

# Neurotoxicology of Chemotherapy in Relation to Cytokine Release, the Blood-Brain Barrier, and Cognitive Impairment

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**Purpose/Objectives:** To review the effects of chemotherapeutic agents on the blood-brain barrier as related to cytokine release and cognitive impairment.

**Data Sources:** PubMed database.

**Data Synthesis:** The recent findings that standard doses of chemotherapy agents reach higher than expected levels in the brain and cerebral spinal fluid are being investigated as a potential etiology for the cognitive impairment seen in patients receiving chemotherapy for cancer. Chemotherapy and chemotherapy-related neurotoxicity are associated with the release of proinflammatory cytokines, substances related to sickness behavior (e.g., decreased ability to concentrate). Chemotherapy-related oxidative stress is an additional mechanism hypothesized to induce cognitive impairment. Cognitive impairment from chemotherapy is estimated to occur in 17%–75% of patients, and 17%–35% may suffer from long-term effects.

**Conclusions:** Further research is needed to identify the patients most at risk for cognitive impairment from chemotherapy. Prospective studies that evaluate appropriate interventions and control for age, intelligence quotient, education level, hormonal status, fatigue, anxiety, depression, chemotherapy regimen, and genetic status are needed.

**Implications for Nursing:** Changes in cognitive function are associated with significant effects on patients' quality of life. Oncology nurses must be aware of chemotherapy's effects on the brain to appropriately assess and educate patients and their families. In addition, nurses should develop plans of care to prevent or manage chemotherapy-related cognitive impairment after more intervention information is obtained.

High-dose chemotherapy is associated with blood-brain barrier penetration (Tuxen & Hansen, 1994), and most chemotherapeutic agents have not been reported to cross the blood-brain barrier in standard doses (Ahles & Saykin, 2001; Saykin, Ahles, & McDonald, 2003) with the exception of methotrexate, cisplatin, cytarabine, ifosfamide, procarbazine, temozolomide, carmustine, lomustine (Wilkes & Barton-Burke, 2007), and topotecan (Wong & Berkenblit, 2004). However, Ahles and Saykin (2001) reported that higher than expected levels of chemotherapeutic agents are found in the brain and cerebral spinal fluid. The finding is being investigated as a potential etiology of the cognitive impairment that can occur in patients receiving chemotherapy for malignancy (Ahles & Saykin, 2001). As a result, this review article will summarize the effects of chemotherapy on the blood-brain barrier, cytokine release, and cognitive impairment.

## Key Points . . .

- ▶ The release of proinflammatory cytokines in the peripheral blood leads to penetration of the blood-brain barrier and production of proinflammatory cytokines in the central nervous system.
- ▶ Proinflammatory cytokine release is associated with sickness behavior, which includes changes in cognitive function.
- ▶ The association of cytokine release and cognitive impairment experienced by patients receiving chemotherapy is under investigation.

## Blood-Brain Barrier Physiology

The blood-brain barrier is composed of tightly packed endothelial cells within the capillaries of the brain. The tight junctions between the cells prevent potentially toxic substances from the peripheral blood from penetrating brain tissue and the central nervous system (CNS) (Brown & Davis, 2002). The junctions can block molecules with a molecular weight greater than 500 daltons. Lipid-soluble drugs and small molecules can penetrate the barrier, but larger molecules must be transported across (Brown & Davis).

The brain, like the eyes and testes, has an almost complete absence of T and B lymphocytes, and, therefore, is an immunoprivileged site (Espejo & Martin, 2007). The blood-brain barrier contributes to the immune privilege of the CNS; however, significant cross talk and bidirectional communication occur between the CNS and the immune system (Maier, 2003). In addition, the release of proinflammatory

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cytokines, including interleukin-1 (IL-1), IL-6, and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) (Maier & Watkins, 1998) in the peripheral blood leads to penetration of the blood-brain barrier as well as the production of proinflammatory cytokines in the CNS.

Several proposed mechanisms explain how cytokines penetrate the blood-brain barrier despite their large molecular size, including active transport; penetration in areas of the blood-brain barrier with fenestrated rather than tight junctions, such as the choroid plexus and circumventricular organs (i.e., organum vasculosum lateralis terminalis, subfornical organ, median eminence, and area postrema) (Maier, 2003); and binding to receptors inside the blood vessels with activation of secondary messengers that enter the brain tissue (Maier & Watkins, 1998). Activation of the vagus nerve also has been implicated in carrying the message of peripheral immune activation to the brain (Maier & Watkins, 1998). Evidence suggests that glial cells in the brain can synthesize and release IL-1, IL-6, and TNF- $\alpha$  (Kronfol & Remick, 2000; Maier & Watkins, 1998). Astrocytes, microglia, and neurons also have the ability to produce cytokines in the brain (Kronfol & Remick).

