugs can activate p38 MAPK in macrophages and similar cells to induce proinflammatory cytokine production has been largely unexplored. In a recent study, the widely used drug etoposide (VP-16), which prevents the unwinding of DNA during replication, thereby blocking new DNA synthesis, was found to activate p38 MAPK in macrophages isolated from mice and induce the production of IL-6 (Wood et al., in press). Blocking p38 MAPK activity with a specific p38 MAPK inhibitor also blocked the VP-16-mediated induction of IL-6 production in the cells (Wood et al.). Similar results were obtained following treatment of macrophages with paclitaxel, which exerts its toxic effect on cancer cells by binding to a cell protein called β -tubulin, an essential component of the cell scaffold (Haldar, Basu, & Croce, 1997). In addition to that effect, paclitaxel binds to toll-like receptor-4 (TLR-4), a protein receptor present on the surface of macrophages that interacts with lipopolysaccharide (LPS), a component of the cell wall of gram-negative bacteria. The interaction between LPS and TLR-4 sets off a chain of events in the macrophage that ultimately leads to the production and release of proinflammatory cytokines (see Figure 2). Mice that lack the receptor do not produce proinflammatory cytokines or develop sickness behavior in response to LPS injection (Segreti, Gheusi, Dantzer, Kelley, & Johnson, 1997). Thus, paclitaxel has a unique property in that it mimics the action of LPS. It is not surprising, then, that the drug can induce IL-1 β and TNF- α (Bogdan & Ding, 1992; Ding, Porteu, Sanchez, & Nathan, 1990) and IL-6. As with VP-16, the induction of IL-6 production by paclitaxel depends on the activity of p38 MAPK (Elsea, Nail, Druker, & Wood, 2006). The findings suggest that the induction of proinflammatory cytokines by mechanistically distinct chemotherapy drugs may be a general phenomena linked to the ability of the drugs to activate p38 MAPK.

Previous studies have shown that injecting mice with LPS induces a rapid increase in serum levels of IL-1 β , TNF- α , and IL-6 (Lyzczak, 2004). Injection of VP-16 into healthy mice also rapidly increased serum levels of IL-6 (Wood et al., in press). The finding is consistent with the idea that, like LPS, VP-16 can activate an immune response in mice—and the activation of the immune response and subsequent production of proinflammatory cytokines causes chemotherapy-related symptoms. Thus, consistent with the finding that VP-16 induces proinflammatory cytokines, VP-16 administration also induces behavioral and physiologic changes indicative of chemotherapy-related symptoms (Wood et al.).

Relationship Between Chemotherapy-Related Symptoms and Interleukin-1 β , Tumor Necrosis Factor- α , and Interleukin-6

Anemia

Anemia is highly prevalent in people with cancer, ranging from 40%–90% depending on stage and type of cancer and chemotherapy intensity (Groopman & Itri, 1999; Knight,



IL-1 β —interleukin-1 β ; IL-6—interleukin-6; LPS—lipopolysaccharide; p38 MAPK—p38 mitogen-activated protein kinase; TLR-4—toll-like receptor-4; TNF- α —tumor necrosis factor- α

Note. Bacterial LPS and the LPS-mimetic paclitaxel interact with the TLR-4 that lies on the surface of macrophages and other immune cells. The interaction leads to the activation of p38 MAPK, which, in turn, triggers the production of IL-1 β , TNF- α , and IL-6. The cytokines are released from the cell into the circulation and cause sickness behavior.

