

# Chemotherapy-Related Cognitive Impairment: Neuroimaging, Neuropsychological Testing, and the Neuropsychologist

**Jamie S. Myers, RN, MN, AOCN®**

Chemotherapy-related cognitive impairment (CRCI) was first described in the 1970s, but significant recognition of CRCI did not emerge with consistency until the late 1990s. Estimates of frequency now range from 17%–75%, and evidence suggests that CRCI, or “chemobrain” as it is referred to in the lay literature, is of significant concern to patients. A variety of potentially associated factors have been identified, including age, education level, intelligence, and social support; anxiety, depression, and fatigue; disease site, stage, and comorbidities; treatment regimen, timing, duration, and concomitant therapies; and hormonal levels, cytokine levels, damage to neural progenitor cells, and the presence of the apolipoprotein E 4 allele. Controversy exists as to the most suitable neurocognitive tests to evaluate this sequela of treatment. Neuroimaging techniques are beginning to reveal affected areas of the brain. A neuropsychologist is essential for the assessment, diagnosis, and recommendation of appropriate management strategies for this patient population. Oncology nurses should be aware of available resources, such as relevant Web sites, support groups, neuropsychologists, and cognitive retraining programs, and provide support for patients concerned about or experiencing CRCI.

**C**hemotherapy-related cognitive impairment (CRCI) occurs in 17%–75% of patients receiving chemotherapy for cancer (Wefel, Lenzi, Theriault, Davis, & Meyers, 2004). CRCI commonly is referred to as “chemobrain” by the lay public and has the potential for significant impact on patients’ quality of life (QOL) (Ahles & Saykin, 2001; Hess & Insel, 2007). This form of cognitive impairment is attributed to standard doses of chemotherapy (as opposed to high-dose or intrathecal regimens) and has only recently been addressed consistently in the literature, although some recognition was published in the 1970s and early 1980s (Silberfarb, 1983; Silberfarb, Philibert, & Levine, 1980; Weiss, Walker & Wienik, 1974). The purpose of this article is to provide a brief historical review, discuss recent literature on neuroimaging and neuropsychological testing, and provide support for the role of neuropsychologists in diagnosis and intervention.

The impact of CRCI typically is subtle and finite. Patients who perceive a deficit in their ability to perform cognitive tasks may score within normal limits on existing measures of cognitive function (Wefel et al., 2004). However, an estimated subset of 17%–35% of patients appears to experience more severe and long-lasting effects (Ahles & Saykin, 2002). The specific domains of cognitive function that may be affected include executive function, information-processing speed, language, motor function, spatial skills, learning, and memory (Jansen, Miaskowski, Dodd, Dowl-

## At a Glance

- ◆ Neuroimaging tests may prove useful in prospective trials to identify areas of the brain affected by standard-dose chemotherapy and provide a rationale for patient self-reports of cognitive impairment despite normal performance on neuro-psychological tests.
- ◆ Current neuropsychologic test batteries are criticized for lack of real-life challenges experienced by cancer survivors.
- ◆ Neuropsychologists are an important component of the multidisciplinary team needed to provide quality cancer care to patients experiencing treatment-related cognitive changes.

ing, & Kramer, 2005a). Patients describe the effects on cognitive function as forgetfulness, absentmindedness, and an inability to focus when performing daily tasks (Hess & Insel, 2007). A variety of potentially associated factors have been identified, including age, education level, intelligence, and social support; anxiety,

Jamie S. Myers, RN, MN, AOCN®, is a doctoral student in the School of Nursing at the University of Kansas Medical Center in Edwardsville. (Submitted November 2008. Accepted for publication December 31, 2008.)

Digital Object Identifier:10.1188/09.CJON.413-421

depression, and fatigue; disease site, stage, and comorbidities; treatment regimen, timing, duration, and concomitant therapies; and hormonal levels, cytokine levels, damage to neural progenitor cells, and the presence of the apolipoprotein E 4 allele (Hess & Insel; Jansen, Miaskowski, Dodd, Dowling, & Kramer, 2005b).

Estimating the cost of CRCI is difficult because prospective trials to ascertain a more precise incidence, risk factors, and specific impact on QOL are ongoing. Patients have expressed concern about CRCI and their subsequent ability to resume previous professional, scholastic, and social activities (Wefel et al., 2004). No data is available on the percentage of patients who miss or lose work because of this adverse event, but anecdotal evidence does exist. For instance, a former critical care nurse who survived breast cancer shared her experience with long-term cognitive deficits at an oncology symposium sponsored by the Metro Denver Chapter of the Oncology Nursing Society. The nurse said she could no longer work in an environment that requires critical thinking. A relatively small percentage of patients appear to have long-lasting deficits, but until more prospective trials are completed, precise descriptions cannot be provided.

CRCI is a significant concern because of the prevalence of the symptom experience (as high as 75%) and patients' concerns about the impact on QOL. Given the significance of CRCI to patients, appropriate measures should be taken to assess and diagnose the problem and recommend interventions to assist patients in coping with changes in function they experience.

## Historical Review

Cognitive impairment in patients with cancer has long been acknowledged as a sequela of disease that is primary or metastatic to the central nervous system (CNS), intrathecal chemotherapy for leukemias or CNS tumors, and some high-dose chemotherapy regimens (Silberfarb, 1983). Silberfarb noted in two studies in the 1980s (Silberfarb; Silberfarb et al., 1980) that evidence of cognitive impairment could be associated with commonly used chemotherapeutic agents of the time. He proposed that a high prevalence of subtle and mild cognitive impairment could be assessed in patients receiving chemotherapy. Silberfarb described decreased cognitive function as subtle loss of ability to think abstractly; loss of cognitive flexibility, such as the ability to sequentially order alternating numbers and letters; difficulty with finding the right word; slight forgetfulness; and complaints of mental fatigue, difficulty concentrating, and irritability. Further contributions to the literature about this phenomenon did not become common until late the 1990s.

Much of the CRCI literature has been devoted to retrospective trials for patients with breast cancer because they typically have a good prognosis and survival time allows evaluation of concurrent and long-term sequelae (Ahles & Saykin, 2002; Castellon et al., 2004; Inagaki et al., 2007; Jansen, Miaskowski, Dodd, & Dowling, 2005; Klemp, Stanton, Kimler, & Fabian, 2006; Kreukels et al., 2006; Olin, 2001; O'Shaughnessy, 2003; Schagen et al., 1999; Servaes, Verhagen, & Bleijenbergh, 2002; Wefel et al., 2004). Ahles and Saykin have published a significant body of literature identifying CRCI as a common sequela to standard-dose chemotherapy, with the recommendation for prospective trials to evaluate causal hypotheses and concomitant factors (Ahles & Saykin, 2001, 2002, 2007; Ahles et al., 2002).

