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Cognitive Function in Breast Cancer Patients Undergoing Chemotherapy

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Cognitive Function in Breast Cancer Patients Undergoing Chemotherapy

by

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DISSERTATION

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COGNITIVE FUNCTION IN BREAST CANCER PATIENTS

UNDERGOING CHEMOTHERAPY

By

CATHERINE E. JANSEN, RN, MS

ABSTRACT

Background: Recent studies suggest that standard dose chemotherapy (CTX) may cross the blood-brain barrier. However, the evidence for CTX-induced cognitive impairments in breast cancer patients is inconsistent.

Purposes: 1) to describe the literature about CTX-induced cognitive impairments in women with breast cancer; 2) to review the domains of cognitive function and their corresponding neuroanatomic structures as well as present current evidence for neurotoxicity associated with specific CTX agents and potential mechanisms for CTX-induced cognitive impairments; 3) to estimate the effect sizes for the effect of CTX on each domain of cognitive function; 4) to determine the sensitivity of neuropsychological tests which have been used to evaluate CTX-induced impairment in various domains of cognitive function in breast cancer patients; and 5) to assess changes in cognitive function over time in breast cancer patients receiving CTX, and evaluate potential relationships between cognitive function and anxiety, depression, fatigue, hemoglobin levels, menopausal status, and perceived cognitive function.

Methods: We performed meta-analyses to measure effect sizes to determine CTX effect on various domains of cognitive function and to determine neurological test sensitivity. In the longitudinal study, we recruited a multicultural sample of thirty women with breast

cancer for neuropsychological testing prior to the initiation and a week after completion of treatment with doxorubicin and cyclophosphamide CTX. Paired t-tests were used to evaluate changes in cognitive scores over time and linear mixed modeling was used to determine whether significant changes remained after controlling for anxiety, depression, fatigue, hemoglobin level, menopausal status, and perceived cognitive function. Findings: Only two domains of cognitive function (i.e., language, visual memory) had small albeit significant negative effect sizes in the meta-analysis of CTX-induced cognitive impairments in breast cancer patients. We evaluated thirty tests used to measure cognitive changes in breast cancer patients who received CTX, but found only six tests to be sensitive in detecting changes in four of eight domains of cognitive function (i.e., language, motor function, visuospatial skill, and verbal memory). In the longitudinal study significant decreases in cognitive function were found after CTX in visuospatial skill ($p \leq .001$) and total cognitive ($p = .001$) scores over time.

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Introduction

Breast cancer is the most common type of cancer in women and the second leading cause of cancer death for women in the United States (Jemal et al., 2007). Chemotherapy (CTX) is an essential component of treatment for breast cancer. Although great strides have been made in eliminating (or at least decreasing) the side effects of CTX, studies consistently confirm that toxicities (e.g., fatigue, infection, nausea, vomiting, diarrhea, stomatitis, alopecia, neuropathy) continue to adversely affect quality of life (Cowley, Heyman, Stanton, & Milner, 2000; Fairclough, Fetting, Cella, Wonson, & Moinpour, 1999; Ganz, 2000). Impairment in cognitive function as a side effect of CTX, is a growing area of research as the numbers of cancer patients who complain of difficulties in their abilities to remember, think, and concentrate increases (Brezden, Phillips, Abdolell, Bunston, & Tannock, 2000; Cole, Scialla, & Bednarz, 2000; Cull et al., 1996).

Cognitive function is a multidimensional concept that describes the domains resulting from healthy brain performance, namely attention and concentration, executive function, information processing speed, language, visuospatial skill, psychomotor ability, learning, and memory (Olin, 2001; Ryan, Morrow, Bromet, & Parkinson, 1987). The potential mechanisms for CTX-induced cognitive impairments are not yet understood. CTX does not appear to cross the blood-brain barrier when given in standard-doses; however, many CTX drugs have the potential to cause cognitive impairments through more than one mechanism. Many patient factors exist that may either be protective or place individuals at a higher risk for cognitive impairments

Several studies have suggested that women with breast cancer experience cognitive changes after the administration of CTX (Ahles et al., 2002; Bender et al., 2006; Brezden, Phillips, Abdolell, Bunston, & Tannock, 2000; Castellon et al., 2004; Hurria et al., 2006; Schagen et al., 1999; Tchen et al., 2003; van Dam et al., 1998; Wieneke & Dienst, 1995). However, other studies have not found CTX-induced cognitive impairments (Hermelink et al., 2007; Jenkins et al., 2006; Wefel et al., 2004). Therefore, the question is whether CTX-induced cognitive impairments do exist.

The purpose of this dissertation project was to describe the literature about CTX-induced cognitive impairments in women with breast cancer, explore the state of the science concerning potential mechanisms of cognitive impairments in cancer patients, to estimate the effect sizes for the effect of CTX on each domain of cognitive function, to determine the sensitivity of neuropsychological tests which have been used to evaluate CTX-induced impairment in various domains of cognitive function in breast cancer patients, and to assess changes in cognitive function over time in breast cancer patients receiving CTX. The dissertation is organized into six chapters.

The first chapter (Chapter 1) is titled: "Chemotherapy-induced cognitive impairments in women with breast cancer: a critique of the literature". The text of this chapter is a reprint of the material as it appears in Jansen, C. E., Miaskowski, C., Dodd, M., & Dowling, G. (2005). *Oncology Nursing Forum, 32*(2): 329-342. The co-authors listed in this publication directed and supervised the research that forms the basis for the dissertation. The article presents a review and critique of current scientific literature. The purpose of this publication was to review and critique the studies that had

investigated CTX-induced impairments in cognitive function in women with breast cancer, including sample characteristics, findings and limitations.

The second chapter (Chapter 2) is titled: "Potential mechanisms for chemotherapy-induced impairments in cognitive function". The text of this chapter is a reprint of the material as it appears in Jansen, C. E., Miaskowski, C., Dodd, M., Dowling, G., & Kramer, J. (2005) *Oncology Nursing Forum, 32*(6): 1151-1163. The co-authors listed in this publication directed and supervised the research that forms the basis for the dissertation. The purpose of this chapter was to 1) review the domains of cognitive function and their corresponding neuroanatomic structures, and 2) to present current evidence for neurotoxicity associated with specific chemotherapeutic agents as well as potential mechanisms for CTX-induced cognitive impairments.

The third chapter (Chapter 3) is titled: "A meta-analysis of studies of the effects of cancer chemotherapy on various domains of cognitive function". The text of this chapter is a reprint of the material as it appears in Jansen, C. E., Miaskowski, C., Dodd, M., Dowling, G., & Kramer, J. (2005) *Cancer, 104*(6): 2222-2233. The co-authors listed in this publication directed and supervised the research that forms the basis for the dissertation. This article presents findings from a meta-analysis of sixteen studies that evaluated cognitive function in CTX patients. The purpose of this chapter was to 1) estimate the effect sizes for the effect of CTX on each domain of cognitive function, and 2) to differentiate effect sizes by each method of comparison of effects (i.e., normative data, control group data, or CTX patients to their baseline data).

The fourth chapter (Chapter 4) is titled: "A meta-analysis of the sensitivity of various neuropsychological tests used to detect chemotherapy-induced cognitive

impairments in patients with breast cancer". The text of this chapter is a reprint of the material as it will appear in Jansen, C. E., Miaskowski, C., Dodd, M., & Dowling, G. (2007) *Oncology Nursing Forum, 34*(5). The co-authors listed in this publication directed and supervised the research that forms the basis for the dissertation. The purpose of this chapter was to 1) identify which neuropsychological tests were used to evaluate CTX-induced impairment in various domains of cognitive function in patients with breast cancer, and 2) to determine the sensitivity of each of these tests, that were used in at least two studies, through an estimation of an effect size.