Figure 2. The Proposed Role of p38 Mitogen-Activated Protein Kinase in the Production of Interleukin-1 β , Tumor Necrosis Factor- α , and Interleukin-6 by Macrophages in Response to Bacterial Lipopolysaccharide and Paclitaxel

Wade, & Balducci, 2004). Cancer-associated anemia has similarities with anemia of chronic disease, which often is termed inflammatory anemia. Considerable data have been generated to suggest that inflammatory anemia results from a defect in iron reutilization that leads to hypoferrremia (low serum iron levels), inhibition of production of erythropoietin (a cytokine synthesized by the kidneys that is required for erythropoiesis), and a decrease in the proliferation or survival of red cell progenitor cells (Jelkmann, Pagel, Wolff, & Fandrey, 1992; Mercadante, Gebbia, Marrazzo, & Filosto, 2000). IL-1 β , TNF- α , and IL-6 govern all of those processes. IL-6 promotes the storage of iron in macrophages and inhibits the uptake of iron from the intestines (Hentze, Muckenthaler, & Andrews, 2004). IL-1 β and TNF- α can negatively regulate erythropoiesis by inhibiting the expression of erythropoietin (Macdougall & Cooper, 2002). TNF- α can have a direct effect on erythroid cells by inhibiting proliferation of immature red

blood cells (proerythroblasts and basophilic erythroblasts) even in the presence of erythropoietin and also inhibiting the maturation of the primitive cells (Testa, 2004). In patients with cancer, anemia increases over the course of chemotherapy treatment (Mercadante et al., 2000), and the fall in red blood cell parameters often is attributed to the direct toxic effects of chemotherapy on the bone marrow or kidneys, resulting in the destruction of erythroid progenitor cells and decreased production of erythropoietin, respectively (Groopman & Itri; Mercadante et al., 2000). The induction of IL-1 β , TNF- α , and IL-6 by chemotherapy drugs as a contributing factor in chemotherapy-related anemia has not been explored.

Anorexia and Cachexia

Anorexia, a loss of appetite and increased satiety, is commonplace in patients with cancer, especially those receiving chemotherapy. The associated decline in nutritional intake

often is associated with progressive weight loss. Several studies have attempted to determine the role of proinflammatory cytokines in food intake. Conflicting data have been generated regarding the role of IL-6 in food intake. Peripheral administration of IL-6 (i.e., IV or intraperitoneal) did not induce anorexia in animal models (Hill, Siegel, Rounds, & Wilmore, 1997; Kent, Bret-Dibat, Kelley, & Dantzer, 1996; Laviano et al., 1999). In the studies, reduction in food intake could be induced only by peripheral administration of IL-1 β (Hill et al.; Kent et al.; Laviano et al.). In another study, peripheral administration of IL-6 was shown to reduce food intake in rats (McCarthy, 2000). Yet weight loss in patients with cancer cannot be attributed to anorexia alone because interventions aimed at increasing caloric intake do not necessarily reverse weight loss (Tisdale, 2004). Unlike the weight loss associated with anorexia, which is predominantly skeletal muscle sparing, cachexia involves the accelerated loss of adipose tissue and skeletal muscle. Experimental animal models have implicated IL-1 β , TNF- α , and IL-6 in cachexia (Enomoto et al., 2004; Zaki, Nemeth, & Trikha, 2004). For instance, Castleman disease is a blood disorder caused by the overproduction of IL-6 by lymphoid cells, which results in a massive increase in the number of the cells and elevated serum levels of IL-6. The disorder presents with lymphadenopathy and several systemic symptoms, including fatigue, anorexia, and progressive wasting (Waterston & Bower, 2004). In a clinical study, a monoclonal antibody tocilizumab, or MRA (Chugai Pharmaceutical Co. Ltd., Roche Group, Tokyo, Japan), that inactivates serum IL-6 was administered via IV to people with Castleman disease (Nishimoto et al., 2005). In a 16-week period, MRA recipients displayed a significant decrease in lymphadenopathy, an increase in weight and food intake, and a decline in fatigue levels (Nishimoto et al.).