A workshop in April 2003 brought together a multidisciplinary group of medical oncologists, radiologists, clinical and experimental psychologists, and patient advocates to compare research results and discuss collaborations. The group deliberated on how to enhance prospective clinical trials to address the scope of the problem; evaluation of cognitive problems; possible mechanisms; and prevention, treatment, and rehabilitation (Tannock, Ahles, Ganz, & Van Dam, 2004). Consensus was achieved that the following were needed.

- Large-scale prospective clinical trials with longitudinal design and appropriate controls to evaluate the probability and magnitude of CRCI, predictive factors, and mechanisms
- Research to identify neuropsychological tests that are sensitive to the subtle changes seen with CRCI and the development and validation of self-report forms
- Expansion of clinical trials to study CRCI in diseases other than breast cancer, particularly including male patients, and to address the influence of hormonal changes
- Priority funding of research to address causal mechanisms, including the development of animal models and the inclusion of imaging techniques

The exact etiology of CRCI is not known, but a variety of etiologies have been proposed, including direct injury to cerebral gray and white matter, microvascular injury (Wefel et al., 2004), DNA damage and oxidative stress (Ahles & Saykin, 2007; Chen, Jungswadee, Vore, Butterfield, & St. Clair, 2007), cytokine-induced inflammatory response (Ahles & Saykin, 2007), chemotherapy-induced anemia (Mancuso, Migliorino, De Santis, Saponiero, & De Marinis, 2006; Massa, Madeddu, Lusso, Gramignano, & Mantovani, 2006), and chemotherapy-induced menopause (Jansen, Miaskowski, Dodd, & Dowling, 2005).

Preclinical investigation has highlighted a potential relationship between injury to neural progenitor cells (NPCs), impaired maintenance of white matter integrity, and subsequent cognitive impairment (Dietrich, Han, Yang, Mayer-Proschel, & Noble, 2006; Dietrich, Monje, Wefel, & Meyers, 2008; Han et al., 2008). Dietrich, Han, et al. noted that self-renewing, lineage-committed NPCs and nondividing mature oligodendrocytes (myelin-forming cells) are the most vulnerable cell populations to chemotherapeutic agents. Repetitive exposure to chemotherapeutic agents exceeded cellular repair potential and resulted in long-term suppression of cell division and apoptosis in the subventricular zone, hippocampus, and major white matter tracts of the CNS in animal models.

The presence of the apolipoprotein (APOE) E 4 allele may predispose patients to cognitive impairment (Ahles et al., 2002). APOE is "a complex glycolipoprotein that facilitates the uptake, transport and distribution of lipids" and appears to have a role in neuronal repair after injury (Ahles & Saykin, 2007, p. 198). The E 4 allele is associated with Alzheimer disease and poor recovery from stroke and traumatic brain injury. Some prospective trials to evaluate CRCI now include genetic measurements to assess whether a genetic predisposition to more significant and longer-lasting injury from chemotherapy exists (Ahles & Saykin, 2007). Those prospective trials may help answer the question of whether some patients are genetically predisposed to long-term damage, and the results could have significant impact on treatment options.

Patients with cancer experience multiple concurrent symptoms from the disease and treatment (Miaskowski et al., 2006).

The term “symptom cluster” has been defined to include two to three concurrent, related symptoms (Dodd, Miakowski, & Paul, 2001; Kim, McGuire, Tulman, & Barsevick, 2005). Symptom cluster studies have examined relationships among fatigue, pain, sleep disturbances, and depression. Dodd et al. reviewed a number of trials and found that fatigue, pain, and depression were interrelated. Relationships also existed among pain, fatigue, and sleep disturbance (Dodd et al.). According to Barsevick (2007), symptom assessment should include fatigue, sleep disturbance (insomnia), pain, and depression because of evidence of clustering. Meyers (2000) noted that fatigue, pain, and anemia may contribute to cognitive deficits.

The symptom experience known as sickness behavior has been postulated to be related to the release of proinflammatory cytokines as a response to the disease and its treatment (Cleeland et al., 2003). Sickness behavior includes fever, fatigue, lethargy, muscle aches, decreased appetite, decreased ability to concentrate, decreased social interaction, and general behaviors consistent with the conservation of energy (Parnet, Kelley, Bluthé, & Dantzer, 2002; Pollmacher, Haack, Schuld, Reichenberg, & Yirmiya, 2002; Wilson, Finch, & Cohen, 2002). Cognitive impairment has been hypothesized to be a component of sickness behavior from cytokine release (Lee et al., 2004).

## Neuroimaging

Advances in neuroimaging have provided a number of opportunities to objectively evaluate structural and functional changes in the brain. The techniques are beginning to be used to assess the impact of standard-dose chemotherapy on the brain. The earliest work in this area was conducted in relationship to high-dose chemotherapy associated with bone marrow transplantation in which magnetic resonance (MR) studies for 13 patients were obtained (Brown et al., 1995). The purpose of the study was to determine if white matter changes in this patient population were associated with neurochemical disturbances. Single-voxel proton MR spectroscopy also was obtained in vivo for 12 of 13 patients and compared with 13 age- and sex-matched control participants without a history of cancer, neurologic symptoms, or neurologic disease. Female patients ( $\bar{X}$  = 47.3 years) with stage II breast cancer who received high-dose chemotherapy followed by autologous stem cell transplantation were included in the study 4–21 months after completing therapy. Only 2 of 13 patients did not exhibit changes in white matter; however, the white matter changes were not associated with major neuronal or axonal damage. The authors concluded that “high-dose chemotherapy-induced white matter change may not be related to neuronal dysfunction or abnormality but rather reflects changes in the free and bound water fraction as a result of chemotherapy” (Brown et al., 1995, p. 2018). The authors also acknowledged that the retrospective design likely underestimated significant neurologic impairment because of the existing evidence in the literature regarding declining function for short-term memory, attention, concentration, and information processing speed and suggested that this type of study should be conducted at baseline and repeated within three months of therapy initiation. They speculated that the incidence of white matter change related to high-dose chemotherapy likely exceeds 50% and may occur as early as one to three months after initiating

treatment. The speculation led to a follow-up study (Brown et al., 1998) in which they investigated the time course for development of white matter changes induced by high-dose chemotherapy. A small, prospective, longitudinal evaluation was conducted for eight patients with advanced breast cancer receiving high-dose chemotherapy followed by autologous stem cell transplantation. MR imaging (MRI) and proton MR spectroscopy were conducted at baseline and at intervals of 1, 3, 6, 9, and 12 months after therapy. Imaging results at the conclusion of therapy were normal; however, increasing volume of white matter changes appeared at 3 months and stabilized between 6–12 months. Again, persistent neurologic symptoms were not observed. The authors concluded that white matter changes were common and appeared to stabilize between 6–12 months and suggested that neuronal damage is limited and likely transient. They also noted that white matter effects predominantly are on the water spaces. Both studies were conducted with extremely small samples and results would need to be validated with larger populations.

