Continuing Nursing Education

Proinflammatory Cytokines and Sickness Behavior: Implications for Depression and Cancer-Related Symptoms

Jamie S. Myers, RN, MN, AOCN®

Purpose/Objectives: To review the relationship between proinflammatory cytokine release and resultant sickness behavior; to explore the implications of sickness behavior related to depression and cancer-related symptoms.

Data Sources: Published articles and book chapters.

Data Synthesis: Proinflammatory cytokines (interleukin-1, interleukin-6, and tumor necrosis factor-α) are released as part of the immune response resulting in a syndrome called sickness behavior that is an adaptive and motivational reaction to disease. Sickness behavior includes lethargy, depression, anorexia, energy conservation, fever, anhedonia, cognitive impairment, hyperalgesia, and decreased social interaction. Sickness behavior is seen in patients with depression or cancer and has been described as a symptom cluster. Sickness behavior in patients with cancer may be the result of both the disease and the treatment. The related symptoms may have a profound effect on patients' quality of life. Treatment strategies that inhibit the release or activity of proinflammatory cytokines and relieve patients from symptoms of sickness behavior are being evaluated.

Conclusions: Further research is needed to pinpoint the exact effects of specific cytokines, identify targets for therapy, and develop viable treatment strategies for preventing or minimizing the detrimental effects of cytokine-induced inflammatory responses.

Implications for Nursing: Sickness behavior resulting from cytokine release may provide a framework to explain many cancer-related symptoms, including depression, cognitive impairment, cachexia, fatigue, and a component of pain perception. Oncology nurses would benefit from awareness and understanding of the relationship between proinflammatory cytokine release and tissue involvement by tumors as well as some cancer-related therapies. Knowledge about the effects of cytokine release on patient behavior and the symptom experience would enhance nurses' ability to assess patients for anticipated side effects and provide appropriate education to patients and their families.

Goal for CNE Enrollees

To enhance nursing knowledge regarding the relationship between proinflammatory cytokines and sickness behavior.

Objectives for CNE Enrollees

1. Define the immune response and its relationship to sickness behavior.
2. Identify proinflammatory cytokines and the symptoms related to sickness behavior.
3. Identify nursing interventions to support patients with sickness behavior.

Key Points . . .

➤ Proinflammatory cytokines are involved with sickness behavior that occurs in association with the immune response and tissue damage caused by malignancy.

➤ Sickness behavior also may be a result of treatment for cancer, particularly biotherapies such as interleukin-2 and several chemotherapy drugs.

➤ Sickness behavior is comprised of various behavioral responses including depression and cognitive impairment, and fits the definition of a symptom cluster.

➤ Cytokine production and release may provide a viable target for treatments to prevent or minimize sickness behavior.

Much has been written about the release of proinflammatory cytokines and their association with the response syndrome of sickness behavior. Cytokine production and release is associated with cancer and cancer therapy. Symptoms associated with sickness behavior are seen in patients with cancer and have been described as a symptom cluster. The goal of this article is to summarize the information and implications for the etiology of depression and other symptoms associated with cancer.

Proinflammatory Cytokine Production

Immune Response

When the human body is exposed to a pathogen (e.g., bacteria, virus), antigenic components of the pathogen (antigens) are recognized by the body's immune system as being foreign or "not self" (Maier & Watkins, 1998). Antigens have

the potential to stimulate the response of the immune system. The pathogen is consumed by macrophages, also known as antigen-presenting cells. As a result, antigens are moved to the cell surface of the macrophages where they can be recognized by a few circulating specific T cells (a form of white blood cell). Once the specific T cells recognize the antigens being presented, they bind to the macrophage and produce additional specific T cells that recognize the particular antigens. Many different types of T cells exist. Cytotoxic T cells kill some types of antigens directly. T-helper cells stimulate increased production of B cells (another form of white blood cell) that have specific cell surface receptors for the antigens being targeted. The B cells secrete an antibody that can destroy the antigen. The macrophages, T-helper cells, and B cells secrete substances called cytokines. Cytokines coordinate and stimulate the cellular interactions necessary for the production of antibodies. Because their primary role is to communicate messages between white blood cells (also known as leukocytes), cytokines have been referred to as interleukins (ILs) (Maier & Watkins, 1998). This whole process is sometimes called specific immunity and is time consuming.