The fifth chapter (Chapter 5) is titled: "Changes in cognitive function in breast cancer patients undergoing chemotherapy". It was presented at the Oncology Nursing Society's 9th National Conference on Cancer Nursing Research, and it will be submitted to Cancer. The co-authors listed in this publication directed and supervised the research that forms the basis for the dissertation. The purpose of this chapter was to (1) to evaluate cognitive function prior to the administration of CTX; (2) to assess changes in cognitive function over time; and (3) to evaluate potential relationships between cognitive function and anxiety, depression, fatigue, hemoglobin level, menopausal status, and perception of cognitive function.

Finally, the sixth chapter (Chapter 6) summarizes the findings from the previous articles and addresses the current state of knowledge regarding CTX-induced cognitive impairments in breast cancer patients.

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Chapter 1.

Chemotherapy-Induced Cognitive Impairments In Women With Breast Cancer:

A Critique Of The Literature

Jansen, C. E., Miaskowski, C., Dodd, M., & Dowling, G. (2005).

Oncology Nursing Forum, 32(2), 329-342.

Abstract

Purpose/Objectives: To review and critique the studies that have investigated chemotherapy-induced impairments in cognitive function in women with breast cancer.

Data Sources: Published research articles and textbooks.

Data Synthesis: Although studies of breast cancer survivors have found chemotherapy-induced impairments in multiple domains of cognitive function, they are beset with conceptual and methodologic problems. Findings regarding cognitive deficits in women with breast cancer who currently are receiving chemotherapy are even less clear.

Conclusions: Although data from published studies suggest that chemotherapy-induced impairments in cognitive function do occur in some women with breast cancer, differences in time since treatment, chemotherapy regimen, menopausal status, and neuropsychological tests used limit comparisons among the various studies. Further studies need to be done before definitive conclusions can be made.

Implications: The potential for chemotherapy-induced impairments in cognitive function may influence patients' ability to give informed consent, identify treatment toxicities, learn self-care measures, and perform self-care behaviors.

Introduction

Breast cancer is the most common type of malignancy and the second leading cause of cancer deaths in women in the United States (Jemal et al., 2005). Advances in breast cancer treatment have increased survival, with a relative five-year survival rate of 98% for early-stage disease (Jemal et al.). The treatment of breast cancer is multimodal and includes some combination of surgery, radiation therapy (RT), chemotherapy (CTX), hormonal therapy, or biologic therapy. Each treatment modality has its own distinct side effects, with accompanying degrees of disruption in quality of life (QOL).

Although great strides have been made in eliminating (or at least decreasing) the side effects of CTX, studies consistently confirm that toxicities (e.g., fatigue, infection, nausea, vomiting, diarrhea, stomatitis, alopecia, neuropathy) continue to adversely affect QOL (Cowley, Heyman, Stanton, & Milner, 2000; Fairclough, Fetting, Cella, Wonson, & Moinpour, 1999; Ganz, 2000). A toxicity that has emerged recently is impairment in cognitive function. Patients with cancer have reported increased difficulties with their abilities to remember, think, and concentrate (Bender, Paraska, Sereika, Ryan, & Berga, 2001; Brezden, Phillips, Abdolell, Bunston, & Tannock, 2000; Cole, Scialla, & Bednarz, 2000; Cull et al., 1996; Ganz, 1998). However, whereas cognitive impairments in children who received cranial RT or CTX have been documented (Copeland et al, 1985; Copeland, Moore, Francis, Jaffe, & Culbert, 1996; Kun, Mulhern, & Crisco, 1983; Marina, 1997; Moore, Kramer, & Ablin, 1986), comparable evidence is lacking in adults. Cognitive function is a multidimensional concept that describes the domains resulting from healthy brain performance, namely attention and concentration, executive function, information processing speed, language, visuospatial skill, psychomotor ability, learning,

and memory (Olin, 2001; Ryan, Morrow, Bromet, & Parkinson, 1987). The purposes of this article are to review and critique the studies that have investigated CTX-induced cognitive impairments in women with breast cancer.

Methods

A search was conducted on PubMed, a service of the National Library of Medicine, for January 1966 – June 2004, for all research studies published in English that evaluated CTX-induced impairments in cognitive function in women with breast cancer. A careful review of the reference lists for the eight studies identified (Ahles et al., 2002; Brezden et al., 2000; Freeman & Broshek, 2002; Schagen et al., 1999, 2002; Tchen et al., 2003; van Dam et al., 1998; Wefel, Lenzi, Theriault, Davis, & Meyers, 2004) uncovered one additional study (Wieneke & Dienst, 1995).

The review and critique of the literature are organized by domains of cognitive function to provide the evidence that exists for CTX-induced cognitive impairments in each of the domains in women with breast cancer. Although some neuropsychological tests can measure more than one domain of cognitive function, for the purpose of this review, each test was assigned to a single domain. Most assignments of tests to a specific domain were done using neuropsychological assessment references (e.g., Hebben & Milberg, 2002; Lezak, Howieson, & Loring, 2004; Spreen & Strauss, 1998), whereas some assignments were made using recent meta-analyses of neuropsychological tests in cancer and HIV populations (Anderson-Hanley, Sherman, Riggs, Agocha, & Compas, 2003; Reger, Welsh, Razani, Martin, & Boone, 2002).

Table 1 summarizes data from the eight cross-sectional studies and one longitudinal study that evaluated CTX-induced impairments in cognitive function in

women with breast cancer. Five studies evaluated breast cancer survivors who had completed CTX from six-and-a-half months to 10 years earlier (Ahles et al., 2002; Schagen et al., 1999, 2002; van Dam et al., 1998; Wieneke & Dienst, 1995), and four studies were done prospectively (Brezden et al., 2000; Freeman & Broshek, 2002; Tchen et al., 2003; Wefel et al., 2004). Each group of studies is critiqued, in terms of design and methodologic issues, in the narrative section of this article. The methods used and findings from each study are evaluated in terms of their contributions to the knowledge about CTX-induced cognitive impairments in patients with breast cancer.

Attention and Concentration

Attention is a cognitive function of the brain that enables a person to triage relevant inputs, thoughts, and actions while ignoring those that distract or are irrelevant (Gazzaniga, Ivry, & Mangun, 2002; Grober, 2002; Heilman, Valenstein, & Watson, 1997). Concentration is the ability to focus and sustain attention (Lezak et al., 2004). Although all of the studies used neuropsychological tests to measure attention and concentration, only eight reported their findings. Of note, the findings regarding CTX-induced impairments in attention and concentration are inconsistent. Only three studies found significant deficits in attention and concentration (Schagen et al., 1999; van Dam et al., 1998; Wieneke & Dienst, 1995), whereas five studies found no deficits (Ahles et al., 2002; Brezden et al., 2000; Freeman & Broshek, 2002; Tchen et al., 2003; Wefel et al., 2004). All of the studies that found deficits were performed in survivors. In one such study (van Dam et al.), significant impairment in attention was found for high-dose but not standard-dose CTX. In the only study of survivors that did not find deficits in attention (Ahles et al., 2002), survivors had been off treatment for almost 10 years,

compared with studies performed with survivors who were off treatment for six months to two years (Brezden et al.; Freeman & Broshek, 2002; Schagen et al., 1999, 2002; van Dam et al.; Wieneke & Dienst, 1995). Also, different tests were used to measure attention. The only test that revealed significant deficits was the Digit Span. Tests that did not yield significant results were the D2 Test (a neuropsychological test of attention), vigilance and distractibility subtests of the Continuous Performance Test, and the attention subtests of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) and High Sensitivity Cognitive Screen (HSCS).

Executive Function

Executive function refers to higher-order cognitive processes, which include initiation, planning, hypothesis generation, cognitive flexibility, decision making, regulation, judgment, feedback utilization, and self-perception (Spreen & Strauss, 1998).

All of the studies used neuropsychological tests to measure executive function, but only seven reported their findings. The findings regarding CTX-induced impairments in executive function are also inconsistent. Only three studies found significant deficits in executive function (Freeman & Broshek, 2002; Schagen et al., 1999; Wefel et al., 2004), whereas four studies found no deficits (Ahles et al., 2002; Brezden et al., 2000; Tchen et al., 2003; Wieneke & Dienst, 1995). All of the studies that found significant deficits were performed in survivors, including two prospective studies that found significant deficits only in the survivor group (Freeman & Broshek) or after CTX was completed (Wefel et al.).