Proton MR spectroscopy is useful for revealing pathophysiologic changes after chemotherapy (Saykin, Ahles, & McDonald, 2003). Saykin et al. recommended the use of diffusion tensor imaging in combination with functional MRI to relate anatomic connectivity to functional activation patterns in visual and motor systems. They noted that diffusion tensor imaging should assist in the determination of whether white matter changes are correlated with changes in cognitive function. Saykin et al. also suggested the use of positron-emission tomography (PET) to detect chemotherapy-related increases in local signal intensity during functional activation. The authors reported results of a small pilot study of long-term cancer survivors (more than five years) in which functional MRI was used to evaluate abnormalities during auditory working memory and event-related episodic memory tasks. Based on positive results for the detection of abnormalities in long-term cancer survivors, they are proceeding with a longitudinal study to further investigate the use of the technology. Saykin et al. also have employed the use of voxel-based morphology, a neuroimaging technique that uses statistical parametric mapping to investigate focal differences in brain anatomy to evaluate cerebral atrophy, gray matter, and white matter changes in long-term cancer survivors treated with chemotherapy. They reported on a sample of 12 cancer survivors compared to age-matched control subjects. The patients with cancer had a history of breast cancer ( $n = 10$ ) or lymphoma ( $n = 2$ ); all had received chemotherapy. The cancer survivors were shown to have local bilateral reduction of neocortical gray matter as well as cortical and subcortical white matter in several regions. No such reduction was observed in the control group. The neuroanatomic pattern of reduction was diffuse, and the authors believed the pattern to be consistent with the type of diffuse effects on neurocognitive function they had observed clinically. They noted that chemotherapy-related deficits occur primarily in the domains of episodic and working memory and affect the executive functions of decision making and psychomotor problem solving.

PET scanning has been used to evaluate regional cerebral metabolism in patients who have been treated with chemotherapy (Silverman et al., 2003). Silverman et al. (2003) selected eight women from a previous study who had demonstrated significant neurocognitive changes following chemotherapy for breast cancer. The California Verbal Learning Test was used to assess cognitive function in addition to other neuropsychological testing

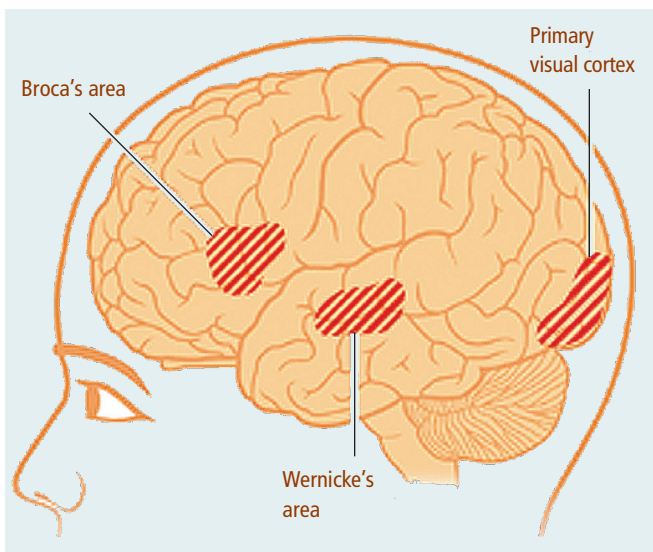
not described (see Table 1). Four of the women had received adjuvant chemotherapy in combination with the anti-estrogenic agent tamoxifen, and four had received chemotherapy alone. Comparisons were made with two breast cancer survivors who were chemotherapy naïve and two healthy participants with no history of breast cancer. The 12 women underwent repeat neuropsychological testing within four days of PET scanning. Brain metabolic activity was assessed in 26 regions of the brain. Results were compared with previously established reference ranges. Significant abnormalities in activity relative to the reference group were seen in the eight women who had received chemotherapy (9% below normal,  $p < 0.0001$  in the superior frontal gyrus of the dorsolateral prefrontal cortex and Broca's area [see Figure 1] with its contralateral counterpart). Hypometabolism was more severe in the four women who received tamoxifen in combination with chemotherapy. Subsequent investigation was conducted by the same group to evaluate the relationship of cerebral blood flow and

metabolism with cognitive function after chemotherapy for breast cancer (Silverman et al., 2007). The sample was comprised of 16 right-handed women with a history of breast cancer treated with chemotherapy within the past 5–10 years; 11 also had received tamoxifen therapy. Comparisons were made to eight right-handed women who had not received chemotherapy, although some had histories of breast cancer. A standard reference group of 10 additional healthy women was included who previously had undergone PET studies. The authors cited previous work in which the Rey-Osterrieth Complex Figure (ROCF) Delayed Recall Task had been used to demonstrate the most significant cognitive deficit ( $p = 0.0007$ ) in a larger study ( $n = 72$ ) evaluating neurocognitive performance following chemotherapy for breast cancer survivors. Cognitive testing was conducted within 72 hours of PET scanning and was supervised and statistically assessed by a licensed clinical neuropsychologist. Patients were evaluated by PET imaging during performance of control (resting) and memory tasks (standard

**Table 1. Summary of Selected Neuropsychological Tests**

TEST	DESCRIPTION	COGNITIVE DOMAINS EVALUATED
California Verbal Learning Test	The respondent must memorize a shopping list and recall the list after a time delay and again after presentation of an alternate list.	Memory
Functional Assessment of Cancer Therapy–Cognitive Function	Self-report on 33 scaled items (version 3) for cognitive function; includes evaluation of mental acuity, attention and concentration, memory, verbal fluency, functional interference, deficits observed by others, change from previous function, and impact on quality of life.	Self-report of cognitive functioning
Grooved Pegboard	Uses a board with 25 randomly positioned slots; a set of pegs must be rotated to be inserted correctly into matching slots, one at a time and as quickly and accurately as possible. Dominant and nondominant hands are tested.	Motor function
Mini-Mental State Examination	A 30-item (10-minute) questionnaire used to screen for dementia; scores are sometimes used as cutoff points for further neuropsychological examination. It includes simple questions related to orientation, repetition of word lists, math problems, language, comprehension, and motor skills.	Memory
Repeatable Battery for the Assessment of Neuropsychological Status	An abbreviated neuropsychological test battery (20–30 minutes) designed to evaluate a number of cognitive domains; individual tests include list learning, story memory, figure copy, line orientation, picture naming, semantic fluency, list recall, list recognition, and figure recall.	Memory (immediate and delayed), visuospatial ability, language, and attention
Rey-Osterrieth Complex Figure Test Delayed Recall Task	The respondent must reproduce a complicated line drawing, first by copying and then from memory.	Visuospatial ability, memory, and executive function
Stroop Interference	The respondent is provided with a sheet or card of words that name a variety of colors; however, the words are printed in a different color ink than the color that the word names. The respondent must substitute an alternative response for a more obvious reaction (i.e., naming the ink color of a word denoting a different color).	Executive function, attention, and concentration
Trail Making Test A and B	Timed two-part test in which one must draw lines to connect consecutively numbered circles on one work sheet (part A) and then connect the same number of consecutively numbered and lettered circles on another worksheet by alternating between consecutive letters and numbers (part B)	Visual, conceptual, and visuomotor tracking; psychomotor speed; attention and concentration; and processing speed
Wechsler Adult Intelligence Scale Digit Symbol	Involves a symbol substitution task; consists of pairing numbers to nonsense symbols as quickly as possible	Visuomotor coordination and psychomotor performance
Wechsler Memory Scale–Revised	Tests immediate and delayed recall from a short paragraph	Memory