Nonspecific immunity is actually the first line of defense against a pathogen or antigen (Maier & Watkins, 1998). Macrophages play a role here, too. Macrophages are able to phagocytize (or engulf and consume) the offending pathogen or antigen. Once that occurs, the macrophages synthesize and release proinflammatory cytokines, including IL-1, IL-6, and tumor necrosis factor-α (TNF-α). These proinflammatory cytokines attract other immune cells to the area to mount an offense, referred to as the acute phase response, and trigger the physical characteristics of sickness behavior (Maier & Watkins, 1998). Pinpointing the specific effects of individual cytokines is difficult; likely they work together to induce behavioral effects (Larson, 2002).

Immune Response and the Brain

The effect that proinflammatory cytokine release has on the initiation of sickness behavior raised the following question: How does the release of cytokines in the peripheral blood induce a behavioral response (Johnson, 2002)? Research revealed that a bidirectional communication occurs between the immune system and the brain (Haddad, Saade, & Safieh-Garabedian, 2002; Maier, 2003).

IL-1 is composed of several molecules. One of these, IL-1β, historically has been considered the endogenous pyrogen responsible for the febrile response (Maier, 2003). However, additional evidence now shows that TNF, interferons β and γ, IL-6 and IL-8, and macrophage inflammatory protein 1 act as endogenous pyrogens (Descotes & Vial, 2007). Cytokines must cross the blood-brain barrier in some fashion or stimulate cells on the other side of this barrier to trigger the febrile response. The presence of cytokine receptors has been demonstrated in the brain (Dantzer, 2004). Several hypotheses have been proposed for how such relatively large molecules could cross the blood-brain barrier or stimulate the production of cytokines within the brain (Johnson, 2002; Larson, 2002).

Humoral routes: A saturable transport system known as active transporters allows cytokines, such as IL-1α, to cross the blood-brain barrier (Maier, 2003; Maier & Watkins, 2003). Other cytokines have been studied less thoroughly, but this also appears to be true for IL-1β, IL-6, and TNF.

Crossing at circumventricular organs: The blood-brain barrier is weak or absent in some areas of the brain (e.g., in the organum vasculosum lateralis terminalis, subfornical organ, median eminence, area postrema, choroid plexus) (Maier, 2003). Prostaglandin E2 and neurotransmitters serve as mediators to activate neural routes to project cytokine signaling to distant target regions within the brain (Maier; Maier & Watkins, 1998, 2003).

Neural routes: The vagus nerve innervates typical sites of pathogen entry (e.g., the lungs) and the immune response (e.g., the lymph nodes). The vagus nerve carries efferent signals from the periphery to the brain. Severing the vagus nerve has been shown to eliminate many of the sickness responses to exogenously administered cytokines (Kelley et al., 2003; Maier, 2003).

Once the message that an immune response is needed reaches the brain, production of cytokines within the brain occurs (Maier, 2003). The microglial cells and perivascular and meningeal macrophages are believed to be the primary sources for the production of IL-1β in the brain (Dantzer, 2004). The cytokines produced in the brain are believed to travel to the periphery and to be responsible for the neural cascade of brain-mediated host responses as well as the regulation of the peripheral responses to infection (Maier).

Relationship of Stress to the Immune Response

Acute exposure to intense stressors has been shown to initiate behavioral characteristics similar to sickness behavior (e.g., reduced intake of food and water, reduced physical activity, reduced sexual behavior, increased sleep) (Maier, 2003). Increased levels of circulating white blood cells and cytokines are observed. The immune system is partially regulated by the central nervous system via the hypothalamic-pituitary-adrenal axis (HPA) (Haddad et al., 2002). Cytokines such as IL-1 and TNF-α can act as autocrine, paracrine, or endocrine factors. Stimulating the HPA provides a buffer to the effects of the proinflammatory cytokines by inducing the release of the neurotransmitters epinephrine, norepinephrine, and glucocorticoids, which, in turn, can induce the release of anti-inflammatory cytokines, IL-4, and IL-10 that can protect the organism from an exaggerated inflammatory response (Elenkov, Iezzoni, Daly, Harris, & Chrousos, 2005). IL-13 also is considered anti-inflammatory (Lee et al., 2004). Glucocorticoids have a direct inhibitory action on the release of proinflammatory cytokines (Parnet, Kelley, Bluthe, & Dantzer, 2002). However, under certain conditions, the anti-inflammatory cytokines actually may facilitate inflammation through activation of IL-1, IL-6, IL-8, IL-18, TNF-α, and C-reactive protein (Elenkov et al.). That dysfunctional neuroendocrine response has been associated with certain chronic conditions such as allergy, depression, atherosclerosis, and autoimmune disorders (Elenkov et al.). Significant chronic stress has been shown to cause cytokine dysregulation (Wilson, Finch, & Cohen, 2002).

