

CONTINUING EDUCATION

Potential Mechanisms for Chemotherapy-Induced Impairments in Cognitive Function

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Purpose/Objectives: To review the domains of cognitive function and their corresponding neuroanatomic structures as well as present current evidence for neurotoxicity associated with specific chemotherapeutic agents and potential mechanisms for chemotherapy-induced cognitive impairments.

Data Sources: Published research articles, review articles, and textbooks.

Data Synthesis: Chemotherapy does not appear to cross the blood-brain barrier when given in standard doses; however, many chemotherapy drugs have the potential to cause cognitive impairments through more than one mechanism. In addition, patient factors may be protective or place individuals at higher risk for cognitive impairments.

Conclusions: Although evidence of chemotherapy-induced impairments in cognitive function exists, no clinical studies have attempted to elucidate the mechanisms for chemotherapy-induced impairments in cognitive function. In addition, further studies are needed to determine predictive factors, potential biomarkers, and relevant assessment parameters.

Implications for Nursing: The ability to identify high-risk patients has important implications for practice in regard to informed consent, patient education about the effects of treatment, and preventive strategies.

Chemotherapy is one of the primary treatments for cancer and has been used successfully to extend patients' lives. Although the occurrence of cognitive impairments following chemotherapy treatment has been documented (Cull et al., 1996; Oxman & Silberfarb, 1980; Peterson & Popkin, 1980; Silberfarb, Philibert, & Levine, 1980), most reports of cognitive impairments in adults are anecdotal. Chemotherapy does not appear to cross the blood-brain barrier when given in standard doses; however, recent studies have substantiated chemotherapy-induced impairments in various domains of cognitive function (Ahles et al., 2002; Brezden, Phillips, Abdoell, Bunston, & Tannock, 2000; Kaasa, Olsnes, & Mastekaasa, 1988; Meyers, Byrne, & Komaki, 1995; Schagen et al., 1999; Tchen et al., 2003; van Dam et al., 1998; Wefel, Lenzi, Theriault, Davis, & Meyers, 2004; Wieneke & Dienst, 1995).

Although cognitive impairment, commonly referred to as "chemo brain," is a growing area of interest among cancer survivors and clinicians, little is known about the potential mechanisms that produce these changes. This article provides a description of the domains of cognitive function and their corresponding neuroanatomic structures. In addition, current evidence for neurotoxicity associated with specific

Key Points . . .

- Cognitive function is a multidimensional concept that describes the domains that result from healthy brain performance, which are attention and concentration, executive function, information-processing speed, language, motor function, visuospatial skill, learning, and memory.
- The mechanisms for chemotherapy-induced impairments in cognitive function most likely are multifactorial.
- Future investigations need to describe the phenomenon of "chemo brain" and elucidate the mechanism or mechanisms responsible for chemotherapy-induced impairments in cognitive function.

Goal for CE Enrollees:

To enhance nurses' knowledge regarding the domains of cognitive function and the effects of chemotherapy on cognitive function.

Objectives for CE Enrollees:

1. Describe two deficits that result from chemotherapy exposure via passage through the blood-brain barrier.
2. Discuss which chemotherapy agents may put patients at higher risk for developing cognitive deficits.
3. Identify other known chemotherapy-related side effects that may have an effect on cognitive function.

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chemotherapy agents as well as potential mechanisms for chemotherapy-induced cognitive impairments are discussed. The article concludes with a discussion of the implications of these impairments for nursing practice.

Cognitive Function

Cognitive function is a multidimensional concept that describes the domains that result from healthy brain performance, which are attention and concentration, executive function, information-processing speed, language, motor function, visuospatial skill, learning, and memory (Olin, 2001; Ryan, Morrow, Bromet, & Parkinson, 1987). The domains of cognitive function and their corresponding components are listed in Table 1.

Although each domain is measured by standardized, scaled tests and discrete activities during a neuropsychological examination, the domains are so inextricably linked that impairment in one invariably will affect another (Lezak, Howieson, & Loring, 2004). To fully comprehend the complex relationships involved in cognitive function, a basic understanding of the anatomy and organization of the brain is essential.

Specific Cognitive Domains and Their Corresponding Neuroanatomic Correlates

Attention and Concentration

A certain level of arousal is a prerequisite for attention. An individual's level of arousal is controlled by neuronal

Table 1. Domains of Cognitive Function and Their Corresponding Components

Cognitive Domain	Components
Attention and concentration	Arousal Selective attention Sustained attention or vigilance Divided attention
Executive function	Initiation Planning Cognitive flexibility Self-monitoring Self-regulation
Information-processing speed	
Language	Verbal or written expression Reception Repetition
Motor function	Speed Strength Coordination Dexterity Apraxia
Visuospatial skill	Perception Construction
Learning and memory	Learning Short- versus long-term memory Recall Recognition Verbal versus visual

projections (referred to as the ascending reticular activating system) in the brain stem. Neuronal projections influence the thalamus, cerebral cortex, and limbic system through extensive relays (Andrewes, 2001; Blumenfeld, 2002). Attention is a cognitive brain mechanism that enables a person to triage relevant inputs, thoughts, or actions while ignoring those that distract or are irrelevant (Gazzaniga, Ivry, & Mangun, 2002; Grober, 2002). The three types of attention are selective, sustained, and directed. Selective attention implies the ability to focus on certain objects, or stimuli, at the exclusion of others for brief periods of time. Sustained attention, also referred to as concentration or vigilance, is the maintenance of attention toward a stimulus for a more extended time period (Filley, 2002). Directed attention refers to the ability to attend to two or more competing tasks simultaneously.