Depression

Proinflammatory cytokines may contribute to the high rate of depression in patients with cancer (Dantzer, 2004b). Musselman et al. (2001) found that serum IL-6 levels were significantly increased in depressed patients compared to their nondepressed counterparts. Consistent with a role for proinflammatory cytokines in depressive illness is the finding that cytokine therapies, such as interferon- α and interleukin-2, are associated with occurrence of significant depressive symptoms in approximately 50% of patients (Capuron, Ravaud, Miller, & Dantzer, 2004; Okereke, 2002; Schaefer, Horn, et al., 2004; Schaefer, Schmidt, Horn, Schmid-Wendtner, & Volkenandt, 2004; Scheibel, Valentine, O'Brien, & Meyers, 2004; Trask, Paterson, Esper, Pau, & Redman, 2004). In addition to IL-6, serum IL-1 β and TNF- α are increased in patients with depression, and the serum levels of the cytokines correlate with symptom severity (Thomas et al., 2005; Tuglu, Kara, Caliyurt, Vardar, & Abay, 2003).

Fatigue

Not only is fatigue the most prevalent symptom associated with cancer chemotherapy, but it also is the most distressing and has a profoundly negative effect on physical functioning and quality of life (Ferrell et al., 1996; Nail & Winningham, 1995; Vogelzang et al., 1997). Healthcare professionals usually measure fatigue by asking patients to rate their energy levels or to rate how tired they feel (Piper, 1990). Several

studies have shown that the subjective measurement of fatigue in patients with breast cancer undergoing chemotherapy correlates with a decrease in voluntary motor activity (Berger, 1998; Berger & Farr, 1999; Berger & Higginbotham, 2000). In the studies, women who reported high levels of fatigue were less active during the day, took more naps, and spent more time resting. In rodent models of sickness behavior, fatigue also is inferred from a decrease in voluntary motor activity (Chao, DeLaHunt, Hu, Close, & Peterson, 1992; Ottenweller et al., 1998; Sheng, Hu, Lamkin, Peterson, & Chao, 1996). Each chemotherapy-related symptom likely can affect the subjective sensation of fatigue in patients with cancer. Considering the potential interrelationship, cancer-related fatigue is considered a multidimensional problem often characterized by weariness, muscle weakness, lack of energy, low motivation, difficulty concentrating, and sleepiness (Glaus, 1998; Winningham et al., 1994). The National Comprehensive Cancer Network described cancer-related fatigue as "an unusual, persistent subjective sense of tiredness related to cancer or cancer treatment that interferes with usual functioning" (Mock et al., 2003, p. 309). In a recent study (Wood et al., in press), serum levels of IL-6 correlated with voluntary wheel-running activity in mice administered VP-16. The levels of IL-6 in the study were measured no later than 24 hours after the last VP-16 dose or measured in mice with significant tumor burden.

Only one clinical study so far has focused on correlating fatigue in patients with cancer and the levels of serum cytokines within days of chemotherapy treatment. Puzstai et al. (2004) attempted to correlate changes in serum levels of IL-1 β , IL-6, and TNF- α in patients with breast cancer during paclitaxel treatment with the subjective symptoms of treatment, including fatigue. Symptoms associated with paclitaxel treatment, such as flu-like symptoms, joint pain, and fatigue, peaked in intensity on day 3, when serum cytokine levels were measured. Patients treated with paclitaxel had increased serum levels of IL-6 but not IL-1 β or TNF- α . Increased serum levels of IL-6 correlated with flu-like symptoms but not with fatigue. However, how the levels of serum proinflammatory cytokines varied over one treatment cycle is unknown. That would have involved performing serial blood draws during or immediately after treatment to just prior to the next treatment cycle to determine the kinetics of serum inflammatory cytokine expression. Without the information, researchers cannot conclude whether the presence or absence of a particular serum cytokine in patients receiving chemotherapy is associated with fatigue over time. If the administration of chemotherapy is the trigger for immune activation and IL-1 β , TNF- α , and IL-6 production, the fact that Puzstai et al. failed to show elevated levels of IL-1 β and TNF- α in the sera of patients administered paclitaxel three days earlier is not surprising, given the transient expression of the cytokines in the serum following immune challenge (Kemna, Pickkers, Nemeth, van der Hoeven, & Swinkels, 2005; Purswani, Eckert, Arora, & Noel, 2002). Researchers know from animal models of sickness behavior that IL-1 β , TNF- α , and IL-6 can be found in the serum within an hour of immune challenge, reach peak levels within several hours, and then rapidly decline toward baseline (Purswani et al.). But the sickness behavior associated with the initial rise in the level of the cytokines, including a decline in voluntary activity, can persist for several days (Chao et al., 1992; Ottenweller et al., 1998; Purswani et al.; Sheng et al., 1996),