**Figure 1. Lateral Brain**

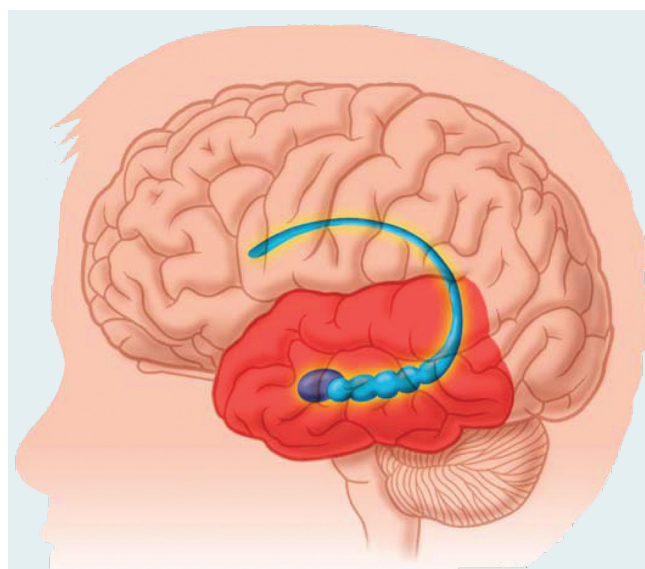
*Note.* From "Lateral Brain 5," by Posit Science Corporation, 2009. Retrieved June 23, 2009, from <http://brainconnection.positscience.com/topics/?main=gal/aphasia-cortex>. Copyright 2009 by Posit Science Corporation. Reprinted with permission.

word-pair association cognitive tasking protocol). Forty-two brain regions were assessed. The group who had received chemotherapy had significant increase in activity (2.3% increase,  $p < 0.0005$ ) in the inferior frontal gyrus; untreated patients had a slight increase ( $p = 0.96$ ). Significant activity also was seen in the treatment group in the contralateral posterior cerebellum near the midline and the superior frontal gyrus ( $p = 0.01$ ,  $p = 0.046$ ; respectively). The chemotherapy group performance on the ROCF Delayed Recall Task averaged 3.2 points (13%) lower than the control group. No significant differences were seen in resting metabolism between the groups. Patients who received tamoxifen therapy had significantly lower metabolism in the lentiform nucleus of the basal ganglia ( $p < 0.01$ ). The results lent support to patients' perceptions of mental slowness and diminished ability to maintain attention, concentrate, and remember things. The three conclusions from the study were (a) altered cortical activation associated with performance of a memory task could be characterized as involving greater recruitment of frontal cortical tissue, (b) chemotherapy-related changes in cerebral activation may be associated with CRCI, and (c) increased frontal activation may be a compensatory response to lower resting metabolism in this area of the brain. The authors acknowledged that the study was limited by the small sample size.

Effects of chemotherapy on hippocampal size also have been evaluated (Yoshikawa et al., 2005). Yoshikawa et al. noted that hippocampal damage has been associated with memory deficits. The authors hypothesized that chemotherapy may damage the hippocampus (see Figure 2), leading to cognitive impairment. The authors evaluated Japanese breast cancer survivors who had ( $n = 44$ ) or had not ( $n = 31$ ) received chemotherapy. The participants were at least three years past diagnosis and had completed a full course of chemotherapy treatment. Hippocampal volume was assessed by MRI, and the Wechsler Memory Scale-Revised (WMS-R) assessed delayed recall and retention percentage as surrogate

markers of hippocampal function. No significant differences were observed in memory function or hippocampal volume between the two groups, although a slight decrease in attention and concentration for the group who had received chemotherapy was noted. The authors speculated that brain regions other than the hippocampus may be related to memory impairment (such as the prefrontal cortex) and that the timeframe of three years prior to assessment may have allowed time for cognitive recovery. A follow-up study was performed to explore regional brain volume differences at intervals of one and three years following treatment with chemotherapy for breast cancer (Inagaki et al., 2007). Patients surviving 3–15 months after diagnosis were eligible and agreed to participate in the one-year evaluation. Of them, 105 also agreed to participate in the three-year evaluation. Age-matched controls participated at one ( $n = 55$ ) and three years ( $n = 37$ ). The WMS-R was used to estimate memory function through the indices of attention and concentration, immediate visual memory, immediate verbal memory, and delayed recall. MRIs were conducted at one and three years. Smaller volumes of the right prefrontal and parahippocampal gyrus were noted in the chemotherapy group at one year, whereas no difference in volume was observed at three years. A subanalysis showed an association between smaller volume and impairment in memory function (attention and concentration and visual memory indices). The authors concluded that structural differences in the superior and prefrontal gyrus may be associated with CRCI and volume changes appear to recover over time.

In a particularly interesting article, monozygotic twins were assessed by functional and structural MRI (Ferguson, McDonald, Saykin, & Ahles, 2007). One twin had received chemotherapy for breast cancer and the other had no history of the disease. The sisters were evaluated in combination with a memory task, and standardized neurocognitive testing was performed. The twins completed self-report tools for cognitive function, anxiety,



**Figure 2. Hippocampus**

*Note.* From "Hippocampus," by Posit Science Corporation, 2009. Retrieved June 23, 2009, from <http://brainconnection.positscience.com/topics/?main=gal/hippocampus>. Copyright 2009 by Posit Science Corporation. Reprinted with permission.

and depression. The women were APOE E 4 allele carriers. Both demonstrated white matter hyperintensities on structural MRI, which is known to occur in carriers of the APOE E 4 allele; however, they were significantly pronounced in the twin who had received chemotherapy (in right and left hemispheres). The twin who had received chemotherapy had significantly higher self-reports of cognitive dysfunction. Neither twin demonstrated anxiety or depression, and both scored within the normal range on standardized neurocognitive tests. The twin who had received chemotherapy demonstrated much broader spatial extent of activation in typical working memory circuitry (bifrontal and biparietal regions) but performed with equal accuracy to the untreated twin. The authors attributed the difference in spatial activation and increased cortical activity to the recruitment of a broader neural network to accomplish a task, indicating that compensation was employed. Such analysis may provide additional information regarding the areas of the brain affected by chemotherapy and a rationale for patient self-reports of cognitive dysfunction despite normal performance on standardized neuropsychological tests.