Sustained attention requires the activation of the right hemispheric prefrontal and parietal regions of the brain, whereas directed attention is dependent on intact functioning of the prefrontal cortex (Blumenfeld, 2002). The anterior cingulate cortex, located in the medial area of the frontal lobe, combined with the amygdala's influence on motivation, gives an individual the ability to focus attention in the midst of distraction (Andrewes, 2001; Blumenfeld). Neurotransmitters such as norepinephrine, dopamine, acetylcholine, and serotonin are necessary to facilitate communication among these areas of the brain to produce arousal and attention (Andrewes).

Attention is the basic building block for cognitive function and is necessary for the expression of other cognitive domains. Attention also acts as a mediator to integrate, direct, and influence memory, perception, and language (Andrewes, 2001). Deficits in attention decrease an individual's awareness, or ability to focus on tasks, thereby hindering his or her independence in carrying out activities of daily living, employment, and social role performance (Groth-Marnat, 2000).

Executive Function

Executive function refers to the higher-order cognitive processes that include initiation, planning, hypothesis generation, cognitive flexibility, decision making, regulation, judgment, feedback utilization, and self-perception (Spreeen & Strauss, 1998). The dorsolateral prefrontal cortex is responsible for the direction and autonomous initiation of the search for and organization and selection of information as well as hypothesis generation, whereas the anterior cingulate cortex most often is associated with the initiation of behavior (Andrewes, 2001; Filley, 2000).

Although executive function is thought to take place primarily in the frontal lobe, impairment in executive function can occur as a result of damage to other areas of the brain (Vanderploeg, 2000). Impairment in executive function affects the ability to categorize or compare information, prepare or organize strategies, and respond to changing stimuli. Impairment also may limit the ability to solve problems, achieve goals, or be creative, adaptive, or flexible. Deficits in executive functioning are manifested by an inability to follow directions, a decrease in the skills needed to handle personal finances, disorganized behavior or thinking, a loss of initiative, and an increased need for external structure, thereby adversely affecting work habits and the ability to plan for the future.

Information-Processing Speed

Information-processing speed refers to the brain's ability to process simple and complex information rapidly (Freeman & Broshek, 2002). Information processing encompasses all aspects of the brain's processing involved in the flow of sensory, perceptual, and conceptual input, from storage and analysis to output (Gazzaniga et al., 2002). The parietal and frontal lobes are responsible for information-processing speed (Andrewes, 2001).

Language

Language incorporates the verbal and written communication used to express thoughts. Impairment in language inhibits an individual's ability to communicate with others and follow directions without the need for repetition or explanation. Language processing involves representing, comprehending, and communicating symbolic information in written or spoken form (Gazzaniga et al., 2002).

The right hemisphere contributes prosody (i.e., variations in tone and pitch that add to the meaning of what is said) to speech (Andrewes, 2001). The left hemisphere specializes in language and contains Wernicke's and Broca's areas. Wernicke's area is a central command center, or neuronal network, that contains information about sounds, words, and the meanings of relationships. Broca's area is responsible for controlling the movements of the tongue, lips, and vocal cords and, consequently, plays an important role in speech.

Other regions in the temporal, parietal, and occipital cortices are responsible for piecing together auditory sequences of oral language and visual representations of written language into neural word representations (Andrewes, 2001; Vanderploeg, 2000). The supplementary motor cortex is believed to play an important role in the initiation and planning of speech output, whereas the prefrontal cortex plays a primary role in the retrieval of words from superordinate (i.e., generic) categories (Vanderploeg). Deficits in language interfere with the ability to comprehend written or spoken words, resulting in difficulty with the accurate use of words and word meanings (Groth-Marnat, 2000).

Motor Function

Motor function relates to motor performance, such as speed, strength, and coordination. Motor function is dependent on the inner workings of and communication among the frontal and parietal lobes of the cortex, the cerebellum, and the brain stem. The frontal lobe contains the premotor and primary motor areas. The premotor area is responsible for the interpretation of sensory information and therefore is vital to the preparation and planning of movement. The primary motor area has a more direct role in the execution of movement, with a focus on the control of direction and force. The nuclei and corresponding feedback system in the basal ganglia assist with communication between the motor areas, thereby initiating movement and maintaining the smooth programming of sequencing movements. The parietal lobe of the cortex contains somatosensory areas that provide sensory information to the premotor area.

The cerebellum receives sensory input from multiple channels (e.g., somatosensory, vestibular, visual, auditory) as well as many other associated areas of the cortex (Gazzaniga et al., 2002). The cerebellar motor system appears to have a more moderating role in facilitating movement because of vast connections to several areas of the central nervous system

(CNS) that are necessary for movement. Using numerous muscle groups, the cerebellar motor system facilitates the contractions required to carry out coordinated movements and controls equilibrium and muscle tone (Andrewes, 2001; Blumenfeld, 2002).

The brain stem contains many of the neural structures of the motor system, some of which are essential for critical reflexes involved in breathing, eating, eye movements, and facial expressions (Gazzaniga et al., 2002). Decreases in the effectiveness of motor skills manifest as gait changes, weakness, tremors, or problems with dexterity.

