An estimated 11.1 million Americans are living with cancer. Many have received chemotherapy, and a portion of patients treated with chemotherapy develop cognitive difficulties, often referred to as “chemo brain.” Chemotherapy-induced cognitive impairment can impact all areas of a patient’s life. Yet little education is given to patients and families regarding the potential side effect prior to initiation of cancer treatment. This is, in part, because nurses may struggle with understanding the scientific causes behind the cognitive disabilities. This article will describe hypothesized pathophysiology, signs and symptoms, and potential contributing factors of chemotherapy-induced cognitive impairment. Potential treatment strategies, including pharmacologic and nonpharmacologic interventions, also will be discussed.

At a Glance

- Chemotherapy-induced cognitive impairment is believed to occur because of alterations in the blood-brain barrier, vascular injury, and myelination changes, and it may have a genetic link.
- The cognitive difficulties from chemotherapy are unique and can last for months to years after treatment.
- Medications, exercise, stress management, nutrition, and support groups may be beneficial in addressing cognitive challenges.

Definition of Chemotherapy-Induced Cognitive Impairment

Chemotherapy-induced cognitive impairment is described as dysfunction, weakening, or impairment (Coyne & Leslie, 2004; Staat & Segatore, 2005) of memory in patients who have been treated with chemotherapy for cancer. Cognitive impairment
also has been noted in patients treated with hormonal therapy (Nelson, Nandy, & Roth, 2007). It has been called mental fatigue and mental cloudiness. Patients complain about difficulty with memory and information processing as well as multitasking, organization, and focusing attention on tasks at hand. Regardless of the terminology used to refer to chemotherapy-induced cognitive impairment, it can be distressing and have negative effects on patients’ personal, academic, and professional lives.

How many or which particular patients will experience cognitive impairment is not known. Studies have shown that cognitive difficulties affect 25%–53% of all patients undergoing systemic chemotherapy (Coyne & Leslie, 2004). Cognitive impairment affects children and adults. Sumpter (2006) noted that “as many as 40% of all pediatric ALL [acute lymphoblastic leukemia] patients treated with chemotherapy alone will develop serious learning disabilities within two to three years following treatment. For children who receive cranial radiation, with or without chemotherapy, the percentage is 80%–90%” (p. 104).

Little is known about potential causes, whether one agent alone causes cognitive difficulties or whether combinations of certain drugs or radiation are needed, and what impact a patient’s genetic make-up has on the severity and duration of cognitive impairment. At present, no definitive medical test can diagnose cognitive impairment from cancer treatment.

In the interest of beginning life-saving treatment, as well as because of a lack of evidence-based approaches and prospective, longitudinal trials, patients are not tested for cognitive ability prior to the initiation of cancer treatment (Myers & Teel, 2008; Wefel, Lenzi, Theriault, Davis, & Meyers, 2004). Consequently, measuring changes from baseline and the impact on individuals, which can range from mild to severe, is difficult.

Cognitive impairment has been studied the most in women with breast cancer, perhaps because of their long-term survival when compared to those with other cancers. The chemotherapy agents used to treat breast cancer also are used to treat other cancers. Therefore, any patient who receives chemotherapy could experience cognitive difficulties. Researchers have begun to study the cognitive impact chemotherapy has on cancers other than those of the breast. Ahles et al. (2002) studied adult patients with breast cancer or lymphoma, showing a negative cognitive impact in areas of memory and concentration. Han et al. (2008) studied 5-fluorouracil, a chemotherapy agent used in the treatment of numerous cancers. The extent and impact on patients with other tumor types warrant additional study.

**Description of Chemotherapy-Induced Cognitive Impairment**

**Pathophysiology**

Several mechanisms of cognitive dysfunction have been suggested. The brain’s primary method of protection from harmful agents is the blood-brain barrier (BBB). Cyclophosphamide and 5-fluorouracil, two commonly used chemotherapy drugs, pass through the BBB easily (Jansen, Miaskowski, Dodd, Dowling, & Kramer, 2005) and are thought to contribute to cognitive disruptions. Other agents, such as cisplatin, doxorubicin hydrochloride, methotrexate, topotecan, and vincristine can penetrate the BBB, leading to cognitive dysfunction (Ahles & Saykin, 2001; Troy et al., 2000; Wong & Berkenblit, 2004).