Sickness Behavior

Hart (1988) reviewed the behavioral patterns of animals and humans in response to the onset of infectious diseases. The patterns included lethargy, depression, anorexia, and reduction in grooming. Hart proposed that this sickness behavior is actually an adaptive response of the organism to infection. Animals and humans both exhibit behavioral changes during the immune

response to infection that exist to conserve energy and resources. The pattern of increasing sleep, seeking warmth, and reducing energy devoted to food seeking and grooming is considered to be an adaptive response to illness. Seeking warmth is enhanced further by increased thermogenesis, raising the set point of body temperature (i.e., fever), and reduction of heat loss (thermolysis) by shivering, curled up posture, and piloerection (Dantzer, 2001). Additional characteristics of sickness behavior include weakness, inability to concentrate, decreased interest in surroundings, decreased social and sexual interaction, anhedonia (inability to experience pleasure from normally pleasurable life events such as eating, exercise, or social and sexual interactions) (Harvey, Pruessner, Czechowska, & Lepage, 2007), enhanced perception of pain (Lee et al., 2004), and impaired learning (Dantzer, 2001; Kelley et al., 2003; Pollmacher, Haack, Schuld, Reichenber, & Yirmiya, 2002).

The proposal that sickness behavior is adaptive has evolved further to infer that sickness behavior is a motivational state (Johnson, 2002). Miller (1964) conducted studies that systematically investigated animal behavior in response to disease. Behavioral changes in activity were shown to be related to the consequence of the behavior, not just the energy required for the behavior itself. For example, rats injected with an endotoxin (to induce the inflammatory response to illness and subsequent sickness behavior) stopped bar-pressing behavior to initiate a water reward. However, the same rats readily drank water when provided in a cup. Therefore, the cessation of bar-pressing behavior was motivated by the goal of conserving energy. A similar test involved placing the endotoxin-injected rats in a mildly aversive rotating drum (Miller, 1964). The rats exhibited bar-pressing behavior to stop the drum rotation. In this case, the energy required to exhibit the bar-pressing activity was motivated by the ultimate goal of energy conservation. The same differentiation is exhibited by humans in response to their environment. For example, a human suffering from influenza may spend the day in bed but would respond appropriately to a house fire by evacuating the premises (Dantzer, 2001; Larson, 2002).

The Role of Cytokines in Sickness Behavior

Pain Perception

Some animal evidence shows that the presence of proinflammatory cytokines enhances the perception of pain (hyperalgesia) (Lee et al., 2004). Maier and Watkins (2003) discussed hyperalgesia as a potentially adaptive response to injury (e.g., energy consumption, favoring the injured area, licking the wound). Studies in mollusks have shown that the release of IL-1β sensitizes withdrawal reflexes to nociceptive stimuli (Maier, 2003). Exogenous administration of IL-1β was shown to induce hyperalgesia in animals (Maier). Maier suggested that cytokines and glial cells in the spinal cord should be targets for pharmaceutical studies of pain control.

Cognitive Impairment

Some understanding of the role of cytokines in induction of sickness behavior evolved from the observations of side effects experienced by patients with cancer receiving treatment with immunomodulating agents such as interferon-α, TNF, and IL-2. The side effect called "flu-like-syndrome" is comprised

of the same behavioral characteristics seen with sickness behavior (De La Garza, 2005). Patients exhibit fever, chills, lethargy, anorexia, and cognitive impairment. Rationale for the cognitive impairment seen in conjunction with cytokine release and exogenous administration is just now emerging. In animal studies, exogenous administration of IL-1β leads to production of IL-1β in the hippocampus where it appears to interfere with memory formation (Maier & Watkins, 2003).