Visuospatial Skill

Visuospatial skill refers to the ability to process and interpret visual information regarding where things are in space (Spree & Strauss, 1998). As the term implies, visuospatial skill is dependent on visual processes that are initiated in the retina, where visual sensations begin. Visual input then is relayed through the thalamus to the primary visual cortex in the posterior occipital lobe (Andrewes, 2001). Pathways between the occipital and temporal lobes are essential for object recognition, whereas pathways between the occipital and parietal lobes provide support for the spatial aspects of vision (Vanderploeg, 2000). Different groups of neurons respond to different properties of visual stimuli, such as color or the orientation of lines or angles (Vanderploeg). Deficiencies in visuospatial skill may become apparent through expressions of altered perception or an inability to recognize familiar objects, which may trigger a diminished ability to perform manual tasks.

Learning and Memory

Learning is the process of acquiring new information. Memory refers to the persistence of learning in a state that can be revealed at a later time (Squire, 1987). Memory is an outcome of learning that is created or strengthened by repetition (Gazzaniga et al., 2002) and implies the ability to acquire, store, and use new information (Grober, 2002). Memory typically is categorized as short- or long-term storage. Short-term memory, more often referred to as working memory, is brief memory storage with a decay rate of a few seconds. Consolidation refers to the neuropsychological mechanism that allows memories to be stored more permanently. Long-term memory storage, also known as semantic memory, contains all of the knowledge and facts that have been learned and remembered (Andrewes, 2001).

Short-term memory requires an intact reticular activating system and the activation of the dorsolateral prefrontal cortex in conjunction with the parietal cortex. The medial temporal lobe, which includes the hippocampus and parts of the thalamus, is critical to the processes involved in forming memories. The prefrontal cortex is involved in encoding and retrieving information (Gazzaniga et al., 2002). The amygdala and orbitofrontal cortex jointly supply the emotional and motivational context to memory that is essential for consolidation (Andrewes, 2001). The primary region of the brain that is crucial for intact semantic (i.e., long-term) memory function is the anterior temporal lobe, particularly the left anterior temporal lobe. In addition, several neurotransmitter systems contribute to normal memory functioning. For example, adrenergic and cholinergic components of the brain stem reticular activating system are responsible for the arousal and attention portions of working memory (Blumenfeld, 2002).

Memory impairment can result from attention, perceptual, motor, or executive dysfunction (Andrewes, 2001). Memory is important not only for learning but also for retaining information used to perform everyday tasks, such as reading or retrieving permanent memories. Any significant deficits in memory have a substantial adverse impact on activities of daily living and the performance of work functions.

The Blood-Brain Barrier

Each domain of cognitive function depends heavily on intact connections among various neuroanatomic regions as well as the functioning of multiple brain regions. Regardless of the mechanism or mechanisms, chemotherapy must gain entry into the brain before any cognitive impairment can occur. An understanding of the neurotoxicity of chemotherapy and its ability to cross the blood-brain barrier is necessary.

The blood-brain barrier is the physiologic barrier of the CNS, located in the tight junctions between capillary endothelial cells (Lattera & Goldstein, 2000). The barrier controls the movement of substances from the extracellular fluids of the body to the extracellular fluids of the brain (Nolte, 2002). Essential substrates (e.g., glucose, amino acids, nucleotides) move across the blood-brain barrier using transporters. Substances that are hydrophilic (i.e., have poor lipid solubility) or have molecular weights greater than 200 daltons are not readily able to diffuse across the endothelial barrier (Chabner & Longo, 2001).

Neurotoxicity of Chemotherapy

Chemotherapy is a systemic treatment that has the greatest impact on rapidly dividing tumor cells. Toxicities emerge because of chemotherapy's deleterious effects on rapidly dividing normal cells in areas of the body such as the bone marrow or gastrointestinal tract. Therefore, neurotoxicity is surprising as a major side effect because the nervous system consists of cells (e.g., glia) that do not divide or divide slowly (Posner, 1995). Furthermore, except for a few areas (e.g., the dorsal root ganglia), the nervous system is protected by the blood-brain barrier against the easy entry of hydrophilic, or water-soluble, agents. As a result, most chemotherapy agents that are injected into parts of the body other than the CNS attain much lower concentrations in the CNS. This section discusses some of the most common chemotherapeutic agents used in the treatment of cancer and what is known about the ability of each to cross the blood-brain barrier.

Cyclophosphamide

Cyclophosphamide is a lipophilic alkylating agent with a molecular weight of 261.08 daltons that is able to cross the blood-brain barrier (Dorr & Von Hoff, 1994; Peterson & Popkin, 1980). Although detecting the drug in the CNS may not be possible, cyclophosphamide does appear in the cerebrospinal fluid (Egorin et al., 1982). The drug causes little or no neurotoxicity when administered in standard doses except for a rarely occurring syndrome involving inappropriate antidiuretic hormone secretion (Schagen, Muller, Boogerd, & van Dam, 2002). Reversible visual blurring, dizziness, and confusion have been reported with cyclophosphamide when administered in high doses (Posner, 1995; Verstappen, Heimans, Hoekman, & Postma, 2003).