Researchers have shown a decrease in the brain’s grey matter and demyelination of white matter fibers (Saykin et al., 2005) after systemic chemotherapy treatment. Vascular injury leading to thrombosis, ischemia, infarction, and parenchymal necrosis (Ahles & Saykin, 2001) has been suggested as contributing to cognitive difficulties. The risk of cognitive impairment may not end with the completion of chemotherapy. Han et al. (2008) showed that the myelination changes in the central nervous system from 5-fluorouracil can be delayed for several months and can become progressive, thereby extending cognitive difficulties of patients far beyond the end of treatment.

A genetic link is under consideration. The presence of the apolipoprotein E ε4 (APOE ε4) gene, the gene associated with Alzheimer disease, has been studied; patients who carry APOE ε4 may be more susceptible to chemotherapy-induced cognitive impairment (Ahles et al., 2003). A genetic factor could shed light on why some patients experience cognitive impairment more than others. Research is ongoing.

**Signs and Symptoms**

Cognitive impairment can be very distressing for patients and their families. Nurses must recognize subtle differences in patients and be astute in detecting them during cognitive assessments. Cognitive impairment can negatively affect short-term memory (CancerSymptoms, 2006), as well as cause problems with judgment and reasoning (Cancer.Net, 2005). Difficulties may be subtle, so only the patient or family may be aware of them. However, cognitive changes may be severe enough to interfere with a patient’s daily functioning, including employment abilities. Regardless of the extent of cognitive difficulty experienced by a patient, feelings of anxiety and fear are common. Sensitivity on the behalf of the healthcare team is essential. Symptoms of cognitive impairment are listed in Figure 1.

Patient complaints regarding cognitive changes often do not correlate with results on standardized neuropsychological testing (Rugo & Ahles, 2003). The Mini Mental State Examination, a clock-drawing task, and a 25-item bedside measurement of executive control or frontal function have been used to assess cognitive function but do not appear to be sensitive enough to detect subtle changes related to chemotherapy treatments (Rugo & Ahles; Tannock, Ahles, Ganz, & van Dam, 2004). To address this issue, the Functional Assessment of Cancer Therapy–Cognitive (FACT-Cog) scale was developed. The scale is a self-report measure that evaluates mental acuity, attention and concentration, memory, verbal fluency, functional interference, deficits observed by others, change from previous functioning, and impact on quality of life (Rugo & Ahles; Tannock et al.). The FACT-Cog currently is in validation studies.
Until the FACT-Cog scale is validated and approved for general use, nurses can conduct complete history and physical assessments on their patients. Special attention should be directed to questions regarding difficulties with memory, concentration, and daily functioning.

### Contributing Factors and Cofactors

Several factors may contribute to development of cognitive difficulties, along with changes in brain tissue, including pain, stress, cytokine-induced inflammatory response, nutritional deficits and fluid and electrolyte imbalances, chemotherapy-induced anemia, and medications. In some cases, cognitive impairment might improve with the correction of the contributing factor, such as clearing an infection, stopping a medication, or correcting a nutritional deficit. Nurses should be astute in assessments and offer interventions to minimize effects on patients.

#### Pain

Pain can be emotionally and physically exhausting. It can be distracting and lead to poor concentration. Patients in pain may have difficulty focusing their attention and struggle with attempts to absorb new information. A study by Sjøgren, Olsen, Thomsen, and Dalberg (2000) demonstrated that “pain itself may deteriorate working memory more than oral opioids” (p. 244). Excellent pain control is essential to ensure that patients are able to focus on tasks at hand.