Proinflammatory cytokines also may play a role in the cognitive decline seen with aging (Wilson et al., 2002). Increasing levels of IL-6 have been associated with cognitive decline and decreases in functional status as measured by changes in activities of daily living and instrumental activities of daily living. Increasing levels of IL-6 have been associated with advancing age in animal studies (Wilson et al.).

Discussion relating proinflammatory cytokines to the development of Alzheimer disease also exists. Some small clinical trials have studied the effect of nonsteroidal anti-inflammatory drugs (NSAIDs) in relationship to Alzheimer disease and found evidence that NSAID users have a lower risk. However, the results of trials have been mixed (Wilson et al., 2002).

Depression

The release of inflammatory cytokines has been associated with symptoms of depression (Dantzer & Kelley, 2007). About 30%–50% of patients receiving chronic exogenous administration of IL-2 for renal cell cancer and metastatic melanoma experienced fatigue, anorexia, sleep disorders, depressed mood, anxiety, and cognitive dysfunction (Dantzer & Kelley). This constellation of symptoms also is seen in patients receiving chronic cytokine administration for hepatitis C. Growing evidence links major depression with elevated levels of IL-6 (Dantzer, 2006). Depressive symptoms may be alleviated by the administration of antidepressants, such as paroxetine (Capuron et al., 2002). Symptoms appear to be prevented with antidepressant prophylactic therapy (Dantzer, 2006). Paroxetine is hypothesized to facilitate endogenous feedback pathways that regulate proinflammatory cytokines. Central nervous system serotonergic activity also may be enhanced (Capuron et al.). Paroxetine has been shown to have an effect on depressive symptoms but not on the fever, fatigue, and anorexia associated with sickness behavior (Dantzer, 2006).

Close linkage between depression and the flulike syndrome experienced by patients being treated with cytokine therapy has been demonstrated (De La Garza, 2005). Hypersecretion of endogenous cytokines is believed to induce chronic activation of the HPA. The use of interferon-α and interferon-β, along with IL-2 for immune, autoimmune, inflammatory, infectious, and malignant disorders has been shown to induce depression-like symptoms in 40% of patients (De La Garza). Pretreatment with paroxetine has been shown to prevent interferon-α–induced depression (Capuron et al, 2002). Further support for cytokines as mediators of depression includes the observations that activation of the immune system is seen in many depressed patients, a higher incidence of depression occurs in patients with immune dysfunction, and several cytokines may activate the HPA (commonly activated in patients with depression) (Dunn, Swiergiel, & de Beaurepaire, 2005). However, Dunn et al. argued that more substantial evidence is needed to prove causality.

Dantzer (2006) described evidence that proinflammatory cytokines are associated with depression seen in chronic

inflammatory conditions such as coronary artery disease. Higher levels of myocardial cytokines and antibody titers against microbial pathogens have been observed in patients with coronary heart disease at the time of coronary bypass. Endothelial cell activation and inflammation were cited as likely causes.

Wilson et al. (2002) noted that much overlap exists in the roles of serum cytokines in depression and cognitive disorders. One hypothesis for depression is a deficit of norepinephrine or serotonin in the brain, and IL-1β may deplete serotonin levels. IL-6 increases with the immune response, but antidepressant therapy has been shown to decrease levels of IL-6 in patients (Wilson et al.). The negative feedback loop of the HPA appears to be defective in depressed patients (Wilson et al.).

Symptoms of Cancer and Cancer Treatment

Proinflammatory cytokines are released during the body's response to cancer cells or by the damage caused by cancer (Miller, 2003). As a result, patients with cancer may suffer from the symptoms of sickness behavior previously described. Unfortunately, some patients continue to manifest these symptoms long after the treatment for cancer is completed (Miller, 2003). Leukemia and myelodysplastic syndrome have been associated with increased levels of cytokines and cognitive impairment prior to treatment (Cleeland et al., 2003). Inflammation has been associated with tumor progression because tumor cells may release the same types of cytokines that initiate the inflammatory response as the tumor invades surrounding tissues and metastasizes to distant sites (Lee et al., 2004).