Doxorubicin

Doxorubicin is a water-soluble, antitumor antibiotic with a molecular weight of 580 daltons (Dorr & Von Hoff, 1994) and is thought to cross the blood-brain barrier only at doses above those used clinically (Dorr & Von Hoff; Peterson & Popkin, 1980). Experimental efforts to increase uptake into the CNS by osmotic disruption produced significant neurotoxicity (Neuwelt, Pagel, Barnett, Glassberg, & Frenkel, 1981). Beck and Kuttesch (1992) suggested that the combination of doxorubicin and cyclosporine may increase doxorubicin concentrations in the brain, leading to potential encephalopathy. Cardiac thrombi, associated with doxorubicin-induced cardiac toxicity, may lead to transient cerebral ischemia or infarction (Posner, 1995).

5-Fluorouracil

The antimetabolite 5-fluorouracil (5-FU) has a molecular weight of 130.08 daltons and is distributed to all areas of the body, including the CNS, by simple diffusion (Dorr & Von Hoff, 1994). The drug easily crosses the blood-brain barrier, and estimates of the levels of the drug in the brain range from minimal to significant, with higher concentrations occurring in the cerebellum (Dorr & Von Hoff; Peterson & Popkin, 1980; Posner, 1995). Patients who are genetically deficient in the enzyme dihydropyrimidine dehydrogenase, which breaks down 5-FU, appear to be at greater risk for neurotoxicity (Perry, 2001; Takimoto et al., 1996). Neurotoxicity also may include acute encephalopathy (i.e., delirium), which is characterized by confusion, disorientation, or altered behavior (Choi et al., 2001; Greenwald, 1976; Kaplan & Wiernik, 1982; Keime-Guibert, Napolitano, & Delattre, 1998; Peterson & Popkin; Posner; Verstappen et al., 2003).

Methotrexate

Methotrexate is a water-soluble antimetabolite with a molecular weight of 454.5 daltons (Dorr & Von Hoff, 1994). Methotrexate-induced neurotoxicity, which causes symptoms ranging from memory and concentration problems to progressive dementia, is a well-established side effect when the drug is given intrathecally (Schagen, Muller, Boogerd, & van Dam, 2002). Acute encephalopathy, characterized by confusion, disorientation, and altered behavior, has occurred with high doses of IV methotrexate (Posner, 1995). Levels of methotrexate in cerebrospinal fluid recorded after high doses were administered have been within the cytotoxic range. However, when conventional oral doses are administered, no clinically significant neurotoxicities have been reported (Dorr & Von Hoff).

Although oral doses of methotrexate do not cross the blood-brain barrier and standard IV doses do so poorly, encephalopathy has occurred following standard IV doses (Genvresse, Dietzmann, Massenkeil, Spath-Schwalbe, & Possinger, 1999; Kaplan & Wiernik, 1982; Keime-Guibert et al., 1998; Kiu et al., 1994; Peterson & Popkin, 1980; Posner, 1995; Verstappen et al., 2003). Magnetic resonance imaging scans have revealed cerebral atrophy, diffuse white matter hyperintensities (i.e., bright white appearance), ventricular enlargement, and occasional cortical calcifications in patients who experienced encephalopathy as a result of methotrexate administration (Verstappen et al.).

Paclitaxel

Paclitaxel is a taxane with poor solubility in water and a molecular weight of 853.9 daltons (Dorr & Von Hoff, 1994).

Although paclitaxel commonly causes peripheral neuropathies, whether it crosses the blood-brain barrier is not clear (Dorr & Von Hoff). Paclitaxel can cause proximal motor weakness in some patients (Posner, 1995), and rare cases of encephalopathy and seizures have been reported, especially at doses higher than 600 mg/m² (Nieto et al., 1999; Verstaappen et al., 2003).

Other Agents

Although IV epirubicin causes neuronal damage to mice, the drug does not appear to cross the blood-brain barrier or cause neurotoxicity in humans (Posner, 1995). Neurotoxicity caused by carboplatin (Dorr & Von Hoff, 1994) is uncommon; however, focal encephalopathy with cortical blindness, seizures, and aphasia have been reported with cisplatin (Troy et al., 2000; Verstaappen et al., 2003), and decreased deep tendon reflexes have been noted with vinorelbine (Dorr & Von Hoff). Capecitabine, docetaxel, doxil, gemcitabine, and mitoxantrone are not known to cross the blood-brain barrier. Despite variable evidence regarding the ability of chemotherapy drugs to cross the blood-brain barrier, the brain appears to be a site for chemotherapy-induced toxicity. Once chemotherapy drugs enter the CNS, the exact mechanism or mechanisms responsible for producing changes in cognitive function are not understood completely.

Potential Mechanisms for Chemotherapy-Induced Impairments in Cognitive Function

Many chemotherapy drugs are known to be irritants or have the potential to cause necrosis if tissues are infiltrated. Some professionals have speculated that chemotherapy drugs, which are toxic chemicals, damage blood vessels and, eventually, the blood-brain barrier (Schagen, Muller, Boogerd, & van Dam, 2002). Once the blood-brain barrier is disrupted, the same poisonous agents, in addition to other medications or toxic substances, have a direct, adverse effect on brain tissue or neurotransmitters. Several potential mechanisms for chemotherapy-induced impairments in cognitive function have been suggested and are listed in Table 2.

Whether one or more of the mechanisms discussed is responsible for chemotherapy-induced impairments in cognitive function still is unknown. Impairments in cognitive function resulting from chemotherapy may occur along a continuum from subtle changes to profound neurologic impairment. One of the most acute types of neurologic impairment associated with chemotherapy is toxic leukoencephalopathy. More subtle changes in cognitive function, commonly referred to as “chemo brain,” likely occur through multiple mechanisms, including cytokine-induced inflammatory response, chemotherapy-induced anemia, chemotherapy-induced menopause, and other patient-, disease-, and treatment-related factors.