## Neuropsychological Testing Challenges

One of the major challenges in the study of CRCI is the selection of appropriate assessment tools. As mentioned previously, the cognitive changes observed in this patient population are subtle. Tests designed to assess gross changes in neurocognitive function associated with severe dementia or head injury are not appropriate for patients experiencing CRCI. Patients who are well educated with high baseline cognitive function may continue to score normally on neurocognitive tests, even though they perceive deficits that interfere with their daily function and QOL (Wefel et al., 2004). The Mini-Mental State Examination (MMSE) has been criticized for those reasons (Meyers & Wefel, 2003). At best, the MMSE may be used as a baseline screen to exclude patients from a prospective trial who have significant cognitive deficits prior to the initiation of therapy.

The battery of neuropsychological tests that would normally be employed to conduct a full cognitive assessment may range in length from four to seven hours (Freeman & Broshek, 2002). Patient burden should be a consideration in determining whether that amount of testing occurs in one or more sessions. An additional challenge exists for patients experiencing the fatigue associated with a cancer diagnosis and treatment (Butt et al., 2008). Several hours of testing may not be practical. In addition, in the context of a clinical trial, the time and expense involved in extensive testing may preclude a complete examination from being included in the protocol (Freeman & Broshek). The search for succinct but reliable clinical tools is ongoing (Tannock et al., 2004). Participants from the multidisciplinary workshop mentioned earlier in this article suggested a two-stage approach to cognitive assessment, depending on the question that was being asked. When the goal is demonstration of a cognitive change in a large sample of patients in a clinical trial, brief validated assessments may be appropriate, such as the Functional Assessment of Cancer Therapy–Cognitive Function scale (a self-report measure) (Wagner, Sweet, Butt, Lai, & Cella, in press). Workshop participants acknowledged that most brief measures do not have sensitivity for executive function deficits and therefore might lead to underreporting of deficits. Patients who demonstrate a

change can then be referred for more thorough assessment with conventional neuropsychological testing (Tannock et al.).

Many investigators have noted the need for multifactorial assessment in the case of CRCI (Ahles & Saykin, 2001). Some studies have demonstrated that cognitive impairment is separable from potentially related conditions such as fatigue and depression (Schagen, Muller, Boogerd, & van Dam, 2002). However, many still recommend attempting to assess and control for those potentially confounding variables as well as pain and anxiety. In addition, recommendations have included the use of tools to assess for hormonal status, cytokine levels, anemia, and genetic status (Ahles & Saykin, 2001). When combined with the need for concomitant neuroimaging, time, energy, and costs escalate significantly.

Studies conducted to date have employed a variety of different neuropsychological tests to evaluate cognitive function. For results to be compared, the use of consistent tests would be very advantageous. One of the recommendations of the multidisciplinary workshop was to identify tests sensitive to the subtle changes observed with CRCI as well as to develop and validate self-report forms (Tannock et al., 2004). As important as objective tests of cognitive function are, patient perception of cognitive function and the resultant impact on QOL remain important aspects of the assessment process (Minisini et al., 2004).

Consensus has not yet been reached regarding the best neuropsychological tests to employ, but efforts have been made to compare and contrast those available (Freeman & Broshek, 2002). Freeman and Broshek published initial results of a study to evaluate tests selected for sensitivity to mild cognitive impairment in other patient populations. The tests were selected to measure attention and concentration, processing efficiency, verbal and visual memory, executive function, sensorimotor function, visuoconstruction, naming, and verbal fluency. At the time of publication, 17 women had been enrolled. The sample of women had received chemotherapy or currently were receiving chemotherapy following a surgical procedure. Significant deficits were observed in the tests, which were the Repeatable Battery for the Assessment of Neuropsychological Status, Grooved Pegboard Nondominant Hand, and Stroop Interference tests. Freeman and Broshek would like to pare the assessment down to a battery of tests of 30–40 minutes.

Additional challenges of the current process of neuropsychological testing for patients experiencing cognitive impairment revolve around the difficulty in replication of a real-life situation. Typically, neuropsychological testing occurs in a laboratory-like environment that has little overlap with a patient's everyday experience (Schagen et al., 2002). Current testing procedures are criticized for low ecologic relevance and sterile conditions with minimal distraction. Patients with cancer who self-report CRCI describe an inability to multitask, which is difficult to replicate in a testing situation (Cimprich, So, Ronis, & Trask, 2005).

## Role of the Neuropsychologist

Neuropsychologists are doctorally prepared registered psychologists who specialize in the study of brain behavior relationships. Neuropsychologists are skilled in the administration and interpretation of neurocognitive tests to link behaviors to underlying normal and abnormal brain processes. Neuropsychologists collaborate with multidisciplinary teams in the use of functional MRI techniques (American Psychological Association, 2004). One

component of the neuropsychologist's role is facilitation of psychosocial support to enhance coping with lifestyle changes and guide efforts in cognitive retraining to maximize patients' potential to return to baseline cognitive function or adapt to long-term deficits.

The role of the neuropsychologist is essential in the assessment, diagnosis, and counseling needed for patients experiencing cognitive changes resulting from chemotherapy. As more information about which regimens and risk factors associated with CRCI become available, referrals for baseline neuropsychological testing will provide valuable information with which to compare ongoing treatment-related changes and early identification of deficits and implementation of interventions. Freeman and Broshek (2002) stated that "it is critical to have the input of neuropsychologists when choosing methods of assessing neurocognitive functioning" (p. S92). Meyers (2000) stressed the importance of "multi-disciplinary assessment of neurocognitive complaints in order to maximize patients' ability to function at the highest level of independence for the longest period of time" (p. 78). Meyers advocated the use of focused rehabilitation efforts in this patient population. She described the use of cognitive rehabilitation and vocational rehabilitation (strategies usually employed for patients with traumatic brain injuries) as being applicable for patients experiencing CRCI. She also recommended education about expected treatment sequelae, counseling, and support groups to prevent patients experiencing side effects from feelings of isolation. Meyers noted that many oncologists and oncology nurses may be unaware of CRCI and may not speak to patients and families about it.

As the body of literature grows, awareness is increasing. Centers are developing Web sites to facilitate education about available resources (see Figure 3). The need for consulting a neuropsychologist also is being recognized (Grober, 2002). Grober outlined the need for a thorough medical, psychological, developmental, and biographic history in addition to several testing sessions followed by a verbal and written consultation summary and treatment plan. Patients who do not have access to that aspect of the multidisciplinary team experience a negative impact on QOL because of adverse effects on vocational and avocational interests, mood, and self-esteem (Grober).

Costs for neuropsychological evaluation vary based on region, practitioner, and the selection of neuropsychologic tests to include. Anecdotal experience in the southeastern region of the United States indicates a range of \$1,000–\$1,500 for neuropsychological screening and \$1,800–\$2,800 for a comprehensive evaluation. Insurance may reimburse the evaluation if a prescription is provided by the referring physician. In these cases, testing was considered to be medical and paid through medical rather than mental health benefits.