## Cytokines and Sickness Behavior

Proinflammatory cytokines are associated with a syndrome of behaviors and symptoms known as sickness behavior (Kronfol & Remick, 2000). Sickness behavior includes fever, fatigue, lethargy, muscle aches, decreased appetite and interest in food, decreased ability to concentrate, decreased social interaction, seeking warmth, and general behaviors consistent with the conservation of energy (Parnet, Kelley, Bluthe, & Dantzer, 2002; Pollmacher, Haack, Schuld, Reichenberg, & Yirmiya, 2002; Wilson, Finch, & Cohen, 2002). Proinflammatory cytokines are released during the body's response to cancer cells or tissue damage caused by cancer (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; tumor cells may release the same types of cytokines that initiate the inflammatory response when the tumor invades surrounding tissues and metastasizes to distant sites (Kronfol & Remick).

## Chemotherapy Agents and the Blood-Brain Barrier

Some chemotherapy agents readily cross the blood-brain barrier. Methotrexate, an antimetabolite and folic acid antagonist, often is administered intrathecally to combat lymphomas that have spread to the CNS. High peripheral doses (1–7.5 m/m<sup>2</sup>) are known to cross the blood-brain barrier (Wilkes & Barton-Burke, 2007). Standard doses typically are not associated with neurotoxicity (Tuxen & Hansen, 1994).

Nitrosoureas (e.g., carmustine, lomustine) are alkylating agents able to cross the blood-brain barrier and have been used to treat primary brain tumors (e.g., gliomas) as well as melanoma and lymphomas that have metastasized to the brain (Verstappen, Heimans, Hoekman, & Postma, 2003). Concomitant administration of dexamethasone or mannitol may be given to reduce the side effect of cerebral edema (Wilkes & Barton-Burke, 2007) when administering the drugs.

Cisplatin, a heavy metal that acts like an alkylating agent (Wilkes & Barton-Burke, 2007), causes peripheral and central neurotoxicity, including ototoxicity (Tuxen & Hansen, 1994). Circulating plasma platinum levels have been found more than 10 years after successful treatment in patients with testicular cancer (Gietema et al., 2000). Sixty-one testicular cancer survivors were tested for plasma platinum levels (median follow-up 14 years, range 10–20 years). The individuals had received four courses of cisplatin, bleomycin, and vinblastine or etoposide every three weeks. Seventeen survivors also had received maintenance therapy with vinblastine and cisplatin for up to one year. Plasma platinum concentrations were compared with those of 20 control patients cured by orchiectomy. Plasma concentrations of platinum in the 61 patients treated with chemotherapy were significantly higher than the control group. The investigators found that cisplatin could remain in the body 20 years after administration and suspected that retained platinum recirculates between the plasma and liver, bone, and muscle stores (Gietema et al.). The finding may have ramifications for long-term sequelae.

Cytosine arabinoside is a pyrimidine nucleoside antimetabolite that crosses the blood-brain barrier. Like methotrexate, cytarabine may be administered intrathecally to treat meningeal leukemia or lymphoma (Tuxen & Hansen, 1994). High peripheral doses can cause neurotoxicity (e.g., lethargy, somnolence) and cerebellar toxicity (e.g., nystagmus; dysarthria; ataxia; slurred speech; decreased ability to make fine, coordinated movements) (Wilkes & Barton-Burke, 2007). Intrathecal doses may cause paraparesis or seizure (Tuxen & Hansen).

Ifosfamide, an alkylating prodrug, is bioactivated by liver metabolism. Ifosfamide and some of its metabolites can penetrate the blood-brain barrier (Verstappen et al., 2003). Unlike cyclophosphamide, ifosfamide is associated with CNS toxicity in 10%–30% of patients treated. Confusion, somnolence, hallucinations, seizures, and extrapyramidal symptoms are some of the CNS effects reported (Tuxen & Hansen, 1994). Side effects can occur within two hours of infusion. Patients with low levels of serum albumin or impaired hepatic function appear to be at higher risk (Tuxen & Hansen).

## Chemotherapy Agents and Peripheral Neuropathy

Microtubule targeting drugs, such as the taxanes (paclitaxel, docetaxel) and vincristine (a vinca alkaloid), are associated with significant neurotoxicity, specifically peripheral neuropathy (Verstappen et al., 2003). Cisplatin also is known for causing significant neuropathy (Troy et al., 2000). Peripheral neuropathy in patients with cancer has been associated with proinflammatory cytokine release (Kronfol & Remick, 2000). Antineoplastic agents increase the serum levels of IL-1 beta, interferon gamma, and TNF- $\alpha$  (see Figure 1). Vincristine raises the level of granulocyte macrophage–colony-stimulating factor and down-regulates the receptor for TNF- $\alpha$  (Lee et al., 2004). The three agents directly activate the nuclear factor-kappa B signaling pathway that is associated with pain activation in neural tissues (Lee et al.). Nuclear factor-kappa B, which affects the stimulation of cytokine release for the immune and stress responses, has been hypothesized to be the potential link between inflammatory cytokine release and cancer-related symptoms (Lee et al.).