Leukoencephalopathy

Leukoencephalopathy is a structural alteration in cerebral white matter (of which myelin suffers the most damage) that may be caused by exposure to chemotherapy agents (Filley & Kleinschmidt-DeMasters, 2001). Chemotherapy-induced leukoencephalopathy may occur as a result of direct toxic effects on myelin, damage to oligodendrocytes that causes disruption of myelin synthesis, or an increase in capillary

Table 2. Potential Mechanisms for Chemotherapy-Induced Impairments in Cognitive Function

Mechanism	Domain of Cognitive Function	Chemotherapy Drugs
Leukoencephalopathy	Attention and concentration Executive function Visuospatial skill Memory	Asparaginase Cisplatin Cyclophosphamide Cytarabine 5-fluorouracil Ifosfamide Methotrexate Nitrosureas Paclitaxel Vincristine
Cytokine-induced inflammatory response	Attention and concentration Executive function ^a Visuospatial skill Memory	Doxorubicin 5-fluorouracil Paclitaxel
Chemotherapy-induced anemia	Attention and concentration Executive function Motor function Memory	Capecitabine Carboplatin Cisplatin Docetaxel Gemcitabine Methotrexate Vinorelbine
Chemotherapy-induced menopause	Attention and concentration Memory	Carboplatin Cisplatin Cyclophosphamide Doxorubicin 5-fluorouracil Methotrexate

^a The effects of cytokine-induced inflammatory response on executive function are unclear.

permeability that leads to edema and subsequent demyelination (Filley, 1999; Schagen, Muller, Boogerd, & van Dam, 2002). The integrity of white matter tracts devoted to cognitive function is damaged significantly by leukoencephalopathy. The damage leads to a disruption in neurotransmission, decreased cerebral neuron conduction, and a subsequent slowing of cognition (Filley, 1998, 1999, 2001). The damage associated with leukoencephalopathy may be transient or permanent (Kaplan & Wiernik, 1982). Patients' potential for recovery is dependent on whether neuronal loss has occurred (Filley, 1998).

Early or mild encephalopathy is evidenced by patchy edema of myelin. However, no axonal loss occurs because the myelin insulation is preserved (Filley, 2001). Patients with mild encephalopathy may be asymptomatic or manifest sustained attention and memory-retrieval impairments (Filley & Kleinschmidt-DeMasters, 2001).

If further white matter damage occurs, moderate encephalopathy is evidenced by widespread edema of the myelin with demyelination, with the axons being spared from harm. Noticeable impairments in the cognitive domains of attention, executive function, visuospatial skill, and memory, with minimal damage to language, have been seen in patients with moderate leukoencephalopathy (Filley & Kleinschmidt-DeMasters, 2001).

Severe leukoencephalopathy leads to the destruction of oligodendrocytes, axonal loss, necrosis, and the blockage of axonal conduction as evidenced by severe global impairment (Filley, 2001). Although spontaneous improvement likely will occur with mild and moderate leukoencephalopathy, progressive deterioration is more common with severe leukoencephalopathy (Keime-Guibert et al., 1998).

Leukoencephalopathy has been reported with many chemotherapy drugs, including asparaginase, cisplatin, cyclophosphamide, cytarabine, 5-FU, ifosfamide, methotrexate (Cohen, Lossos, & Polliack, 2002), nitrosureas, paclitaxel, and vincristine (Choi et al., 2001; Cohen et al.; Cossaart, SantaCruz, Preston, Johnson, & Skikne, 2003; Kaplan & Wiernik, 1982; Keime-Guibert et al., 1998; Lee, Nauert, & Glass, 1986; Mizutani, Morimatsu, & Hayakawa, 1984; Moore, 2003; Verstappen et al., 2003). Severe leukoencephalopathy has occurred following the administration of high-dose methotrexate (Tuxen & Hansen, 1994), cisplatin (Troy et al., 2000), and paclitaxel (Nieto et al., 1999). Although the severity of leukoencephalopathy may increase with higher doses, whether other factors, such as repeated exposure or treatment with combined modalities, influence the degree of encephalopathy is unclear (Kaplan & Wiernik; Peterson & Popkin, 1980; Tuxen & Hansen).

Cytokine-Induced Inflammatory Response

Chemotherapy drugs also may disrupt the normal physiology of the brain through direct injury to neurons as a result of uncontrolled inflammatory processes that are mediated primarily by cytokines. Cytokines are proteins that are released by activated immune cells (i.e., macrophages) in response to inflammation, stress, or direct injury to neurons (Maier, 2003). Interleukin (IL)-1 α , IL-1 β , tumor necrosis factor- α (TNF- α), and IL-6 are proinflammatory cytokines that augment the immune system's response to facilitate prompt resolution of injury (Kronfol & Remick, 2000). Because chemotherapy causes injury to normal tissues, the plausibility exists that it could induce the release of cytokines. Proinflammatory cytokines have been implicated directly in the endoneurial swelling that produces peripheral neuropathic pain associated with vinca alkaloids, taxanes, and cisplatin in rats (Aley, Reichling, & Levine, 1996; Authier, Fialip, Eschaliere, & Coudore, 2000; Polomano, Mannes, Clark, & Bennett, 2001).