## Intervention

The Memory and Attention Adaptation Training is a brief cognitive behavioral treatment aimed at helping breast cancer survivors manage CRCI (Ferguson, Ahles, et al., 2007). The program was piloted in 29 women, with a mean survival of eight years after chemotherapy. It was comprised of four cognitive behavioral components: education on memory and attention; self-awareness training; self-regulation emphasizing arousal reduction through relaxation training, activity scheduling, and pacing; and cognitive compensatory strategies training. Patients were provided with a

### American Cancer Society ([www.cancer.org](http://www.cancer.org))

- **Chemo Brain**  
[www.cancer.org/docroot/MBC/content/MBC\\_2\\_3x\\_Chemobrain.asp?sitearea=MBC](http://www.cancer.org/docroot/MBC/content/MBC_2_3x_Chemobrain.asp?sitearea=MBC)
- **Researchers Verify "Chemo Brain" in Cancer Survivors**  
[www.cancer.org/docroot/NWS/content/NWS\\_1\\_1x\\_Researchers\\_Verify\\_%E2%80%98Chemo\\_Brain%E2%80%99\\_in\\_Cancer\\_Survivors.asp](http://www.cancer.org/docroot/NWS/content/NWS_1_1x_Researchers_Verify_%E2%80%98Chemo_Brain%E2%80%99_in_Cancer_Survivors.asp)
- **Seeking Solutions to "Chemo-Brain": What Causes It? Who's at Risk?**  
[www.cancer.org/docroot/NWS/content/NWS\\_2\\_1x\\_Seeking\\_Solutions\\_to\\_Chemo-Brain.asp](http://www.cancer.org/docroot/NWS/content/NWS_2_1x_Seeking_Solutions_to_Chemo-Brain.asp)
- **What Are the Possible Side Effects of Chemotherapy?**  
[www.cancer.org/docroot/ETO/content/ETO\\_1\\_4X\\_What\\_Are\\_The\\_Side\\_Effects\\_of\\_Chemotherapy.asp?sitearea=ETO](http://www.cancer.org/docroot/ETO/content/ETO_1_4X_What_Are_The_Side_Effects_of_Chemotherapy.asp?sitearea=ETO)

### CancerCare ([www.cancercare.org](http://www.cancercare.org))

- **CancerCare Chemobrain Information Series: Cognitive Problems After Chemotherapy**  
[www.cancercare.org/pdf/fact\\_sheets/fs\\_chemobrain\\_cognitive.pdf](http://www.cancercare.org/pdf/fact_sheets/fs_chemobrain_cognitive.pdf)
- **CancerCare Chemobrain Information Series: Doctor, Can We Talk About Chemobrain?**  
[www.cancercare.org/pdf/fact\\_sheets/fs\\_chemobrain\\_doctor\\_talk.pdf](http://www.cancercare.org/pdf/fact_sheets/fs_chemobrain_doctor_talk.pdf)
- **Combating Chemobrain: Keeping Your Memory Sharp**  
[www.cancercare.org/pdf/fact\\_sheets/fs\\_chemobrain\\_memory.pdf](http://www.cancercare.org/pdf/fact_sheets/fs_chemobrain_memory.pdf)

### M.D. Anderson Cancer Center ([www.mdanderson.org](http://www.mdanderson.org))

- **Cognitive Dysfunction in Cancer**  
[www2.mdanderson.org/depts/oncolog/articles/06/2-feb/2-06-dialog.html](http://www2.mdanderson.org/depts/oncolog/articles/06/2-feb/2-06-dialog.html)
- **OncoLog**  
[www2.mdanderson.org/depts/oncolog/index.html](http://www2.mdanderson.org/depts/oncolog/index.html)

## Figure 3. Chemotherapy-Related Cognitive Impairment Resources for Patients and Families

workbook, four individual visits (one per month), and four phone contacts (between visits). Visits and phone contacts were conducted to provide support and review compensatory strategies designed to cope with high-risk situations for memory failure. The strategies included covert verbal self-guidance during task performance, verbal rehearsal of auditory information, schedule making, external cuing, and outlining written material. Participants were assessed at baseline, just following completion of chemotherapy, and two and six months later. Measures included the Multiple Ability Self Report Questionnaire, QOL-Cancer Survivors Scale, and a rating of satisfaction with the program (scale of 0–8, with higher scores indicating higher satisfaction). Five neuropsychological tests were employed and improvements were observed in self-report of cognitive function, QOL, and neuropsychological test performance. However, generalizability may be limited because of the high educational level of participants and the possibility of practice effect on the neuropsychological tests. Other interventions being tested include erythropoietin-stimulating agents to correct anemia, neurostimulants, and investigation of neuroprotective agents (Tannock et al., 2004).

## Conclusion

CRCI is a significant concern to the healthcare community because of the estimated prevalence and impact on patients' QOL.



As causal factors are as of yet undetermined, much work remains to be done to ascertain the etiologies and risk factors for this problem. Once causal factors are specified, preventative strategies can be developed and applied. Future research should be focused on the determination and development of appropriate neurocognitive testing. Tests should be selected or developed based on sensitivity to the subtle changes observed in patients with cancer and the need to replicate a real-life setting for assessment of patients' ability to focus on tasks despite competing stimuli. Patient burden and fatigue should be taken into consideration when tools are selected and developed. Assessment of potential confounding and exacerbating factors, such as fatigue, depression, anxiety, pain, hormonal status, anemia, and genetic makeup, should be included. The use of neuroimaging techniques should accompany neuropsychological assessments to further define the areas and function of the brain that are effected.

Oncology nurses are in an excellent position to educate patients, families, and the community about the risks of CRCI and to assess the community for resources such as access to support groups, neuropsychologists, and cognitive retraining programs. Oncology nurses may be instrumental in the development of clinical pathways to identify patients experiencing cognitive changes and facilitate appropriate referrals for neuropsychological testing and intervention.

*The author takes full responsibility for the content of the article. The author did not receive honoraria for this work. The content of this article has been reviewed by independent peer reviewers to ensure that it is balanced, objective, and free from commercial bias. No financial relationships relevant to the content of this article have been disclosed by the author, planners, independent peer reviewers, or editorial staff.*

**Author Contact:** Jamie S. Myers, RN, MN, AOCN®, can be reached at [jamyers@swbell.net](mailto:jamyers@swbell.net), with copy to editor at [CJONEditor@ons.org](mailto:CJONEditor@ons.org).