and the persistence of such behavior is associated with the expression of the cytokines in the brain, not the serum (Sheng et al., 1996).

Probably the most compelling evidence to suggest a role for IL-1 β , TNF- α , and IL-6 in the induction of fatigue has come from studies of several chronic inflammatory diseases in which the cytokines have been proposed to play a central role. For instance, the fatigue associated with Castleman disease can be decreased by administration of monoclonal antibodies that block the activity of IL-6 (Nishimoto et al., 2005). Fatigue also is a common symptom of rheumatoid arthritis. IL-1 β and TNF- α have been implicated in the etiology of rheumatoid arthritis (Goldblatt & Isenberg, 2005), and monoclonal antibodies that block the activity of the cytokines in the blood and in the synovial fluid of the affected joints have proven effective at reducing the severity of disease and levels of fatigue (Omdal & Gunnarsson, 2004; Weinblatt et al., 2003).

Pain

Peripheral neuropathy, which is nerve damage (usually affecting the feet and legs) that causes pain, numbness, or a tingling feeling, is a common dose-limiting toxicity in patients with cancer undergoing treatment with paclitaxel, cisplatin, or vincristine (Dropcho, 2004; Ocean & Vahdat, 2004). Chemotherapy drugs recently have been used to develop animal models of neuropathic pain (Nakamura, Shimizu, Nishijima, Ueno, & Arakawa, 2001; Ogawa et al., 2001; Ozturk, Erdogan, Anlar, Kosem, & Taspinar, 2005; Polomano, Mannes, Clark, & Bennett, 2001). In addition to peripheral neuropathic pain, myalgia and arthralgia also can occur after treatment with paclitaxel and other taxanes. Increased levels of IL-1 β , TNF- α , and IL-6 have been implicated in neuropathic pain, inflammatory pain, and hyperalgesia, an extreme sensitivity to pain (Sommer & Kress, 2004). The first evidence to suggest a role for IL-1 β , TNF- α , and IL-6 in hyperalgesia came from studies of rats injected with each of the cytokines. When IL-1 β , TNF- α , and IL-6 were administered by injection into the peritoneum or paws of rats, pain sensitivity increased (Watkins, Goehler, Relton, Brewer, & Maier, 1995; Woolf, Allchorne, Safieh-Garabedian, & Poole, 1997; Zhong, Dietzel, Wahle, Kopf, & Heumann, 1999).

Sleep Problems

Difficulty falling and staying asleep and restlessness at night are common in patients with cancer (Ancoli-Israel, Moore, & Jones, 2001; Anderson et al., 2003; Berger et al., 2003; Carpenter et al., 2004; Davidson, MacLean, Brundage, & Schulze, 2002; Lee, 2001; Lee, Cho, Miaskowski, & Dodd, 2004; Mercadante, Girelli, & Casuccio, 2004). Human studies have shown direct relationships between sleep and proinflammatory cytokine levels. IL-6 and TNF- α are increased in sleep deprivation (Vgontzas et al., 1997, 1999, 2004). Animal studies have shown that LPS promotes sleep disturbance by enhancing time spent in non-rapid-eye-movement sleep (Krueger, Obal, Fang, Kubota, & Taishi, 2001) through the action of IL-1 β and TNF- α (Krueger & Majde, 1994).