The Trail Making Test-Part B, categories test, and Stroop tests demonstrated significant deficits compared to the similarities test and the self-regulation and planning

subtest of the HSCS. However, why the Trail Making Test-Part B revealed significant deficits for survivors in one study (Schagen et al., 1999) but not in others (Ahles et al., 2002; van Dam et al., 1998; Wefel et al., 2004; Wieneke & Dienst, 1995) is unclear. One possible explanation for the difference is the heterogeneous nature of the CTX treatments that the survivors received. Additionally, the Stroop test found significant deficits for survivors in one study (Freeman & Broshek, 2002) but not in two other studies (Schagen et al., 1999; van Dam et al.). One possible explanation for the inconsistent findings is the difference in comparison groups. The study that found significant deficits compared survivors with patients who currently were receiving CTX (Freeman & Broshek), whereas the studies that did not find deficits compared survivors to women who had received local therapy (i.e., surgery or RT) (Schagen et al., 1999; van Dam et al.). Although the categories test revealed significant deficits in the longitudinal study (Wefel et al.), it did not find deficits in the cross-sectional studies (Freeman & Broshek; Wieneke & Dienst).

Information Processing Speed

Information processing speed refers to the brain's ability to rapidly process simple and complex information (Freeman & Broshek, 2002). Because the input of information may be tactile, auditory, verbal, or visual, this domain is inter-related with all of the other domains of cognitive function and may have a direct influence on the ability to store such information into memory.

Seven studies used neuropsychological tests to measure information processing speed, but only six of the studies reported their findings. Of note, the findings regarding CTX-induced impairments in processing speed are inconsistent. Five studies found

significant deficits in information processing speed (Ahles et al., 2002; Schagen et al., 1999; van Dam et al., 1998; Wefel et al., 2004; Wieneke & Dienst, 1995) whereas one found no difference (Freeman & Broshek, 2002). All of the studies that found significant deficits were conducted with survivors. In one study, significant impairment in information processing speed was found for high-dose, but not standard-dose CTX (van Dam et al.)

Tests that found significant differences included the Paced Auditory Serial Addition Test, Digit Symbol, Trail Making Test-Part A, and Fepsy visual reaction (versus the Fepsy binary choice and Fepsy visual searching, which did not). In four studies (Ahles et al., 2002; Schagen et al., 1999; Van Dam et al., 1998; Wefel et al., 2004), the digit symbol test demonstrated significant deficits but not in another study (Wieneke & Dienst, 1995). Two possible explanations for these differences are the length of time since the administration of CTX or differences in the comparison groups. Studies that found significant impairments had survivors who had been off treatment 2-10 years compared to the control group (Ahles et al.; Schagen et al., 1999; van Dam et al.) or survivors who had been off treatment for three weeks compared to patients' own baselines (Wefel et al.). The study that did find deficits compared the test scores of survivors who had been off CTX for only six months with normative scores for the various neuropsychological tests.

Language

Language incorporates oral and written communication when used to express thoughts. Impairment in language inhibits the ability to communicate with others and follow directions without needing repetitions and explanations. Language processing

involves representing, comprehending, and communicating symbolic information, either written or spoken (Gazzaniga et al., 2002).

All of the studies used neuropsychological tests to measure language, but only eight reported their findings. Again, the findings regarding CTX-induced impairments in language are inconsistent. Four studies found significant deficits in language (Brezden et al., 2000; Schagen et al., 1999; Tchen et al., 2003; Wieneke & Dienst, 1995), whereas four studies found no differences (Ahles et al., 2002; Freeman & Broshek, 2002; van Dam et al., 1998; Wefel et al., 2004). All of the studies that found significant deficits were conducted with survivors, with the exception of one study (Brezden et al.).

Tests that yielded significant differences included word fluency tests and the language subtest of the HSCS. The Boston Naming Test, vocabulary and reading subtests of Wide Range Achievement Test, and language subtest of RBANS did not find deficits. Word fluency tests revealed significant deficits in all but one study of survivors (van Dam et al., 1998). A potential explanation for these differences may be the heterogeneity of CTX regimens that the survivors received.

Motor Function

Motor function relates to motor performance, such as speed, strength, and coordination. All of the studies used neuropsychological tests to measure motor function, but only eight reported their findings. Once again, the findings regarding CTX-induced impairments in motor function are inconsistent. Five studies found significant deficits in motor function (Ahles et al., 2002; Brezden et al., 2000; Schagen et al., 1999; van Dam et al., 1998; Wieneke & Dienst, 1995), but three found no differences (Freeman & Broshek, 2002; Tchen et al., 2003; Wefel et al., 2004). All of the studies that found significant

deficits were performed in survivors. In one of those studies, significant impairment in motor function was found with high-dose but not for standard-dose CTX (van Dam et al.). All of the tests used (i.e., grooved pegboard, fingertapping, thumb-finger sequencing, and the visual-motor subtest of the HSCS) yielded significant differences.

Visuospatial Skill

Visuospatial skill refers to the ability to process and interpret visual information regarding where things are situated in space (Spreen & Strauss, 1998). Although all of the studies used neuropsychological tests to measure visuospatial skill, only eight reported their findings. Of note, the findings regarding CTX-induced impairments in visuospatial skill are inconsistent. Only three studies found significant deficits in visuospatial skill (Freeman & Broshek, 2002; Wefel et al., 2004; Wieneke & Dienst, 1995), whereas five studies found no differences (Ahles et al., 2002; Brezden et al., 2000; Schagen et al., 1999; Tchen et al., 2003; van Dam, 1998). One possible explanation for the inconsistent findings is the various comparison groups. Studies that found significant deficits compared survivors with patients who currently were receiving CTX (Freeman & Broshek), with baseline scores (Wefel et al.), or with normative scores for the various neuropsychological tests (Wieneke & Dienst). In contrast, studies that did not find deficits compared survivors with a control group (Ahles et al.; Brezden et al.; Schagen et al., 1999; Tchen et al.; van Dam et al.).

The tests that yielded significant differences were the complex figure copy, block design, and the visual-construction subtest of the RBANS. The spatial subtest of the HSCS did not reveal any deficits. Although the complex figure copy was used in three studies, significant deficits were found in only one study (Wieneke & Dienst, 1995). In

contrast to the other studies, survivors in the Wieneke and Dienst study were only six months from treatment (versus approximately two years), and results were compared to normative data rather than to a control group. Similarly, the block design also was used in three studies, but significant deficits were found in only the longitudinal study (Wefel et al., 2004).

Memory

Memory is an outcome of learning that is created and strengthened by repetition (Gazzaniga et al., 2002). Memory infers the ability to acquire, store, and use new information (Grober, 2002). The most common types of memory are visual and verbal. Although all of the studies used neuropsychological tests to measure verbal memory, only eight reported their findings. Again, the findings regarding CTX-induced impairments in verbal memory are inconsistent. Four studies found significant deficits in verbal memory (Brezden et al., 2000; Schagen et al., 1999; Wefel et al., 2004; Wieneke & Dienst, 1995), but four found no differences (Ahles et al., 2002; Freeman & Broshek, 2002; Tchen et al., 2003; van Dam, 1998). Deficits were found in survivors and patients receiving CTX.

Tests that revealed significant deficits were the California Verbal Learning Test (CVLT), Rey Auditory Verbal Learning Test (RAVLT), Verbal Selective Reminding Test, and the memory subtest on the HSCS. However, the tests detected deficits in only half of the studies in which they were used. For example, the CVLT revealed significant deficits in survivors who were six months from treatment (Wieneke & Dienst, 1995) but did not show deficits in survivors who had been treated approximately 10 years prior (Ahles et al., 2002). A possible explanation for the differences with the RAVLT may be

the differences in CTX regimens. Patients in the study that found significant deficits with the RAVLT had received cyclophosphamide, methotrexate, and 5-fluorouracil (Schagen et al., 1999) versus 5-fluorouracil, epirubicin, and cyclophosphamide with or without cyclophosphamide, thiotepa, and carboplatin in the study that did not find deficits (van Dam et al., 1998). A potential explanation for the difference in test results with the memory subtest of the HSCS is not forthcoming. Deficits were not found with the logical memory test, memory subtest of the RBANS, and the Hopkins Verbal Learning Test.