## References

- Ahles, T.A., & Saykin, A. (2001). Cognitive effects of standard-dose chemotherapy in patients with cancer. *Cancer Investigation, 19*(8), 812-820.
- Ahles, T.A., & Saykin, A. (2002). Breast cancer chemotherapy-related cognitive dysfunction. *Clinical Breast Cancer, 3*(Suppl. 3), S84-S90.
- Ahles, T.A., & Saykin, A.J. (2007). Candidate mechanisms for chemotherapy-induced cognitive changes. *Nature Reviews Cancer, 7*(3), 192-201.
- Ahles, T.A., Saykin, A.J., Furstenberg, C.T., Cole, B., Mott, L.A., Skalla, K., et al. (2002). Neuropsychologic impact of standard-dose systemic chemotherapy in long-term survivors of breast cancer and lymphoma. *Journal of Clinical Oncology, 20*(2), 485-493.
- American Psychological Association. (2004). Official position of the division of clinical neuropsychology on the role of neuropsychologists in clinical use of fMRI: Approved by the Division 40 Executive Committee July 28, 2004. *Clinical Neuropsychologist, 18*(3), 349-351.
- Barsevick, A.M. (2007). The elusive concept of the symptom cluster. *Oncology Nursing Forum, 34*(5), 971-980.
- Brown, M.S., Simon, J.H., Stemmer, S.M., Stears, J.C., Scherzinger, A., Cagnoni, P.J., et al. (1995). MR and proton spectroscopy of white matter disease induced by high-dose chemotherapy with bone marrow transplant in advanced breast carcinoma. *American Journal of Neuroradiology, 16*(10), 2013-2020.
- Brown, M.S., Stemmer, S.M., Simon, J.H., Stears, J.C., Jones, R.B., Cagnoni, P.J., et al. (1998). White matter disease induced by high-dose chemotherapy: Longitudinal study with MR imaging and proton spectroscopy. *American Journal of Neuroradiology, 19*(2), 217-221.
- Butt, Z., Wagner, L.I., Beaumont, J.L., Paice, J.A., Peterman, A.H., Shevrin, D., et al. (2008). Use of a single-item screening tool to detect clinically significant fatigue, pain, distress, and anorexia in ambulatory cancer practice. *Journal of Pain and Symptom Management, 35*(1), 20-30.
- Castellon, S.A., Ganz, P.A., Bower, J.E., Petersen, L., Abraham, L., & Green-dale, G.A. (2004). Neurocognitive performance in breast cancer survivors exposed to adjuvant chemotherapy and tamoxifen. *Journal of Clinical and Experimental Neuropsychology, 26*(7), 955-969.
- Chen, Y., Jungsuwadee, P., Vore, M., Butterfield, D.A., & St. Clair, D.K. (2007). Collateral damage in cancer chemotherapy: Oxidative stress in nontargeted tissues. *Molecular Interventions, 7*(3), 147-156.
- Cimprich, B., So, H., Ronis, D.L., & Trask, C. (2005). Pre-treatment factors related to cognitive functioning in women newly diagnosed with breast cancer. *Psychooncology, 14*(1), 70-78.
- Cleland, C.S., Bennett, G.J., Dantzer, R., Dougherty, P.M., Dunn, A.J., Myers, C.A., et al. (2003). Are the symptoms of cancer and cancer treatment due to a shared biologic mechanism? A cytokine-immunologic model of cancer symptoms. *Cancer, 97*(11), 2919-2925.
- Dietrich, J., Han, R., Yang, Y., Mayer-Proschel, M., & Noble, M. (2006). CNS progenitor cells and oligodendrocytes are targets of chemotherapeutic agents in vitro and in vivo. Retrieved June 18, 2009, from <http://jbiol.com/content/pdf/jbiol50.pdf>
- Dietrich, J., Monje, M., Wefel, J., & Meyers, C. (2008). Clinical patterns and biological correlates of cognitive dysfunction associated with cancer therapy. *Oncologist, 13*(12), 1285-1295.
- Dodd, M.J., Miaskowski, C., & Paul, S.M. (2001). Symptom clusters and their effect on the functional status of patients with cancer. *Oncology Nursing Forum, 28*(3), 465-470.
- Ferguson, R.J., Ahles, T.A., Saykin, A.J., McDonald, B.C., Furstenberg, C.T., Cole, B., et al. (2007). Cognitive-behavioral management of chemotherapy-related cognitive change. *Psychooncology, 16*(8), 772-777.
- Ferguson, R.J., McDonald, B.C., Saykin, A.J., & Ahles, T.A. (2007). Brain structure and function differences in monozygotic twins: Possible effects of breast cancer chemotherapy. *Journal of Clinical Oncology, 25*(25), 3866-3870.
- Freeman, J.R., & Broshek, D.K. (2002). Assessing cognitive dysfunction in breast cancer: What are the tools? *Clinical Breast Cancer, 3*(Suppl. 3), S91-S99.
- Grober, S.E. (2002). Resources for treatment of chemotherapy-related cognitive difficulty. *Cancer Practice, 10*(4), 216-218.
- Han, R., Yang, Y.M., Dietrich, J., Luebke, A., Mayer-Proschel, M., & Noble, M. (2008). Systemic 5-fluorouracil treatment causes a syndrome of delayed myelin destruction in the central nervous system. Retrieved June 18, 2009, from <http://jbiol.com/content/pdf/jbiol69.pdf>
- Hess, L.M., & Insel, K.C. (2007). Chemotherapy-related change in cognitive function: A conceptual model. *Oncology Nursing Forum, 34*(5), 981-994.
- Inagaki, M., Yoshikawa, E., Matsuoka, Y., Sugawara, Y., Nakano, T., Akechi, T., et al. (2007). Smaller regional volumes of brain gray and white matter demonstrated in breast cancer survivors exposed to adjuvant chemotherapy. *Cancer, 109*(1), 146-156.
- Jansen, C.E., Miaskowski, C., Dodd, M., & Dowling, G. (2005). Chemotherapy-induced cognitive impairment in women with breast cancer: A critique of the literature. *Oncology Nursing Forum, 32*(2), 329-342.