The brain interprets increased levels of proinflammatory cytokines as signals of sickness (Dantzer, 2001), mobilizes all resources in the defense against infection and tissue injury, and subsequently exhibits what has been labeled as "sickness behavior" (Maier & Watkins, 1998). Evidence suggests that circulating levels of cytokines increased to only two-to-three times normal levels may produce sickness behavior (Pollmacher, Haack, Schuld, Reichenberg, & Yirmiya, 2002). Nonspecific symptoms of sickness behavior include weakness, decreased mobility, malaise, anorexia, an inability to concentrate, listlessness, and a decreased ability to learn (Dantzer). The symptoms are similar to the toxicities induced by the systemic administration of proinflammatory cytokines such as IL-1, IL-2, and TNF- α for the treatment of cancer (Cleeland et al., 2003). Similar sickness behaviors, including cognitive impairments, are seen with chemotherapy (Cleeland et al.; Maier & Watkins, 2003). Chemotherapy agents that have been shown to induce the production of proinflammatory cytokines in human or mu-

rine cell lines include doxorubicin, 5-FU, and paclitaxel (Niiya et al. 2003; Wichmann et al., 2003; Zaks-Zilberman, Zaks, & Vogel, 2001).

Although evidence of specific receptors for IL-1, IL-6, and TNF- α in the brain exists, the cytokines are relatively large and lipophobic and are not likely to be able to cross the blood-brain barrier via passive diffusion (Maier & Watkins, 1998; Wilson, Finch, & Cohen, 2002). Therefore, some have suggested that cytokines may enter the CNS through passive diffusion at areas unprotected by the blood-brain barrier (e.g., circumventricular regions), by active transport, or by stimulating prostaglandins that signal the brain to induce cytokine synthesis in the brain (Maier, 2003; Pollmacher et al., 2002). Glial cells are a major source of cytokines in the brain. Glial cells synthesize and release IL-1, IL-6, and TNF- α (Hopkins & Rothwell, 1995; Maier & Watkins, 2003; Schobitz, de Kloet, & Holsboer, 1994).

Cytokine-mediated mechanisms in the CNS may contribute to cognitive impairments through interactions between neurons and glial cells that facilitate neuronal regeneration or damage (Wilson et al., 2002). Neuronal damage also may cause deficits in neurotransmitters, such as acetylcholine or dopamine, that transmit messages in the brain and facilitate cognition (Ahles & Saykin, 2001; Wilson et al.). In addition, cytokines can impair erythroid colony formation in response to erythropoietin, decrease the life span of erythrocytes, impede erythropoietin production, prevent the normal use of iron, and, ultimately, cause anemia (Ludwig, 1999; Means, 1999).

Chemotherapy-Induced Anemia

Anemia has been associated with increased risk for cognitive impairments in patients with Alzheimer disease (Beard, Kokmen, O'Brien, Ania, & Melton, 1997), renal disease (Stivelman, 2000), and vascular dementia (Milward et al., 1999). Such cognitive dysfunction may be related to oxygen deprivation that, if acute, has been shown to cause damage to the frontal and temporal lobes as well as the hippocampus, basal ganglia, and cerebellum (Lezak et al., 2004). Insufficient brain oxygenation is known to cause impairments in alertness, attention and concentration, memory, motor function, and mental flexibility (Lezak et al.).

Chemotherapy can cause or exacerbate anemia in patients with cancer by reducing erythropoietin production or damaging progenitor and mature hematopoietic cells (Gordon, 2002). Anemia is a complication of myelosuppressive chemotherapy that occurs in more than 50% of patients (Glaspy, 1997). The incidence of chemotherapy-induced anemia is dependent on the intensity of treatment, and the proportion of patients with anemia increases with cumulative cycles.

Reports of grade III or IV anemia with conventional single-agent or combination chemotherapy regimens occur in < 1%–30% of patients who receive standard doses and in as many as 80% of patients who receive high-dose regimens (Groopman & Itri, 1999). Specific chemotherapy drugs or regimens that cause anemia include cisplatin, methotrexate (especially in high doses), and the combination of cyclophosphamide, methotrexate, and 5-FU (Brown et al., 2001). Chemotherapy-induced anemia may cause cognitive dysfunction, such as decreased mental alertness, poor concentration, and memory problems (Cunningham, 2003). Although

cognitive impairments may occur with anemia, the hematocrit level that is most appropriate for optimizing cognitive function is not known. Some have suggested that difficulty concentrating may occur at a hemoglobin level lower than eight or a hematocrit less than 25% (Brown et al.).

Chemotherapy-Induced Menopause

In women, chemotherapy-induced menopause may be another mechanism for cognitive impairment. Hormones such as estrogen are chemical substances that are able to act on cells located at a distance. Estrogen receptors exist in multiple locations throughout the brain, especially in regions involved with attention, memory, and learning, such as the cerebral cortex, hippocampus, and amygdala (Baxter & Chiba, 1999; Everitt & Robbins, 1997; Shilling, Jenkins, Fallowfield, & Howell, 2001). Estrogen increases the level of choline acetyl-transferase, the enzyme required for the synthesis of acetylcholine, which is thought to be involved in the process of memory consolidation in the basal forebrain, frontal cortex, and hippocampus (Shapiro & Henderson, 1994; Sherwin, 1998). Some studies measuring cognitive function in women on estrogen replacement therapy have suggested that estrogen is protective against cognitive impairments in multiple domains, especially verbal memory (Jacobs et al., 1998; Maki & Hogervost, 2003; McEwen, Alves, Bulloch, & Weiland, 1997; Shilling et al.).