Although seven studies used neuropsychological tests to measure visual memory, only six of them reported their findings. Of note, the findings regarding CTX-induced impairment in visual memory are inconsistent. Four studies found significant deficits in visual memory (Schagen et al., 1999; van Dam et al., 1998; Wefel et al., 2004; Wieneke & Dienst, 1995), whereas two studies found no differences (Ahles et al., 2002; Freeman & Broshek, 2002). All of the studies that found significant deficits were conducted with survivors. In one of those studies, impairment in visual memory was found with high-dose but not standard-dose CTX (van Dam et al.). The complex figure recall, nonverbal Selective Reminding Test, and Wechsler Memory Scale recall instruments revealed significant deficits. The only study of survivors that did not find deficits in visual memory consisted of an older sample of survivors who had been treated 10 years prior and used the visual reproduction test (Ahles et al.).

Summary

This review of studies that evaluated CTX-induced impairments in cognitive function in women with breast cancer provides some insights into the specific cognitive domains that are affected by CTX. Table 2 summarizes the findings from all of the

studies. In the study of survivors, impairments in speed of information processing and motor function were identified most frequently. The limited number of studies of patients who received concurrent CTX does not permit definitive conclusions to be drawn on the effects of CTX on various domains of cognitive function.

Only nine studies were found that evaluated CTX-induced deficits in cognitive function in women with breast cancer, with a total sample size of 720. Because only eight studies reported detailed findings (i.e., means and standard deviations), the sample size available for this critique was 617. Only 139 of these women with breast cancer currently were receiving CTX. Of the 239 breast cancer survivors who had received CTX, 205 had received standard-dose CTX and 34 had received high-dose CTX. The remaining 239 women were from the control groups.

The control groups consisted of 103 patients with breast cancer who had received only local therapy (i.e., surgery or RT) and 136 healthy women. Individual study sample sizes ranged from 18-200, with 18-100 patients receiving CTX or survivors. Although only one study reported a power calculation (Tchen et al., 2003), it was not the only study to find CTX-induced deficits in various domains of cognitive function.

Of the studies that reported findings, at least half found significant CTX-induced impairments in breast cancer survivors in speed of information processing (83%), motor function (71%), visual memory (67%), and language (50%). Deficits in attention and concentration (43%), executive function (43%), verbal memory (43%), and visuospatial skill (29%) were not found as frequently.

In the one longitudinal study (Wefel et al., 2004), significant deficits were found three weeks after completion of CTX in five of the seven domains that were assessed.

Wieneke and Dienst's (1995) study, which evaluated patients approximately six months after CTX, found significant deficits in seven of the eight cognitive domains assessed. In the three studies that evaluated women about two years after CTX, results were inconsistent, with cognitive deficits found in two of the six (Brezden et al., 2000), four of the eight (van Dam et al., 1998), and seven of the eight (Schagen et al., 1999) domains assessed. One study that evaluated patients almost 10 years after CTX (Ahles et al., 2002) found deficits in only two of the seven domains assessed, information processing speed and motor function. Although CTX-induced deficits are believed to decrease over time, additional research is needed to confirm this hypothesis.

Findings regarding cognitive deficits in women with breast cancer who currently were receiving CTX were even less clear. Of the three prospective studies, one involved a pilot study with only 17 women (Freeman & Broshek, 2002). Because Freeman and Broshek's findings were compared with data from survivors who had received CTX, rather than a control group or normative data, accurately interpreting the results is difficult.

The two remaining studies (Brezden et al., 2000; Tchen et al., 2003) used the HSCS to measure six of the eight cognitive domains (i.e., attention and concentration, executive function, language, motor function, visuospatial skill, and verbal memory). Although the pilot study (Brezden et al.) found significant deficits in language and verbal memory, the subsequent study (Tchen et al.) found significant deficits in language only. The HSCS was not used in any of the retrospective studies or the other prospective study (Freeman & Broshek, 2002). Therefore, whether this test is not sensitive enough to

detect deficits in women with breast cancer currently receiving CTX, or whether the deficits are more pronounced after CTX is completed, is unclear.

Two studies (Brezden et al., 2000; Tchen et al., 2003) used the subtests of one test, the HSCS, to evaluate each cognitive domain, whereas the other seven studies (Ahles et al., 2002; Freeman & Broshek, 2002; Schagen et al., 1999, 2002; van Dam et al., 1998; Wefel et al., 2004; Wieneke & Dienst, 1995) used one to five different tests to evaluate each cognitive domain. Therefore, determining whether the variable findings, which resulted from the 40 tests or subtests that were used to measure the eight cognitive domains, were a result of a lack of deficits or the fact that some of the instruments were not sensitive enough to detect CTX-induced impairments is difficult. Despite these findings, the results reveal a number of conceptual and methodological issues that should be addressed in future studies.

Conceptual Issues

The lack of a conceptual definition of cognitive function and its corresponding domains was identified as a problem in this review. Only Freeman and Broshek (2002) defined the cognitive domains that were measured. Although all of the studies referenced their tests by cognitive domains, the number of domains identified was inconsistent. Half of the studies identified seven cognitive domains (Ahles et al., 2002; Schagen et al., 1999, 2002; van Dam et al., 1998; Wefel et al., 2004), but three acknowledged only six domains (Brezden et al., 2000; Freeman & Broshek, 2002; Tchen et al., 2003), and one (Wieneke and Dienst, 1995) included depression, for a total of nine domains. In addition, in some studies the domains were not specified clearly. For example, Ahles et al. (2002) separated verbal and visual memory into two distinct domains, but others did not

(Freeman & Broshek; Schagen et al., 1999; van Dam et al.; Wefel et al.; Wieneke & Dienst).

Other differences in distinguishing cognitive domains are not as obvious, and some of the confusion may be a function of their interdependence. Certain cognitive domains are so inextricably linked that impairment in one domain invariably affects another (Lezak et al., 2004). Additionally, some neuropsychological tests (e.g., Digit Symbol, Trail Making Tests-Parts A and B, word fluency) may measure aspects of more than one domain, which makes assignment of the findings to a specific domain or multiple domains inconsistent over studies.

Methodologic Issues

Forty-three different tests and subtests were used by the various studies in this review, and each test was assigned to a single domain as listed in Table 3. The number of tests used to assess any specific domain of cognitive function ranged from one to five. With the exception of the HSCS, the investigators did not provide details on the reliability and validity of the tests used. Therefore, the findings from the studies are difficult to compare and interpret because of the lack of information about the psychometric strengths of the tests specific to the measurement of cognitive function.

Implementing procedures to ensure that each investigator performs reliable and valid coding of an instrument is important (Lezak et al., 2004). Adequate training may be required to accurately administer and score tests, because even the slightest deviations from standard procedures and inconsistencies in administration can affect the validity of test results (Hebben & Milberg, 2002). Although scoring of the instruments used was consistent with standardized procedures, information regarding the training of those

responsible for the testing (including the number of people involved) was available in only one study (Ahles et al., 2002).

Many valid and reliable instruments are available to assess cognitive function. Selection of the most appropriate instrument depends on the research questions, characteristics of the patient population, and specific domains to be measured. A single instrument (or a battery of instruments) may be used to measure each cognitive domain. Most studies used a lengthy battery of tests, which took from two to three hours to administer (Ahles et al., 2002; Freeman & Broshek, 2002; Schagen et al., 1999, 2002; van Dam et al., 1998; Wefel et al., 2004; Wieneke & Dienst, 1995). Participant burden is an important consideration in the development of future studies of CTX-induced impairment in cognitive function in patients with cancer. Patients who currently are receiving CTX may be experiencing other side effects that may limit their ability or willingness to complete lengthy evaluations.