Cognitive impairment: A significant body of literature exists with respect to cognitive impairment related to the treatment of cancer with antineoplastic therapy. This is a complicated topic and multiple factors have been postulated as to the cause of what the lay public calls "chemo brain." Some of those factors include anxiety, anemia, decreased estrogen and testosterone, aging, neurotoxicity of the antineoplastic agents, and the associated release of cytokines in response to antineoplastic agents (Jansen, Miaskowski, Dodd, Dowling, & Kramer, 2005). A variety of antineoplastic agents has been shown to induce production of proinflammatory cytokines on cell lines (Maier & Watkins, 2003; Niiya et al., 2003; Wichmann et al., 2003; Zaks-Zilberman, Zaks, & Vogel, 2001). Inhibition of estrogen using the selective estrogen receptor modulator, tamoxifen, has been shown to impair cognition as a result of the interaction with proinflammatory cytokines as well as serotonin and dopamine depletion (Lee et al., 2004). Neurotoxicity related to antineoplastic therapy has been associated with changes in both gray and white matter of the brain. Prospective imaging studies are recommended to further understand how the changes may relate to cognitive impairment (Ahles & Saykin, 2002).

Cognitive dysfunction in patients with cancer can include memory loss, distraction, difficulty with multitasking, and mood disturbance (Lee et al., 2004). The symptoms tend to cluster (e.g., a frontal subcortical impairment cluster may include deficits in memory, motor dexterity, and executive functions) (Cleeland et al., 2003). Memory impairment may include difficulty in processing information and simultaneously completing multiple tasks; however, the hippocampal components of memory, such as retention and consolidation, may not be impaired (Lee et al.).

Peripheral neuropathy: Peripheral neuropathy in patients with cancer has been associated with proinflammatory cytokine release (Lee et al., 2004). Antineoplastic agents, cisplatin, and paclitaxel increase serum levels of IL-1β, interferon γ, and TNF-α. Vincristine raises the level of granulocyte macrophage–colony-stimulating factors and down-regulates the receptor for TNF-α, thereby increasing serum levels (Lee et al.). The three agents directly activate the nuclear factor-κ B signaling pathway that is associated with pain activation in neural tissues (Lee et al.). Nuclear factor-κ B plays a role in the stimulation of cytokine release for the immune and stress responses and has been hypothesized to be the potential link between inflammatory cytokine release and cancer-related symptoms (Lee et al.).

Fatigue and cachexia: Both fatigue and cachexia in patients with cancer have been linked to proinflammatory cytokines (Lee et al., 2004). A close relationship has been suggested between depression and cachexia in patients with cancer (Illman et al., 2005). Depression and cachexia frequently occur together in this patient population. TNF-α levels have long been associated with cachexia. Newer evidence has been shown to link the release of IL-6 from tumor cells with cachexia (Illman et al.).

Symptom clusters: Symptom clusters have been defined as two to three or more concurrent symptoms that are related to one another (Barsevick, 2007; Dodd, Miaskowski, & Paul, 2001; Kim, McGuire, Tulman, & Barsevick, 2005). Sickness behavior has been described as a symptom cluster occurring in patients with cancer (Cleeland et al., 2003; Lee et al., 2004) with strong preclinical and clinical evidence to support an association with cytokine production and release. The sickness behavior model provides a framework for evaluation of symptoms in patients with cancer (Barsevick).

Implications for Future Therapy

Symptoms previously described that are connected to the release of proinflammatory cytokines have a profound effect on patients' lives. Proinflammatory cytokines have been associated with inducing sickness behavior motivated by inflammatory response to infection and disease, which provides the basis for some intriguing pharmaceutical targets. A number of compounds are being investigated that target or antagonize the action of cytokines (Wilson et al., 2002). Etanercept is a TNF receptor antagonist that has shown effectiveness in the treatment of rheumatoid arthritis. Patients receiving this therapy describe improvements in a sense of well-being. Etanercept is a receptor-antibody fusion protein that combines the Fc (Fragment, crystallizable) region of human immunoglobulin with the TNF II receptor (Illman et al., 2005). A phase I trial of etanercept in combination with IL-2 in 24 patients with cancer demonstrated decreased levels of TNF-α as well as partial suppression of IL-1, IL-6, IL-8, and C-reactive protein. Etanercept also is being studied in a phase III trial to evaluate efficacy against cancer-related cachexia (Illman et al.).