#### Stress

Stress can be a powerful enemy to cognitive function (Ahles & Saykin, 2001; Jansen et al., 2005). Anyone who has heard the words “You have cancer” can attest to emotional stress and anxiety. The threat to survival can be overwhelming and lead to lack of concentration and poor memory. Once treatment begins, juggling numerous medical appointments while attempting to continue with everyday life can be challenging. Learning medical jargon and coping with treatment side effects can contribute to poor memory, distraction, and difficulty with comprehension and understanding. Stress management is important for any cancer survivor.

### Cytokine-Induced Inflammatory Response

Cytokines are hormone-like proteins that play a role in immune responses and inflammation (Jansen et al., 2005; Saykin et al., 2003) and are produced in response to injury, infection, or stress. The exact mechanism of cytokines’ effects is not clear, but they can impact cognition in several ways, including a syndrome associated with elevated cytokines known as sickness behavior. Symptoms of sickness behavior include fever, lethargy, weakness, reduced mobility, decreased learning ability, inability to concentrate, listlessness, anorexia, and decreased libido (Jansen et al., 2005; Wilson, Finch, & Cohen, 2002).

Chemotherapy destroys cancer cells and normal, healthy cells. The destruction of healthy cells produces physiologic stress. The brain interprets this inflammatory response and the increased release of cytokines as stress, which can result in decreased ability to learn, memory difficulties, and poor concentration (Jansen et al., 2005; Saykin et al., 2003). Additionally, impairment of the BBB via cytokine binding to the endothelial receptors in the brain’s vasculature (Wilson et al., 2002) elevates overall stress to the brain. With BBB impairment, more toxic chemotherapeutic agents may be allowed access to the brain which, under normal circumstances, would not usually gain entry. Exercise, stress management, and diet all play roles in mediating the cytokine-induced inflammatory response.

### Nutritional Deficits and Fluid and Electrolyte Imbalances

Several factors affect the nutritional status and fluid intake of a patient with cancer. This can result in electrolyte imbalances and exacerbate cognitive difficulties. Chemotherapy can cause nausea, reducing a patient’s appetite. Elevated cytokine levels can induce anorexia and result in nutritional deficits, such as vitamin B deficiency, which can result in cognitive impairment (Wilson et al., 2002).

Nausea, vomiting, and diarrhea can result in electrolyte imbalances. Medications to treat various side effects can lead to dry mouth and taste alterations, also decreasing the desire to eat. Dehydration and electrolyte imbalances can result in an overall decline in cognitive functioning.

### Chemotherapy-Induced Anemia

Anemia occurs in approximately 50% of patients with cancer (Gordon, 2002; Jansen et al., 2005). It can be exacerbated or caused by chemotherapy. In anemia, a decrease in the oxygen-carrying capacity of blood occurs, as well as brain ischemia and hypoxia, with resulting decreases in several areas of cognitive performance. The areas include decreases in mental alertness, attention, and concentration (Jansen et al.). Cytokines, produced in response to stress induced by the administration of chemotherapy, can decrease production of erythropoietin, decrease the life span of erythrocytes, interfere with the body’s ability to absorb and metabolize iron (Cunningham, 2003; Gordon, 2002), and increase the likelihood of anemia.
Medications

Medications are an important part of cancer treatment and disease control. Without certain medications, such as antiemetics and pain medications, side effects could be unbearable and lead patients to prematurely discontinue therapy, impacting overall survival. Pharmaceutical interventions are necessary in controlling untoward side effects of the actual cancer process and its treatment, but they can contribute to cognitive issues.

Antiemetics such as prochlorperazine and ondansetron can cause sedation and lead to a feeling of mental fogginess. As with any sedating drug, reaction times can be slowed. Additionally, the medications can cause adverse affects in judgment and memory.

Glucocorticosteroids have a multitude of uses in cancer treatment. They are used to decrease inflammation, and they sometimes are part of actual chemotherapeutic treatment regimens in cancers such as lymphoma (Saykin et al., 2003). Glucocorticosteroids reduce cerebral blood flow and can contribute to cognitive difficulties (Saykin et al.).