Education level 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). Additionally, cognitive decline occurs with aging. All but one (Freeman & Broshek, 2002) of the studies in this review stated that they controlled for age and educational level, but most of the neuropsychological tests have normative data based on age and gender. These data were not used for comparative purposes in most of the studies.

Of the seven studies that used a control group, five matched women in the control group with those in the CTX group by age (Ahles et al., 2002; Schagen et al., 1999, 2002; Tchen et al., 2003; van Dam et al., 1998), whereas one did not (Brezden et al., 2000).

Other potential confounding covariates, such as depression, anxiety, fatigue, and hormonal status, were not measured as consistently.

The influence of decreased sex steroid hormones such as estrogen on cognitive function has been implicated in deficits in learning and memory, especially verbal memory (Cutter, Norbury, & Murphy, 2003; Erlanger, Kutner, Jacobs, 1999; O'Shaughnessy, 2003; Sherwin, 1996, 1998). CTX is known to affect ovarian function, leading to temporary or permanent amenorrhea in women, especially in those old than 40 (Aikin, 1995; Knobf, 1998; Padmanabhan, Wang, Moore, & Rubens, 1987). Only one study controlled for menopausal status in the analysis (Brezden et al., 2000). However, the authors did not state whether that factor influenced their findings. Tchen et al. (2003) measured menopausal symptoms but did not find any association with cognitive deficits.

Eight of the nine studies in this review measured depression. Although two found a significant inverse relationship with cognitive deficits, as measured by the Center for Epidemiological Studies Depression Inventory (CES-D) or the Hopkins Symptom Checklist (Freeman & Broshek, 2002; Schagen et al., 2002), five studies did not find any correlations between cognitive deficits and depression, as measured by the CES-D, Hopkins Symptom Checklist, Minnesota Multiphasic Personality Inventory (MMPI) depression scale, or the Beck Depression Inventory (Ahles et al., 2002; Schagen et al., 1999; van Dam et al., 1998; Wefel et al., 2004; Wieneke & Dienst, 1995). One study (Brezden et al., 2000) assumed that a correlation between depression and cognitive deficits did not exist because no differences existed in mood disturbances, as measured by the Profile of Mood States (POMS), between the CTX and control groups.

Six of the nine studies measured anxiety. Five of the studies did not find significant correlations between cognitive deficits and anxiety as measured by the State-Trait Anxiety Inventory, Hopkins Symptom Checklist, or the anxiety scale of the MMPI (Ahles et al., 2002; Schagen et al., 1999, 2002; van Dam et al., 1998; Wefel et al., 2004). All of the studies that did not find a relationship between anxiety and cognitive deficits were performed in survivors. The one prospective study (Brezden et al., 2000) did not examine the relationship between anxiety and cognitive deficits, because no differences were found in mood disturbances, as measured by POMS, between the CTX and control groups. Similarly, in the five studies that measured fatigue with the Fatigue Symptom Inventory, European Organization for Research and Treatment-Quality of Life Cancer-30 questionnaire, or the Functional Assessment of Cancer Therapy-Fatigue, none found a significant correlation with cognitive deficits (Ahles et al.; Schagen et al., 1999, 2002; Tchen et al., 2003; van Dam et al.).

Although anxiety, depression, and fatigue can reduce performance on neuropsychological tests, one reason for the absence of correlations in studies of survivors may be the length of time since treatment. The experience of fatigue and psychological factors, such as depression and anxiety, may be different in survivors compared to patients who currently are receiving CTX. Another potential explanation for the lack of correlations might be the choice of the comparison group. Patients with breast cancer who received local therapy may share some emotional and physical concerns with those who receive CTX. Overall, differences in psychological and physical status of survivors compared to women who currently are receiving CTX, along with the small

number of available studies, suggest the need for further investigation of those potential covariates.

Another potential risk factor not included in any of the aforementioned studies is the presence of the apolipoprotien E (APOE) ε4 gene, which has been associated with decreased cognitive function in aged individuals (Haan, Shermanski, Jagust, Manolio, & Kuller, 1999; Yaffe, Cauley, Sands, & Browner, 1997). One preliminary study of cancer survivors found a greater risk for deficits in visual memory and visuospatial skills in those who had at least one ε4 allele of APOE (Ahles et al., 2003).

Interpretation of these findings is complicated further by the cross-sectional design used by eight of the studies reviewed. Because only one study (Wefel et al., 2004) had information regarding the baseline cognitive function of patients, readers cannot determine whether patients had worsening, stable, or improved cognitive functioning after the initiation and completion of treatment. Longitudinal studies need to be performed to determine when CTX-induced deficits in cognitive function occur, which domains of cognitive function are affected, and whether different domains are affected at different times after the administration of CTX.

All of the studies used a convenience sample. Although this approach is the most common method to obtain participants, the ability to obtain a representative sample often is a problem (Polit & Hungler, 1999). All of the studies reviewed have the potential for selection bias. For example, the studies that included survivors required patients to be free of disease or other medical complications, which excluded sicker patients with potentially more cognitive deficits. In addition, whether patients who declined to participate had greater cognitive deficits is unknown.

Only one study failed to describe its inclusion and exclusion criteria (Freeman & Broshek, 2002). Although the remaining eight studies provided explicit information regarding sample selection, only seven provided response rates, which ranged from 70%-80% (Ahles et al., 2002; Schagen et al., 1999, 2002; Tchen et al., 2003; van Dam et al., 1998; Wefel et al., 2004; Wieneke & Dienst, 1995). In two of the studies (Tchen et al.; Wieneke & Dienst), participants were recruited from more than one site. Of the two prospective studies that used healthy women as a control group, one matched for age (Tchen et al), but the other did not (Brezden et al., 2000). The remaining prospective study compared women currently receiving CTX to survivors (Freeman & Broshek).

Only one retrospective study did not have a control group (Wieneke & Dienst, 1995). The control groups in the other studies of survivors consisted of women who had received only local treatment and were matched for age with the CTX survivors (Ahles et al., 2002; Schagen et al., 1999, 2002; van Dam et al., 1998). In two of the studies, no statistically significant differences were found between the individual neuropsychological test scores of the patients in the control group and the published norms for those tests (Schagen et al., 1999; van Dam et al.).

Suggestions for Future Research

Although research is beginning to elucidate the presence of cognitive impairments in survivors, the limited number of published studies is beset with multiple methodological and conceptual issues. The paucity of scientific knowledge is even more pronounced for patients with breast cancer who currently are receiving CTX. The use of conceptual models or theoretical frameworks would aid future research and help identify variables that explain or predict the relationships among CTX, clinical and patient

characteristics, and cognitive impairments. In addition, the incorporation of qualitative research methodologies would enhance the understanding of the complexity of patients' experiences with cognitive impairments.

Further investigation is needed to identify the tests are most valid, reliable, sensitive, and specific for detecting short-term and persistent CTX-induced cognitive impairments. Researchers of future studies may want to use the instruments that consistently distinguish deficits, such as the digit span for attention and concentration; digit symbol, Fepsy visual reaction, and Trail Making Test-Part A for information processing speed; word fluency for language; fingertapping or grooved pegboard for motor function; and complex figure copy and recall for visuospatial skill and visual memory. Although instruments that have demonstrated an ability to detect deficits should used, multiple measures may be preferable for the domains for which measures that possess sufficient sensitivity or specificity have not been identified. Regardless of which tests are chosen, participant burden is an important consideration.

The published findings suggest that CTX-induced impairments in cognitive function do occur in some women with breast cancer, but differences in time since treatment, CTX regimen, menopausal status, and tests used have limited comparisons among the various studies. Therefore, ascertaining whether deficits were associated with a particular drug in a CTX regimen, with CTX-induced menopause, or even with the use of tamoxifen is difficult. Further studies are necessary to understand potential cognitive deficits induced by CTX, but the conceptual and methodologic problems identified in this review also must be addressed.