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- Cisplatin
  - Docetaxel
  - Etoposide
  - Paclitaxel
  - Vincristine
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**Figure 1. Drugs Associated With Proinflammatory Cytokine Release**

## Chemotherapy Agents and Cognitive Impairment

Standard-dose chemotherapy has been associated with cognitive impairment, also referred to as “chemo brain” (Ahles & Saykin, 2001). Cognitive impairment has been observed in patients receiving standard-dose chemotherapy for lymphoma and cancers of the breast, lung, and testes (Ahles & Saykin, 2001; Shapiro et al., 2005). The cognitive difficulties typically are subtle and most commonly include trouble with concentration, memory, ability to focus, organizational skills, and working with numbers (Ahles & Saykin, 2001). Executive function, which includes attention regulation, planning and initiating purposeful activity, anticipating the consequences of one’s actions, problem solving, and inhibition of inappropriate activity (Grigsby, Kaye, Kowalsky, & Kramer, 2002), also has been affected (Saykin et al., 2003). The subtlety of cognitive impairment is reflected by patients’ perceptions of difficulty as compared to scores within the normal range on standard neurocognitive testing (Tannock, Ahles, Ganz, & Van Dam, 2004). The potential to significantly affect an individual’s quality of life exists, regardless of the severity of the side effect (Ahles & Saykin, 2001; Saykin, et al.; Tannock et al.).

## Other Factors Related to Cognitive Impairment

A variety of factors may be associated with the cognitive issues experienced by individuals being treated with chemotherapy, including age, intelligence quotient, education level, hormonal status, anemia, fatigue, anxiety, and depression (Ahles & Saykin, 2001; Mancuso, Migliorino, De Santis, Saponiero, & De Marinis, 2006; O’Shaughnessy, 2003). Clinical trials that controlled for fatigue, anxiety, and depression still demonstrated significance for chemotherapy-related cognitive impairment (Ahles & Saykin, 2001, 2007). Several agents have been associated with cognitive impairment (Ahles & Saykin, 2001) (see Figure 2).

Studies conducted on patients shortly after the completion of adjuvant treatment demonstrated an incidence of mild-to-moderate cognitive impairment ranging from 17%–75% (O’Shaughnessy, 2003). A subgroup of patients (about 17%–35%) appeared to have long-term cognitive effects (Ahles & Saykin, 2001). Concomitant factors may include type of treatment regimen, level of education, or genetics. The apolipoprotein E4 allele has been associated with predisposition to CNS damage (Espejo & Martin, 2007) and poor repair following brain trauma (Ahles & Saykin, 2007). To date, prospective studies are ongoing to evaluate the presence of the apolipoprotein E4 allele in relation to risk, incidence, and duration of cognitive impairment secondary to chemotherapy (Ahles & Saykin, 2007). One such study evaluated neuropsychological performance in long-term

survivors after post standard-dose chemotherapy. Survivors with at least one apolipoprotein E4 allele scored lower on neurocognitive tests than those who did not carry the gene (Ahles & Saykin, 2007).

## Hypotheses for Cognitive Impairment

Several hypotheses have been generated for the cognitive and memory deficits associated with standard-dose chemotherapy, including direct neurotoxic injury to cerebral parenchyma (e.g., microglia, oligodendrocytes, neuronal axons), producing demyelination or altered water content; secondary inflammatory response, an immunologic mechanism including allergic hypersensitivity and autoimmune vasculitis; microvascular injury leading to vessel obstruction, thrombosis, ischemia or infarction, and parenchymal necrosis; indirect chemical toxicity and oxidative damage; and altered neurotransmitter levels, particularly among brain amines and metabolites (Ahles & Saykin, 2001; Saykin et al., 2003).

Secondary inflammatory response has been related to the sickness behavior seen with proinflammatory cytokine release. Some understanding of the role of cytokines in induction of sickness behavior evolved from observing the side effects experienced by patients with cancer receiving treatment with immunomodulating agents, such as interferon alpha, TNF, and IL-2. The side effect called “flu-like syndrome” is comprised of the same 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 the release and exogenous administration of cytokines is emerging. In animal studies, exogenous administration of IL-1 beta lead to its production in the hippocampus, where IL-1 beta appears to interfere with memory formation (Maier & Watkins, 2003).