Another TNF-α antibody being studied is infliximab (Illman et al., 2005), which has been approved for use in rheumatoid arthritis, Crohn disease, and ankylosing spondylitis. Animal studies have shown efficacy for treatment of cachectic symptoms. A phase II trial is being conducted to evaluate infliximab in combination with antineoplastic therapy as a treatment for cancer-related cachexia in patients with pancreatic cancer (Illman et al.).

In theory, reducing the TNF-α–induced inflammation may preserve cognition in neurodegenerative disorders such as Alzheimer disease (Wilson et al., 2002). Other anticytokine strategies being studied include cytokine synthesis inhibitors, soluble cytokine receptors, antibodies against cytokine receptors, and other novel cytokine receptor antagonists (Wilson et al.). IL-6 inhibition is proving to be an interesting target. BE-8 is an IL-6 antibody that has been studied in small samples of patients with multiple myeloma, metastatic renal cell carcinoma, and B-lymphoproliferative disorder. Decreased levels of C-reactive protein were demonstrated as were toxicities related to IL-6 expression. Reduction in malignant hypercalcemia, fever, and tumor mass was seen in patients with multiple myeloma. Additional studies are being conducted (Illman et al., 2005).

Strategies to inhibit the nuclear factor-κ B pathway also have been proposed. Glucocorticoids (e.g., dexamethasone, prednisone), NSAIDs, cyclopentenone prostaglandins, and flavonoids all can interfere with nuclear factor-κ B activation. The proteosome inhibitor PS-341 and an immunosuppressive agent that blocks c-Rel translocation, FK-506, also may inhibit this pathway (Lee et al., 2004).

Conclusions

Much study has been devoted to the role of proinflammatory cytokines as they relate to the immune response, sickness behavior, and a variety of diseases including depression. The sickness behavior symptom cluster may be used as a framework to explain many of the symptoms associated with cancer and cancer treatment, including depression, cognitive impairment, cachexia, fatigue, and a component of pain perception. Additional work is needed to pinpoint the exact effects of specific cytokines, identify targets for therapy, and develop viable treatment strategies for preventing or minimizing the detrimental effects of cytokine-induced inflammatory responses.

Implications for Nursing

Oncology nurses play a key role in the assessment of patients with cancer throughout the trajectory of diagnosis, treatment, survival, and supportive care. Assessment skills are enhanced by understanding the etiology of disease and treatment-related sequelae. This knowledge is used to guide clinical practice and provide support for specific nursing interventions. Understanding the relationship between proinflammatory cytokine release and tissue involvement by tumors and some cancer-related therapies will benefit oncology nursing. The symptom experience referred to as sickness behavior provides a framework for oncology nurses to plan targeted assessment and supports the development of tools to evaluate multiple concurrent symptoms. This framework also can be used to support nursing research designed to describe and predict symptom clusters.

Patients should be assessed for signs of depression. Particular attention should be paid to patients receiving biologic therapy, such as IL-2, and consideration should be given to proactive intervention with antidepressant therapy in this patient population. In addition, oncology nurses should be alert to the potential for increased pain perception, fatigue, anorexia and cachexia, and cognitive impairment. The underlying etiology of proinflammatory cytokines can be woven into the explanations provided to patients when discussing the potential for side effects of disease and treatment. Patient education regarding anticipated clusters of symptoms related to cancer and cancer therapy will continue to be important for patient understanding of the sequelae of the disease and treatment.

Understanding the underlying etiology of cytokine release has led to the development and testing of targeted interventions. As this research creates new treatment strategies, oncology nurses will be involved in the implementation of these therapies and the design of appropriate education for patients and their families.

Author Contact: Jamie S. Myers, RN, MN, AOCN®, can be reached at jamyers@swbell.net, with copy to editor at ONFEditor@ons.org.

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