Implications for Nursing

Impairments in cognitive function adversely affect the immediate treatment experience and a return to normal life after treatment is completed. The immediate complications of such cognitive dysfunction also may impair the ability of patients to give informed consent, identify treatment toxicities, learn self-care measures, and perform self-care behaviors. Increasing awareness among cancer survivors and healthcare professionals regarding such negative impacts of CTX has given rise to a growing number of important studies and further emphasizes the need to understand the influence of CTX on cognitive function.

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TABLE 1

Studies of Chemotherapy-Induced Cognitive Impairments in Women With Breast Cancer

Study	Sample Characteristics	Findings	Limitations
Ahles et al., 2002 Purpose: to compare the neuro-psychologic functioning of long-term survivors of breast cancer who were treated with standard-dose (SD) systemic chemotherapy (CTX) or local therapy only Design: retrospective study of survivors	• N = 70; survivors = 35, controls = 35 • Mean age of survivors = 59.1 ± 10.7; controls = 60.6 ± 12.1 • Mean educational level (years): survivors = 15.2 ± 2.3; controls = 14.0 ± 2.7 • Mean time since treatment (years): survivors = 9.4 ± 4.5; controls = 9.9 ± 5.8 • CTX regimens: 40% CMF, 40% CAF, 9% AC, 9% other • 37% of the survivor group and 14% of the control group had taken tamoxifen • No differences were found for anxiety, depression, or fatigue	Attention/concentration: Continuous Performance Test vigilance and distractibility subtests: No difference was found between groups on both subtests. Executive Function: HRNB TMT Part B: Difference between groups for this instrument was not reported. Information processing speed: WAIS digit symbol subtest and HRNB TMT Part A: Survivors had significantly poorer overall information processing speed compared to control group (p = 0.05). Difference between groups for each instrument was not reported. Language: Boston Naming Test, MAE COWA subtest, WAIS vocabulary subtest and Wide Range Achievement Test reading subtest: No differences were found between groups in verbal ability. Differences between groups for individual instruments were not reported. Motor function: HRNB finger tapping subtests and thumb-finger sequencing: Survivors scored significantly lower than controls (p = 0.05). Visuospatial Skill: WAIS block design subtest: No difference was found between groups. Verbal memory: CVLT and WMS logical memory subtest: No differences were found between groups on both tests. Visual memory: WMS visual reproduction subtest: No difference was found between groups.	• Small sample size for multiple CTX regimens and variability in stage of disease and time since last treatment. • Basis for Neuropsycho-logical Performance Index was unclear, especially because group differences were evaluated with multiple thresholds. • Lacked information about menopausal status
Brezden et al., 2000 Purpose: to investigate whether cognitive impairment is present in women receiving SD adjuvant CTX for breast cancer Design: prospective study of patients currently receiving CTX and survivors	• N = 107; on CTX = 31, survivors = 40, controls = 36 • Median age: current CTX= 49; survivors = 46; controls = 41.5 • Educational level: current CTX 48% secondary, 52% postsecondary; survivors 37.5% secondary, 62.5% post-secondary; controls 36% secondary, 64% postsecondary • Median time since treatment (years): current CTX N/A; survivors = 25 months • CTX regimen: current CTX group: 39% CMF and 51% CEF; survivors: 53% CMF, 43% CEF, and 4% other • 45% of the survivor group were treated with tamoxifen, none in the current CTX group. • No differences were found among groups for depression or anxiety	Attention/concentration: HSCS attention/ concentration subtest: No difference was found among groups. Executive Function: HSCS self-regulation and planning subtest: No difference was found among groups, but a trend existed toward increased scores (indicating decreased executive function) in survivors compared to controls (p = 0.07) Information processing speed: Not measured. Language: HSCS language subtest: Significantly increased scores (indicating decreased language) were found in the current CTX and survivor groups as compared to the control group (p = 0.03) for current CTX; p = 0.05 for survivors). Motor function: HSCS visual motor subtest: Significantly lower scores in survivors were found compared to controls (p = 0.02). A trend existed toward decreased motor function in the current CTX group compared to the control group (p = 0.09). Visuospatial Skill: HSCS spatial subtest: No difference was found between groups. Verbal memory: HSCS memory subtest: Significantly decreased scores were found in the current CTX group compared to the control group (p = 0.02). No difference was found between the survivor and control groups. Visual memory: Not measured.	• Multiple CTX regimens, variable duration of regimens, and variability in time since last treatment. • The control group had significantly younger participants compared to the current CTX (p = 0.01) and survivor groups (p = 0.03). • The treatment groups (current CTX, p = 0.01; survivors, p = 0.03) had significantly more post-menopausal women compared to the control group. • Information regarding fatigue was lacking.

TABLE 1

Studies of Chemotherapy-Induced Cognitive Impairments in Women With Breast Cancer (cont.,)

Study	Sample Characteristics	Findings	Limitations
Freeman & Broshek, 2002 Purpose: to determine which tools are most sensitive in detecting the effects of "chemobrain" Design: prospective study of patients currently receiving CTX and survivors	• N = 17; current CTX = 8, survivors = 9 • Mean age: current CTX = 52.6 ± 7.0; survivors = 51.1 ± 7.0 • Mean educational level (years): current CTX = 16 ± 2.9; survivors = 17.3 ± 2.2 • Mean time since treatment (years): current CTX = N/A; survivors not reported (within 6-12 months) • CTX regimens: not reported. • All were post-menopausal with the exception of one in the survivor group • No difference was found between groups for depression, but a trend existed for higher scores in the survivor group (p = 0.14)	Attention/concentration: RBANS attention subtest: Although findings were not reported, the article implied that no difference was found between groups because other significant findings and trends were reported. Executive Function: HRNB TMT Part B: Although findings were not reported, the article implied that no difference was found between groups because other significant findings and trends were reported. HRNB categories subtest: Although findings were not reported, the article implied that no difference was found between groups because other significant findings and trends were reported. Stroop test: The survivor group scored significantly lower than the current CTX group (p = 0.03). Information processing speed: HRNB TMT Part A: Although findings were not reported, the article implied that no difference was found between groups because other significant findings and trends were reported. PASAT: Although findings were not reported, the article implied that no difference was found between groups because other significant findings and trends were reported. Language: RBANS language subtest: No difference was found between groups, but a trend existed toward decreased scores in the current CTX group as compared to survivors (p = 0.15). MAE COWA subtest: Although findings were not reported, the article implied that no difference was found between groups because other significant findings and trends were reported. Motor function: Grooved pegboard: No difference was found between groups, but a trend existed toward decreased scores with non-dominant side in the current CTX group compared to survivors (p = 0.15). Visuospatial Skill: RBANS visual-construction subtest: Significantly lower scores were found in the current CTX group compared to survivors (p = 0.002). Verbal memory: Hopkins Verbal Learning Test: Although findings were not reported, the article implied that no difference was found between groups because the authors reported other significant findings and trends. RBANS memory subtest: No difference was found between groups, but a trend existed toward decreased scores in the current CTX group with immediate memory compared to survivors (p = 0.15) Visual memory: WMS facial recognition subtest: Although findings were not reported, the article implied that no difference was found between groups because other significant findings and trends were reported.	• Small sample size • The article compared results between current CTX and survivor groups rather than test norms or a control group. • Information was lacking regarding anxiety and fatigue

TABLE 1

Studies of Chemotherapy-Induced Cognitive Impairments in Women With Breast Cancer (cont.,)