Chemotherapy-induced side effects are similar to those seen in the sickness behavior attributed to proinflammatory cytokine release (Wood, Nail, Gilster, Winters, & Elsea, 2006). A variety of antineoplastic agents induce production of proinflammatory cytokines in various cell lines in vitro (Maier & Watkins, 2003; Niiya et al., 2003; Wichmann et al., 2003; Zaks-Zilberman, Zaks, & Vogel, 2001). Etoposide induces production of proinflammatory cytokines in animal studies (Wood et al.); resultant sickness behavior, including decreased food intake and physical activity, was observed. The taxanes (paclitaxel and docetaxel) have been associated with increased plasma levels of IL-6, IL-8, and IL-10 (Ahles & Saykin, 2007).

An important mechanism hypothesized to be related to chemotherapy-induced cognitive impairment is oxidative stress, which occurs when the generation of reactive oxygen and nitrogen species exceed cellular adaptive and repair capacities (Chen, Jungsuwadee, Vore, Butterfield, & St. Clair, 2007). Fifty-six of the 132 anticancer agents approved by the U.S. Food and Drug Administration have been reported to

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- 5-fluorouracil
  - Cisplatin
  - Cyclophosphamide
  - Doxorubicin
  - Etoposide
  - Methotrexate
  - Vincristine
  - Vinblastine
- 

**Figure 2. Drugs Associated With Cognitive Impairment**

induce oxidative stress. Agents and classes specifically indicated include anthracyclines, cyclophosphamide, cisplatin, busulfan, mitomycin, fluorouracil, cytosine arabinoside, and bleomycin.

Oxidative stress associated with doxorubicin therapy occurs in nontargeted tissues and leads to injury of normal tissue (Chen et al., 2007). Doxorubicin kills cancer cells through topoisomerase II inhibition and DNA intercalation and induces oxidative stress in the heart, kidney, and brain. Doxorubicin, like other chemotherapy agents administered in standard doses, is not believed to cross the blood-brain barrier. However, doxorubicin has been associated with increased circulating levels of TNF- $\alpha$  in animal models. TNF- $\alpha$  can penetrate the blood-brain barrier and activate glial cells in the CNS to further TNF- $\alpha$  production in the brain. The synthesis of TNF- $\alpha$  in the CNS is related to the induction of nitric oxide synthase (Chen et al.). As a result, the generation of reactive nitrogen species, including nitric oxide, increases (Tangpong et al., 2007). Animal study results support the role of nitric oxide in doxorubicin-mediated CNS injury (Tangpong et al.). In addition, the neurotoxicity associated with doxorubicin-induced TNF- $\alpha$  resembles the free radical mechanisms implicated in Alzheimer disease (Tangpong et al.).

## Implications for Future Research

Additional research is necessary to identify the patients most at risk for cognitive impairment from chemotherapy. A need also exists for study regarding appropriate interventions to prevent the occurrence of cognitive impairment as well as strategies to regain function once a deficit occurs. Research is being conducted to develop a rehabilitation program that focuses on compensatory skills and reduction of anxiety (Ahles & Saykin, 2001).

Research is ongoing in the field of cytoprotectants, particularly neuroprotectants such as amifostine (Ahles &

Saykin, 2001). Evidence has shown a reduction of peripheral neurotoxicity from the use of amifostine in conjunction with cisplatin administration and supports the activity of amifostine in binding and detoxifying cytotoxic drugs and scavenging the free radicals produced by oxidative damage. Clinical trials evaluating cytoprotectants may determine whether cognitive impairment as well as neurotoxicity can be reduced.

Saykin et al. (2003) suggested that because parallel mechanisms exist between neurodegenerative and neuroimmunologic diseases (e.g., Alzheimer disease) with chemotherapy-induced cognitive impairment, similar interventions that are successful with Alzheimer disease may help treat chemotherapy-induced cognitive impairment. Pharmacologic interventions suggested for future study include hormonal therapy, antioxidants, monoamine oxidase inhibitors, growth factors, dopamine agonists, cholinesterase inhibitors, and anti-inflammatory agents (Barton & Loprinzi, 2002).

## Implications for Nursing

Oncology nurses should stay apprised of research results about the effects of chemotherapy on cognitive function. Changes in cognitive function can significantly affect patients' quality of life. Awareness of chemotherapy effects on the brain, including penetration of the blood-brain barrier, cytokine release and production, and resultant sickness behaviors (e.g., cognitive impairment), is key to nursing assessment and appropriate patient and family education. When the research results provide enough information, knowledgeable oncology nurses can develop appropriate interventional care plans to prevent or manage cognitive impairment related to chemotherapy.

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