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

Jamie S. Myers, RN, MN, AOCN®, Janet Pierce, DSN, ARNP, CCRN, and Thomas Pazdernik, PhD

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

Jamie S. Myers, RN, MN, AOCN®, is a doctoral student and Janet Pierce, DSN, ARNP, CCRN, is a professor, both in the School of Nursing, and Thomas Pazdernik, PhD, is a professor in the Department of Pharmacology, Toxicology, and Therapeutics, all at the University of Kansas Medical Center in Kansas City. *No financial relationships to disclose. Mention of specific products and opinions related to those products do not indicate or imply endorsement by the* Oncology Nursing Forum *or the Oncology Nursing Society. (Submitted November 2007. Accepted for publication January 7, 2008.)*

Digital Object Identifier: 10.1188/08.ONF.916-920