Chemotherapy affects ovarian function and can lead to temporary or permanent amenorrhea in women, especially in those older than age 40 (Knobf, 1998; Padmanabhan, Wang, Moore, & Rubens, 1987). Seventy-five percent of breast cancer diagnoses occur in women older than age 50, whereas 25% occur in premenopausal women (Poniatowski, Grimm, & Cohen, 2001). Menopausal symptoms may start in as few as 6–12 weeks after beginning chemotherapy treatment in premenopausal women (Dnistrian et al., 1983). Amenorrhea generally occurs within 6–12 months of treatment; however, the frequency varies and depends on the type, dose, and duration of the chemotherapy treatment as well as a patient's age (Chiarelli, Marrett, & Darlington, 1999). Amenorrhea occurs in more than 90% of women older than age 40 and in approximately 25% of women younger than age 40 who receive chemotherapy (Knobf; Meirrow, 2000; Padmanabhan et al.; Saarto et al., 1997). Chemotherapy drugs most commonly associated with decreased ovarian function include alkylating agents and doxorubicin (Kaplan, 1992; Meirrow; Saarto et al.; Shapiro & Henderson, 1994).

Estrogen deficiency is associated with cognitive impairments in the domains of learning and memory, especially verbal memory (Cutter, Norbury, & Murphy, 2003; Erlanger, Kutner, & Jacobs, 1999; Sherwin, 1996, 1998). However, estrogen deficiency appears to have little effect on visual or spatial memory (Sherwin, 1998). Women who become menopausal as a result of chemotherapy experience a more rapid drop in estrogen than they would during natural menopause. Whether the accelerated decrease causes greater impairments in cognitive function is not clear (Shilling et al., 2001).

Other Influencing Factors

In addition to chemotherapy-related mechanisms, a number of patient factors may be protective against cognitive impairments or place individuals at higher risk for impairments in cognitive function. Education levels and intelligence have

strong, positive relationships with neuropsychological test performance and have been found to be protective against cognitive impairments associated with brain trauma (Lezak et al., 2004). Although cognitive decline occurs with aging, most neuropsychological tests have normative data for various age groups.

Psychological factors such as stress, anxiety, and depression can reduce performance on neuropsychological testing. Anxiety and depression have been shown to negatively influence cognitive function, especially in the domains of attention, concentration, and memory (Lezak et al., 2004). Psychological disturbances are common when individuals are confronted with a cancer diagnosis or the initiation of cancer treatment.

Fatigue is the most commonly reported side effect of chemotherapy and often persists for a prolonged period of time after treatment is completed (Brown et al., 2001). Physical or mental fatigue can affect cognitive function negatively (Meyers, 2000). One study of breast cancer survivors found slower reaction times and increased complaints of cognitive impairments in individuals with severe fatigue (Servaes, Verhagen, & Bleijenberg, 2002).

The presence of the apolipoprotein E (APOE) $\epsilon 4$ gene has been associated with decreased cognitive function in older adults (Haan, Shemanski, Jagust, Manolio, & Kuller, 1999; Yaffe, Cauley, Sands, & Browner, 1997). One preliminary study of cancer survivors found a greater risk of deficits in visual memory and visuospatial skills in patients who had at least one $\epsilon 4$ allele of APOE (Ahles et al., 2003).

Implications for Clinical Practice

The prevalence, severity, and duration of chemotherapy-induced impairments in cognitive function are unknown. However, a growing body of evidence supports the idea that “chemo brain” does occur to varying degrees in patients who receive chemotherapy. Oncology nurses need to be aware of this potential effect of chemotherapy and conduct ongoing assessments of patients. Although no valid and reliable clinical tools exist to assess for chemotherapy-induced cognitive impairments, nurses can evaluate patients for changes in attention and concentration or in the ability to perform routine cognitive tasks (e.g., balancing a checkbook).

Impairments in cognitive function affect patients' ability to provide informed consent, identify treatment toxicities, and learn and perform self-care measures. In addition, impairments in cognitive function may adversely affect patients' ability to perform routine daily activities or return to work following the completion of treatment. Although the mechanisms of chemotherapy-induced impairments in cognitive function most likely are multifactorial, some patients may be at higher risk. As more information becomes available about the mechanism or mechanisms of chemotherapy-induced cognitive impairments, the ability to identify high-risk patients will become easier and help direct important nursing interventions, such as ongoing assessment, patient education and counseling, the initiation of appropriate interventions, and preventive strategies.

Figure 1 illustrates various chemotherapy-related, concomitant effects of cancer and treatment and individual patient factors that may contribute to the development of cognitive impairments, or “chemo brain.” Indirect factors