Current State of Research

Studying proinflammatory cytokines as a possible cause of chemotherapy-related symptoms in humans has been difficult because of a complex set of ethical, methodologic,

and logistic challenges inherent in human studies on the topic. Examples of challenges include separating tumor effects from the effects of chemotherapy alone, obtaining serial time-critical samples and behavioral observations in a population of outpatients, controlling confounding variables such as comorbid conditions and the therapies used to treat such conditions, use of combination chemotherapy regimens or multimodal treatments that make it difficult to assess the effect of a single agent, and variation in symptom management protocols.

The observation that chemotherapy-related symptoms are similar to the symptoms associated with sickness behavior prompted the authors to develop an animal model to experimentally evaluate the associations among cancer chemotherapy; IL-1 β , TNF- α , and IL-6; and chemotherapy-related symptoms by adapting previously established mouse models of sickness behavior. As mentioned previously, in mouse models of sickness behavior, voluntary wheel-running activity often is used as a proxy for fatigue as evidenced by a decline from baseline (Ottenweller et al., 1998; Sheng et al., 1996; Sheng, Hu, Ding, Chao, & Peterson, 2001). Similarly, malaise and anorexia or cachexia are indicated by a decline in food intake or weight loss, respectively (Bluthe, Laye, et al., 2000; Cahlin et al., 2000; McCarthy, 2000). Thus, preliminary studies have demonstrated the feasibility of using an animal model to address questions about the role of proinflammatory cytokines in the etiology of chemotherapy-related symptoms. In addition to its applicability with anorexia, anemia, fatigue, and cachexia, the model also can be expanded to include the assessment of pain and depression. Mouse models of pain and depression have been established and can be assessed without affecting the measurement of other symptoms. Although sleep disturbance is a common symptom, its assessment can interfere with the assessment of other symptoms in animal models. Monitoring sleep and wakefulness in animal models involves insertion of electrodes into the brains of test animals for polygraphic sleep monitoring. The electrodes are connected to a recording device by means of a cable and swivel, allowing free displacement in the cage. Rats, not mice, usually are the animals of choice for the studies, simply because they are larger, allowing for easier surgical manipulation of the electrodes. The connection of electrodes to a cable and swivel allows free movement of animals around the cage, but it would prevent voluntary wheel-running activity. Nonetheless, monitoring of sleep disturbance in chemotherapy-treated animals is an important goal that can be performed in independent experiments.

Developing a mouse model of chemotherapy-related symptoms with which to determine the relationship among cancer chemotherapy drugs; IL-1 β , TNF- α , and IL-6; and specific symptoms has several benefits. First, the ability of individual chemotherapy drugs to induce IL-1 β , TNF- α , and IL-6 production in the absence of tumor burden can be assessed. Second, unlike in patients with cancer, researchers have the ability to access the central nervous system (CNS) in experimental animals, which is important considering that several behavioral components of sickness behavior (e.g., pain, anorexia, sleep disturbance), although initiated by the peripheral increase in IL-1 β , TNF- α , and IL-6, are mediated by the expression of the cytokines in the CNS (Dantzer, 2004a, 2004b; Dantzer et al., 1999). Thus, to determine whether IL-1 β , TNF- α , and IL-6 are associated with specific symptoms, researchers may

want to explore changes in the levels of the cytokines not only in the serum, but also in the CNS. Third, gene knockout mice that lack IL-1 β , TNF- α , and IL-6 can be used to determine the requirement of cancer chemotherapy drugs for the cytokines in inducing symptoms in mice (Kozak et al., 1998; Pasparakis, Alexopoulou, Episkopou, & Kollias, 1996; Poli et al., 1994). Moreover, the finding by Wood et al. (in press) that inhibition of p38 MAPK activity could block VP-16-mediated induction

of IL-6 production in macrophages from mice suggests that the inhibitors could provide useful tools to determine the role of IL-6 and other proinflammatory cytokines in chemotherapy-related symptoms and may lead to new treatment strategies (Wood et al.).

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