- Jansen, C.E., Miaskowski, C., Dodd, M., Dowling, G., & Kramer, J. (2005a). A metaanalysis of studies of the effects of cancer chemotherapy on various domains of cognitive function. *Cancer*, *104*(10), 2222-2233.
- Jansen, C.E., Miaskowski, C., Dodd, M., Dowling, G., & Kramer, J. (2005b). Potential mechanisms for chemotherapy-induced impairments in cognitive function. *Oncology Nursing Forum*, *32*(6), 1151-1163.
- Kim, H.J., McGuire, D.B., Tulman, L., & Barsevick, A.M. (2005). Symptom clusters: Concept analysis and clinical implications for cancer nursing. *Cancer Nursing*, *28*(4), 270-282.
- Klemp, J.R., Stanton, A.L., Kimler, B.F., & Fabian, C.J. (2006, October). *Evaluating the effects of chemotherapy on cognitive function and quality of life in pre-menopausal women with breast cancer*. Poster presented at the meeting of the San Antonio Breast Cancer Symposium, San Antonio, TX.
- Kreukels, B.P., Schagen, S.B., Ridderinkhof, K.R., Boogerd, W., Hamburger, H.L., Muller, M.J., et al. (2006). Effects of high-dose and conventional-dose adjuvant chemotherapy on long-term cognitive sequelae in patients with breast cancer: An electrophysiologic study. *Clinical Breast Cancer*, *7*(1), 67-78.
- Lee, B.N., Dantzer, R., Langley, K.E., Bennett, G.J., Dougherty, P.M., Dunn, A.J., et al. (2004). A cytokine-based neuroimmunologic mechanism of cancer-related symptoms. *Neuroimmunomodulation*, *11*(5), 279-292.
- Mancuso, A., Migliorino, M., De Santis, S., Saponiero, A., & De Marinis, F. (2006). Correlation between anemia and functional/cognitive capacity in elderly lung cancer patients treated with chemotherapy. *Annals of Oncology*, *17*(1), 146-150.
- Massa, E., Madeddu, C., Lusso, M.R., Gramignano, G., & Mantovani, G. (2006). Evaluation of the effectiveness of treatment with erythropoietin on anemia, cognitive functioning and functions studied by comprehensive geriatric assessment in elderly cancer patients with anemia related to cancer chemotherapy. *Critical Reviews in Oncology/Hematology*, *57*(2), 175-182.
- Meyers, C.A. (2000). Neurocognitive dysfunction in cancer patients. *Oncology*, *14*(1), 75-79.
- Meyers, C.A., & Wefel, J.S. (2003). The use of the Mini-Mental State Examination to assess cognitive functioning in cancer trials: No ifs, ands, but, or sensitivity. *Journal of Clinical Oncology*, *21*(19), 3557-3558.
- Miaskowski, C., Cooper, B.A., Paul, S.M., Dodd, M., Lee, K., Aouizerat, B.E., et al. (2006). Subgroups of patients with cancer with different symptom experiences and quality-of-life outcomes: A cluster analysis [Online exclusive]. *Oncology Nursing Forum*, *33*(5), E79-E89. Retrieved June 18, 2009, from <http://ons.metapress.com/content/45j041752130j582/fulltext.pdf>
- Minisini, A., Atalay, G., Bottomley, A., Puglisi, F., Piccart, M., & Biganzoli, L. (2004). What is the effect of systemic anticancer treatment on cognitive function? *Lancet Oncology*, *5*(5), 273-282.
- Olin, J.J. (2001). Cognitive function after systemic therapy for breast cancer. *Oncology*, *15*(5), 613-618.
- O'Shaughnessy, J. (2003). Chemotherapy-related cognitive dysfunction in breast cancer. *Seminars in Oncology Nursing*, *19*(4, Suppl. 2), 17-24.
- Parnet, P., Kelley, K.W., Bluthé, R.M., & Dantzer, R. (2002). Expression and regulation of interleukin-1 receptors in the brain. Role in cytokines-induced sickness behavior. *Journal of Neuroimmunology*, *125*(1-2), 5-14.
- Pollmacher, T., Haack, M., Schuld, A., Reichenberg, A., & Yirmiya, R. (2002). Low levels of circulating inflammatory cytokines—Do they affect human brain functions? *Brain, Behavior, and Immunity*, *16*(5), 525-532.
- Saykin, A.J., Ahles, T.A., & McDonald, B.C. (2003). Mechanisms of chemotherapy-induced cognitive disorders: Neuropsychological, pathophysiological, and neuroimaging perspectives. *Seminars in Clinical Neuropsychiatry*, *8*(4), 201-216.
- Schagen, S.B., Muller, M.J., Boogerd, W., & van Dam, F.S. (2002). Cognitive dysfunction and chemotherapy: Neuropsychological findings in perspective. *Clinical Breast Cancer*, *3*(Suppl. 3), S100-S108.
- Schagen, S.B., van Dam, F.S., Muller, M.J., Boogerd, W., Lindeboom, J., & Bruning, P.F. (1999). Cognitive deficits after postoperative adjuvant chemotherapy for breast carcinoma. *Cancer*, *85*(3), 640-650.
- Servaes, P., Verhagen, C.A., & Bleijenbergh, G. (2002). Relations between fatigue, neuropsychological functioning, and physical activity after treatment for breast carcinoma: Daily self-report and objective behavior. *Cancer*, *95*(9), 2017-2026.
- Silberfarb, P.M. (1983). Chemotherapy and cognitive defects in cancer patients. *Annual Review of Medicine*, *34*, 35-46.
- Silberfarb, P.M., Philibert, D., & Levine, P.M. (1980). Psychosocial aspects of neoplastic disease: II. Affective and cognitive effects of chemotherapy in cancer patients. *American Journal of Psychiatry*, *137*(5), 597-601.
- Silverman, D.H., Castellon, S.A., Abraham, L., Dy, C.J., Pio, B.S., & Ganz, P.A. (2003, June). *Abnormal regional brain metabolism in breast cancer survivors after adjuvant chemotherapy is associated with cognitive changes*. Paper presented at the meeting of the American Society of Clinical Oncology, Los Angeles, CA.
- Silverman, D.H., Dy, C.J., Castellon, S.A., Lai, J., Pio, B.S., Abraham, L., et al. (2007). Altered frontocortical, cerebellar, and basal ganglia activity in adjuvant-treated breast cancer survivors 5-10 years after chemotherapy. *Breast Cancer Research and Treatment*, *103*(3), 303-311.
- Tannock, I.F., Ahles, T.A., Ganz, P.A., & Van Dam, F.S. (2004). Cognitive impairment associated with chemotherapy for cancer: Report of a workshop. *Journal of Clinical Oncology*, *22*(11), 2233-2239.
- Wagner, L., Sweet, J. J., Butt, Z., Lai, J., & Cella, D. (in press). Measuring patient self-reported cognitive function: Qualitative findings and initial development of the Functional Assessment of Cancer Therapy-Cognitive Function (FACT-TOG) instrument. *Journal of Supportive Oncology*.
- Wefel, J.S., Lenzi, R., Theriault, R.L., Davis, R.N., & Meyers, C.A. (2004). The cognitive sequelae of standard-dose adjuvant chemotherapy in women with breast carcinoma: Results of a prospective, randomized longitudinal trial. *Cancer*, *100*(11), 2292-2299.
- Weiss, H.D., Walker, M.D., & Wirnik, P.H. (1974). Neurotoxicity of commonly used antineoplastic agents. *The New England Journal of Medicine*, *292*, 75-81.
- Wilson, C.J., Finch, C.E., & Cohen, H.J. (2002). Cytokines and cognition—The case for a head-to-toe inflammatory paradigm. *Journal of the American Geriatric Society*, *5*(12), 2041-2056.
- Yoshikawa, E., Matsuoka, Y., Inagaki, M., Nakano, T., Akechi, T., Kobayakawa, M., et al. (2005). No adverse effects of adjuvant chemotherapy on hippocampal volume in Japanese breast cancer survivors. *Breast Cancer Research and Treatment*, *92*(1), 81-84.

Receive free continuing nursing education credit for reading this article and taking a brief quiz online. To access the test for this and other articles, visit <http://evaluationcenter.ons.org>. After entering your Oncology Nursing Society profile username and password, select CNE Listing from the left-hand tabs. Scroll down to *Clinical Journal of Oncology Nursing* and choose the test(s) you would like to take.