Pain control should be a high priority in patients with cancer. However, pain medications, which are used frequently, can lead to mental haziness and decreased concentration. For example, opioids can cause disorientation and delirium (Wilson, Shannon, & Stang, 2005). Several attempts with different medications may be necessary to achieve effective pain control while minimizing the negative cognitive impact.

Other Factors

Several other factors may impact the development of cognitive impairment, including infections and organ failure, which can cause a buildup of toxicities in the blood. Chemotherapy-induced menopause and the resulting reduction in estrogen levels for women have been implicated in cognitive struggles, whereas men are confronted with reduced testosterone levels from hormonal therapy for the treatment of prostate cancer (Ahles & Saykin, 2001; Jansen et al., 2005; Staat & Segatore, 2005). Changes in white matter of the brain, known as chemotherapy-induced leukoencephalopathy, also have been found to contribute to the development of cognitive impairment (Saykin et al., 2005). In addition, radiation therapy has been implicated as causing additive effects with cognitive difficulties from chemotherapy (Hess & Insel, 2007).

Nursing Interventions

Chemotherapy-induced cognitive impairment must be distinguished from brain metastases and other medical conditions. Focus can turn to chemotherapy-induced cognitive impairment once other conditions such as disease progression are ruled out. Chemotherapy-induced cognitive impairment is a complex problem and must be tackled from several different angles. No easy or quick fix is available. Medications, exercise, stress management, nutrition, and support groups may be beneficial in combating cognitive challenges. Nurses must be aware of the development of cognitive impairment and begin treatment in the early stages. The earlier the side effect is recognized, the earlier potential treatments can begin, perhaps minimizing the impact on patients. Potential interventions can be categorized as pharmacologic (see Figure 2) and nonpharmacologic (see Figure 3).

Medications

Several medications, prescription and nonprescription, are under study for the treatment of chemotherapy-induced cognitive impairment. Each medication needs individual attention because some are contraindicated during chemotherapy treatment or in combination with other medications. Some medications, such as erythropoietin alfa, can be administered only when indicated based on blood studies, in light of potential cardiac events (Staat & Segatore, 2005). Close medical supervision is recommended.

Exercise

The benefits of exercise have been well studied in oncology (Hacker, 2009), for the prevention and treatment of a number of problems, and for general health promotion. The usefulness of exercise in mediating the cognitive side effects related to chemotherapy should not be surprising. Exercise improves blood flow and oxygenation to the brain (Nelson et al., 2007), thereby leading to improved cognitive functioning. Long-term exercise programs reduce cytokine levels and shifts them from pro-inflammatory to anti-inflammatory (Wilson et al., 2002), with improvements in cognition noted. Additionally, exercise increases the overall sense of well-being, reduces stress levels, and promotes clear thinking. Regular exercise should be encouraged throughout the treatment cycle and continue for life.

- Aspirin prevents microagulation caused by chemotherapy and suppresses production of prostaglandins, which enhance tumor cell growth.
- Antioxidants decrease free radical formation and prevent oxidative damage to the brain.
- Donepezil improves cognitive function in Alzheimer disease and may be beneficial in chemotherapy-induced cognitive impairment.
- Erythropoietin and epoetin alfa treat chemotherapy-induced anemia, increase the oxygen-carrying capacity of blood, decrease brain ischemia and hypoxia, improve cognitive performance, and may have a neuroprotective effect.
- Ginkgo biloba may have neuroprotective and antioxidant effects.
- Methylphenidate improves cognitive function in children, fights fatigue, is believed to increase extracellular dopamine levels, improves attention, and reduces distractibility.
- Monoamine oxidase inhibitors have antioxidant properties which may provide neuroprotective effects in addition to antidepressant actions.

Figure 2. Pharmacologic Treatments for Chemotherapy-Induced Cognitive Impairment

Note. Based on information from Barton & Loprinzi, 2002; Coyne & Leslie, 2004; Cunningham, 2003; Nelson et al., 2007; Pine Street Foundation, 2007; Staat & Segatore, 2005; Tannock et al., 2004.
Stress Management

To say that cancer and its required treatments are stress provoking would be an understatement. Stress can wreak havoc on otherwise healthy bodies (Wilson et al., 2002). Controlling stress is essential to cognitive health as well as physical health. Stress can be addressed several ways, such as exercise, support groups, personal confidants or spiritual advisors, development or refinement of hobbies, or other personal interests. At times, patients also may require anti-anxiety medications.