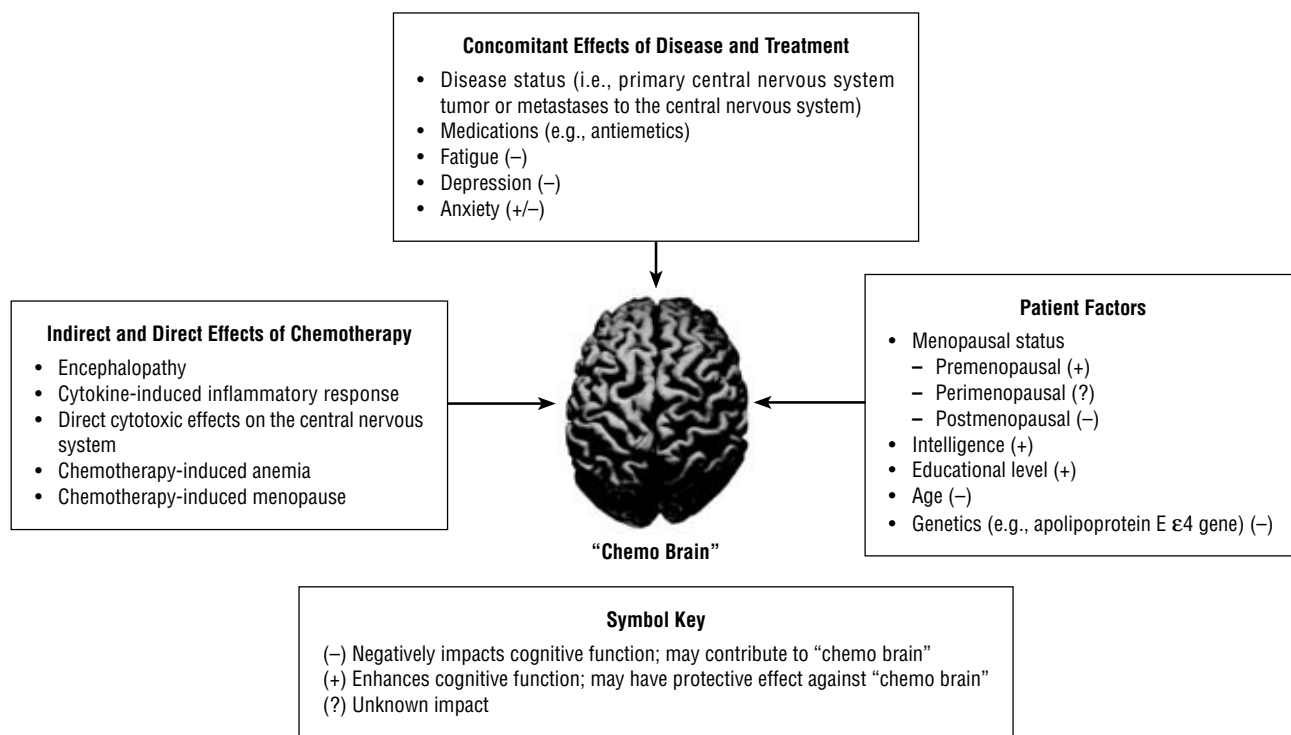


Figure 1. Potential Contributing Factors for Chemotherapy-Induced Impairments

Note. Photo from “The Human Brain: Chapter 5: The Cerebral Hemispheres,” by T.H. Williams, N. Gluhbegovic, & J.Y. Jew, 2005. Retrieved September 29, 2005, from <http://www.vh.org/adult/provider/anatomy/BrainAnatomy/Ch5Text/Section01.html>. Copyright 2005 by T.H. Williams, N. Gluhbegovic, J.Y. Jew, and the University of Iowa. Reprinted with permission.

that may exacerbate impairments in cognitive function include genetic predisposition (e.g., the presence of the APOE ε4 gene), nutritional deficiencies, metabolic abnormalities, accompanying medications, depression, anxiety, or fatigue (Saykin, Ahles, & McDonald, 2003). Any one of these factors may contribute to patients’ risk for cognitive impairments; however, further research is needed to determine whether factors may have sequential or cumulative effects in patients receiving chemotherapy. In addition, knowledge regarding the phenomenon of “chemo brain” needs to be expanded in terms of the characteristics and impact on patients.

Even mild toxicity to the CNS can cause discernible changes in cognitive function (Posner, 1995). Earlier studies have suggested that most of the effects of chemotherapy on cognition are acute and reversible (Meyers & Scheibel, 1990). However, more recent studies of breast cancer survivors revealed cognitive impairments from six months to 10 years following the completion of chemotherapy (Ahles et al., 2002; Brezden et al., 2000; Schagen et al., 1999; van Dam et al., 1998; Wieneke & Dienst, 1995).

These cross-sectional studies suggest that the effects of chemotherapy on cognitive function may be long-term. Because each study used a cross-sectional design, whether “chemo brain” is transient, progressive, or permanent cannot be determined. One follow-up study found improvements in breast cancer survivors two years after initial testing (Schagen, Muller, Boogerd, Rosenbrand, et al., 2002). Although this

finding indicates that cognitive impairments may improve over time, the study was limited by significant attrition. Longitudinal studies are needed to further elucidate the phenomenon of “chemo brain” and describe its characteristics (e.g., onset, severity, duration).

Implications for Research

Evidence of chemotherapy-induced impairments in cognitive function exists; however, much still needs to be discovered. Future studies should focus on the development of animal models to isolate the mechanism or mechanisms that cause alterations in cognitive function associated with specific chemotherapy agents. In addition, longitudinal studies are needed to further describe the phenomenon of “chemo brain” and elucidate the mechanism or mechanisms responsible for chemotherapy-induced cognitive impairments. As a more thorough description of the “chemo brain” phenomenon is developed, future studies need to determine the predictors, biomarkers, and relevant assessment parameters for this significant clinical problem. Knowledge of the mechanisms that underlie the development of chemotherapy-induced impairments in cognitive function is crucial to the development of preventive strategies to lessen or eliminate their occurrence.

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