Study	Sample Characteristics	Findings	Limitations
Schagen et al., 1999 Purpose: to examine the neuropsychological functioning of patients with breast cancer following standard adjuvant CTX with CMF Design: retrospective study of survivors	• N = 73; survivors = 39, controls = 34 • Mean age of survivors = 47.1 ± 6.9; controls = 46.1 ± 5.2 • Educational level: survivors = 31% primary, 25% secondary, 36% university or graduate; controls = 41% primary, 41% secondary, 18% university or graduate • Mean time since treatment 1.9 years • All were receiving CMF • Approximately 50% were treated with tamoxifen for three years • Survivors had significantly higher scores on the depression subscale than controls (p = 0.01). • No difference was found between groups for anxiety. • No difference was found between groups, but a trend existed for higher scores on the fatigue scale for survivors (p = 0.16).	Attention/concentration: WAIS digit span forward subtest: No difference was found between groups. WAIS digit span backward subtest: Survivors scored significantly lower than controls (p = 0.02). D2 test: No difference was found between groups, but a trend existed for decreased scores in survivors (p = 0.06). Executive Function: HRNB TMT Part B: Survivors had significantly higher scores (indicating decreased executive function) compared to controls (p = 0.01). Stroop test: No difference was found between groups. Information processing speed: Fepsy visual reaction (dominant): Survivors scored significantly higher (indicating decreased information processing speed) than controls (p = 0.02). Fepsy visual reaction (non-dominant): Survivors scored significantly higher (indicating decreased information processing speed) than controls (p = 0.01). Fepsy binary choice and visual search subsets: No difference was found between groups. HRNB TMT Part A: No difference was found between groups, but a trend existed for increased scores (indicating decreased information processing speed) in survivors (p = 0.08). WAIS digit symbol subtest: Survivors scores significantly lower than controls (p = 0.04). Language: S.A.N. word fluency subtest: Survivors scored significantly lower than controls (p = 0.03). Motor function: Fepsy fingertapping (dominant): Survivor group scored significantly lower than control group (p = 0.04). Fepsy fingertapping (non-dominant): Survivor group scored significantly lower than control group (p = 0.003). Visuospatial Skill: RCFT copy: No difference was found between groups. Verbal memory: RAVLT: No difference was found between groups for recall or recognition, but significantly lower scores were found in survivors compared to controls for delayed recall (p = 0.03). Visual memory: RCFT recall: Survivor group scored significantly lower than control group (p = 0.03). WMS visual reproduction subtest, immediate and delayed recall: Survivor group scored significantly lower than control group for immediate recall (p = 0.01) and delayed recall (p = 0.006).	• Significant difference between survivors and the control group in regard to educational level • All of the survivors were postmenopausal, compared to only 38% of the control group

TABLE 1

Studies of Chemotherapy-Induced Cognitive Impairments in Women With Breast Cancer (cont.,)

Study	Sample Characteristics	Findings	Limitations
Schagen et al., 2002 Purpose: to obtain more insight into the long-term neuropsychological sequeale following CTX and their course over time Design: retrospective study of survivors	• N = 103; survivors (HD CTX) = 22, survivors (SD CTX) = 54, controls = 27 • Mean age: survivors (SD CTX) = 50.4 ± 5.3; survivors (HD CTX) = 47 ± 4.8; controls = 48.8 ± 5.0 • Educational level: not reported • Mean time since treatment (years): survivors (SD) = 3.6, survivors (HD) = 3.3 • CTX regimens: survivors (SD CTX) 57% CMF, 43% FEC; survivors (HD CTX) = FEC + CTC	Attention/concentration: WAIS digit span and D2 test: findings not reported. Executive Function: HRNB TMT Part B and Stroop test: findings not reported. Information processing speed: Fepsy binary choice, visual reaction and visual search subsets, HRNB TMT Part A, and WAIS digit symbol subtest: findings not reported. Language: S.A.N. word fluency subtest: findings not reported. Motor function: Fepsy fingertapping: findings not reported. Visuospatial Skill: RCFT copy: findings not reported. Verbal memory: RAVLT: findings not reported. Visual memory: RCFT recall: findings not reported.	• Significant differences existed in length of survival (time since treatment) between groups. • The study had sample bias because of attrition. • A lack of information regarding menopausal status existed.
Tchen et al., 2003 Purpose: to evaluate cognitive function, fatigue, and menopausal symptoms and to explore the relationships among them in a substantial series of patients receiving adjuvant CTX for breast cancer Design: prospective study of patients currently receiving CTX	• N = 200; current CTX = 100, controls = 100 • Median age: current CTX = 48, controls = 47 • Educational level: current CTX = 38% secondary, 62% postsecondary; controls = 30% secondary, 70% postsecondary, • Median time since treatment: N/a • CTX regimens: 64% CEF, 17% AC, 11% CMF, 8% other • 5% of patients were taking tamoxifen • The treatment group had significantly higher levels of fatigue compared to the control group ($p < 0.0001$).	Attention/concentration: HSCS attention/ concentration subtest: No difference was found between groups, but a trend existed toward increased scores (indicating decreased attention) in the CTX group compared to controls ($p = 0.09$). Executive Function: HSCS self-regulation and planning subtest: No difference was found among groups, but a trend existed toward increased scores (indicating decreased executive function) in the CTX group compared to controls ($p – 0.09$) Information processing speed: Not measured. Language: HSCS language subtest: The CTX group had significantly increased scores (indicating decreased language) compared to the control group ($p = 0.005$). Motor function: HSCS visual motor subtest: No difference was found between groups. Visuospatial Skill: HSCS spatial subtest: No difference was found between groups, but a trend existed toward decreased visuospatial skills in the CTX group compare to the control group ($p = 0.07$). Verbal memory: HSCS memory subtest: No difference was found between groups. Visual memory: Not measured.	• The study had a variability in the timing of measurement in the treatment group (36% after third, 28% after fourth, 14% after fifth, 20% after sixth, and 2% after seventh cycle). • The study accounted for fatigue, but anxiety and depression were not measured.

TABLE 1

Studies of Chemotherapy-Induced Cognitive Impairments in Women With Breast Cancer (cont.,)

Study	Sample Characteristics	Findings	Limitations
van Dam et al., 1998 Purpose: to assess systematically the prevalence of cognitive deficits in a group of women receiving adjuvant CTX for high-risk breast cancer and to investigate whether HD CTX impairs cognitive functioning more than SD CTX in this patient population Design: retrospective study of survivors	• N = 104; survivors (HD CTX) = 34, survivors (SD CTX) = 36, controls = 34 • Mean age: survivors (HD CTX) = 46.5 ± 6.2; survivors (SD CTX) = 48.1 ± 6.8; controls = 46.1 ± 5.2 • Educational level: survivors (HD CTX) = 32% primary, 32% secondary, 36% university or graduate; survivors (SD CTX) = 31% primary, 25% secondary, 36% university or graduate; controls = 41% primary, 41% secondary, 18% university or graduate • Mean time since treatment (years): survivors (HD) = 1.6; survivors (SD) = 1.9 • CTX regimens: survivors (SD CTX) = four to five cycles of FEC, survivors (HD CTXy) = four cycles of FEC, then CTC • Both groups were treated with tamoxifen for two years • Survivors (HD CTX) group had significantly elevated scores on the depression subscale in comparison with the control group (p = 0.041), but not with the survivors (SD CTX) group. No difference was found between the survivor (SD CTX) and control groups. • No differences were found among three groups for anxiety.	Attention/concentration: WAIS digit span forward subtest: No difference was found among the three groups. WAIS digit span backward subtest: Survivor (HD CTX) group scored significantly lower than control group (p = 0.041). No difference was found between survivor (HD CTX) and survivor (SD CTX) or survivor (SD CTX) and control groups. D2 test: No differences were found among the three groups. Executive Function: HRNB TMT Part B: No differences were found among the three groups. Stroop test: No differences were found among the three groups. Information processing speed: Fepsy visual reaction (dominant): The survivor (HD CTX) group scored significantly higher (indicating decreased information processing speed) than the control group (p = 0.011). No differences were found between the survivor (HD CTX) and survivor (SD CTX) or survivor (SD CTX) and control groups. Fepsy visual reaction (nondominant): Survivor (HD CTX) group scored significantly higher (indicating decreased information processing speed) than survivor (SD CTX) and control groups (p = 0.008). No differences were found between the survivor (SD CTX) and control groups. Fepsy binary choice and visual search subsets: No differences were found among the three groups. WAIS digit symbol subtest: The survivor (HD CTX) group scored significantly lower than the control group (p = 0.017). No differences were found between the survivor (HD CTX) and survivor (SD CTX) or survivor (SD CTX) and control group. Language: Dutch Aphasia Society Test word fluency subtest: No difference was found among the three groups. Motor function: Fepsy finger-tapping (dominant): The survivor (HD CTX) group scored significantly lower than the control group (p = 0.041). No difference was found between the survivor (HD CTX) and survivor (SD CTX) or survivor (SD CTX) and controls. Fepsy fingertapping (non-dominant): The survivor (HD CTX) group scored significantly lower than the control group (p = 0.004). No difference was found between the survivor (HD CTX) and survivor (SD CTX) or survivor (SD CTX) and controls. Visuospatial Skill: RCFT copy: No differences were found among the three groups. Verbal memory: RAVLT: No differences were found among the three groups for recall, delayed recall, or recognition. Visual memory: RCFT recall: The survivor (HD CTX) group scored significantly lower than the control group (p = 0.028). No difference was found between the survivor (HD CTX) and survivor (SD CTX) or survivor (SD CTX) and control groups.	• Significant differences existed among the two survivor groups and the control group in relation to menopausal status • The study accounted for anxiety and depression, but fatigue was not measured.