Acupuncture

Interest is increasing in acupuncture for the treatment of cognitive difficulties related to cancer therapies. Studies have not directly linked acupuncture to improvement in cognitive impairment, but the approach has been studied in patients with dementia. Acupuncture has been shown to dilate cerebral blood vessels, improve circulation, and increase oxygenation to the brain (Johnston et al., 2007). More research is needed to examine acupuncture for this indication.

Nutrition

The impact of nutrition on the cognitive effects of chemotherapy is under investigation. Nutritional deficits can contribute to anemia in patients with cancer (Gordon, 2002). Diets high in antioxidant fruits and vegetables can mediate the effects of oxidative stress (Barton & Loprinzi, 2002); iron, folic acid, and B vitamins can decrease the impact of anemia on cerebral functioning.

Support Groups

Support groups are essential to patients and families. Newfound tactics for dealing with chemotherapy-induced cognitive impairment from those who have “gone before” can calm anxieties and can keep patients from feeling as though they are verging on cognitive breakdown. To date, no nationally known cognitive impairment support groups exist. Consideration should be given to developing local groups.

Patient Education

More patients with cancer are living longer thanks to advancements in treatment options. Cognitive side effects of cancer treatment have gained more attention with the increase in life expectancy. Chemotherapy-induced side effects, such as nausea and vomiting, are transient and self-limiting. Cognitive difficulties are unique and can last for months to years after treatment. Ahles et al. (2002) demonstrated that the impact of chemotherapy-induced cognitive impairment can reach as far as 10 years beyond treatment discontinuation.

Patients need proper education before treatment begins regarding the potential for cognitive difficulties. To begin chemotherapy without knowing the cognitive consequences, a patient would not truly be giving informed consent. Educational materials should be updated to reflect this as a potential side effect. Patients must understand the importance of reporting cognitive impairment and offered options for dealing with it. Complaints of cognitive difficulty must be taken seriously and given consideration by the healthcare team.

• Acupuncture dilates cerebral blood vessels, improving blood flow and oxygenation in patients with dementia, and it may be beneficial in treatment of chemotherapy-induced cognitive impairment.
• Antioxidant foods such as fruits and vegetables are high in vitamin C and E, and they mediate the effects of oxidative stress.
• Increasing fluid intake prevents dehydration and helps flush toxins from the body.
• Informing family and friends can generate support and understanding.
• Mental exercises, such as crossword and sudoku puzzles, create a positive feedback loop.
• Physical exercise increases blood flow to the brain, improves oxygenation, and reduces cytokine levels.
• Relaxation activities decrease stress. Listening to music, communing with nature, and pursuing other hobbies can be soothing.

Figure 3. Nonpharmacologic Treatments for Chemotherapy-Induced Cognitive Impairment

Note. Based on information from American Cancer Society, 2008; Barton & Loprinzi, 2002; Johnston et al., 2007; Wilson et al., 2002.

Conclusion

As with pain, nausea, vomiting, and peripheral neuropathy, variations exist in the incidence and experience of cognitive impairment. Predicting which patients will experience cognitive impairment, to what extent, or for how long is difficult. However, even a slight amount of cognitive difficulty can have a significant impact on a patient’s quality of life, both personally and professionally. Baseline memory, concentration, and daily functioning assessments should be included in a patient’s initial assessment prior to administration of chemotherapy. Patients should be reassessed routinely, at each follow-up visit, for the development of cognitive impairment, just as they are for other side effects. Patients need to be informed prior to the initiation of cancer treatment about the potential development of cognitive difficulties. If and when cognitive impairment develops, patients need to be taken seriously and treated with sensitivity. Although some may joke about it, chemo brain is not a laughing matter.

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