TABLE 1

Studies of Chemotherapy-Induced Cognitive Impairments in Women With Breast Cancer (cont.,)

Study	Sample Characteristics	Findings	Limitations
Wefel et al., 2004 Purpose: to evaluate the incidence, nature, severity, and chronicity of cognitive dysfunction among patients with breast carcinoma who are treated with a SD of adjuvant CTX Design: prospective study of survivors	• N = 18 • Mean age = 45.4 ± 6.7 • Mean educational level = 14 ± 2.6 years • Mean time since treatment: N/A at baseline, three weeks, and one year • CTX regimens: CAF • One-third of the participants were postmenopausal	Attention/concentration: WAIS digit span subtest: No differences were found among the three time periods. WAIS arithmetic subtest: No differences were found among the three time periods. Executive Function: Category Booklet Test: Patients had significantly higher scores (indicating decreased executive function) three weeks post-CTX compared to baseline ($p < 0.01$). No differences were found at one year after CTX compared to baseline. HRNB TMT Part B: No differences were found among the three time periods. WAIS similarities subtest: No differences were found among the three time periods. Information processing speed: HRNB TMT Part A: No differences were found among the three time periods. WAIS digit symbol subtest: Patients had significantly higher scores (indicating decreased speed of information processing) at short-term (three weeks) post-CTX compared to baseline ($p < 0.05$). No difference was found between long-term (one year) post-CTX compared to baseline. Language: No measured. Motor function: Grooved pegboard (dominant): No differences were found among the three time periods. Grooved pegboard (non-dominant): No differences were found among the three time periods. Visuospatial Skill: WAIS block design subtest: Patients had significantly higher scores (indicating decreased visuospatial skill) at short-term (three weeks) post-CTX compared to baseline ($p < 0.05$). No difference was found between long-term (one year) post-CTX compared to baseline. Verbal memory: Buschke verbal selective reminding test: long-term storage and delayed recall. Patients had significantly lower scores at short-term (three weeks) post-CTX compared to baseline ($p < 0.05$). No difference was found between long-term (one year) post-CTX compared to baseline. Visual memory: Buschke non-verbal selective reminding test: long-term storage and delayed recall. Patients had significantly lower scores at short-term (three weeks) post-CTX compared to baseline ($p < 0.05$). No difference was found between long-term (one year) post-CTX compared to baseline.	• Small sample size • Significant attrition • The study accounted for depression and anxiety, but fatigue was not measured.

TABLE 1

Studies of Chemotherapy-Induced Cognitive Impairments in Women With Breast Cancer (cont.,)

Study	Sample Characteristics	Findings	Limitations
Wieneke & Dienst, 1995 Purpose: to determine whether objective evidence exists for deterioration in cognitive function and whether further large-sample prospective research is warranted Design: retrospective study of survivors	• N = 28 • Mean age = 42 ± 6.7 • Mean educational level = 16 ± 2.1 • Mean time since treatment = 6.6 months • CTX regimens: 61% CMF, 14% CAF, 25% combination of both • Average course of therapy = 6.7 months • 39% were on tamoxifen • 11% of survivors had evidence of depression	Attention/concentration: WAIS digit span subtest: Survivors had significantly lower scores compared to test norms ($p = 0.007$). Executive Function: Category Booklet Test: No difference was found. HRNB TMT Part B: No difference was found. WAIS similarities subtest: No difference was found. Information processing speed: HRNB TMT Part A: Survivors had significantly higher scores (indicating decreased information processing speed) compared to norms ($p < 0.011$). PASAT: Survivors had significantly lower scores than test norms ($p < 0.003$). WAIS digit symbol subtest: No difference was found. Language: MAE COWA: Survivors had significantly lower scores than test norms ($p = 0.017$). Motor function: Grooved pegboard (dominant): Survivors had significantly lower scores than test norms ($p < 0.001$). Grooved pegboard (non-dominant): Survivors had significantly lower scores than test norms ($p < 0.025$). Visuospatial Skill: RCFT copy: Survivors had significantly lower scores compared to norms ($p < 0.0001$). WAIS block design subtest: No difference was found. Verbal memory: CVLT: No difference was found. CVLT short delay: No difference was found. CVLT long delay: Survivors had significantly lower scores compared to test norms ($p = 0.049$). Visual memory: RCFT recall: Survivors had significantly lower scores than test norms ($p < 0.001$).	• Small sample size, especially for multiple CTX regimens, variable duration of regimens, and variability in time since last treatment • No information regarding menopausal status • Accounted for depression, but anxiety and fatigue were not measured.

Abbreviations: AC = doxorubicin and cyclophosphamide; CAF = cyclophosphamide, doxorubicin and 5-fluorouracil; CCC = cyclophosphamide, cisplatin, and carmustine; CEF = cyclophosphamide, epirubicin, 5-fluorouracil; CMF = cyclophosphamide, methotrexate, 5-fluorouracil; COWA = Controlled Oral Word Association; CTC = cyclophosphamide, thiotepa, and carboplatin; CTX = chemotherapy; CVLT = California Verbal Learning Test; FEC = 5-fluorouracil, epidoxorubicin, and cyclophosphamide; HD = high dose; HRNB = Halstead-Reitan Neuropsychological Test Battery; HSCS = High Sensitivity Cognitive Screen; MAE = Multilingual Aphasia Examination; N/A = not applicable; PASAT = Paced Auditory Serial Addition Test; RAVLT = Rey Auditory Verbal Learning Test; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; RCFT = Rey Complex Figure Test; SD = standard dose; TMT = Trail Making Test; WAIS = Wechsler Adult Intelligence Scale; WMS = Wechsler Memory Scale

TABLE 2

Chemotherapy-Induced Cognitive Impairments Found in Studies of Women With Breast Cancer

Authors	Attention	Executive Function	Speed of Information Processing	Language	Motor Function	Visuospatial Skill	Verbal Memory	Visual Memory
Studies of survivors								
Ahles et al., 2002	-	N/A	X	-	X	-	-	-
Brezden et al., 2000	-	-	N/A	X	X	-	-	N/A
Freeman & Broshek, 2002	-	X	-	-	-	-	-	-
Schagen et al., 1999	X	X	X	X	X	-	X	X
Schagen et al., 2002 [a]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
van Dam et al., 1998	X	-	X	-	X	-	-	X
Wefel et al., 2004	-	X	X	N/A	-	X	X	X
Wieneke & Dienst, 1995	X	-	X	X	X	X	X	X
Studies of patients currently receiving chemotherapy								
Brezden et al., 2000	-	-	N/A	X	-	-	X	N/A
Freeman & Broshek, 2002	-	-	-	-	-	X	-	-
Tchen et al., 2003	-	-	N/A	X	-	-	-	N/A

Note: N/A indicates not assessed, X indicates significant impairment, and – indicates no significant impairment.

TABLE 3

Neuropsychological Tests Used to Assess Chemotherapy-Induced Impairments By Cognitive Domain

Cognitive Domain	Tests Used
Attention and concentration	• Continuous Performance Test: distractibility and vigilance tests • D2 Test • High Sensitivity Cognitive Screen (HSCS): attention subtest • Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): attention subtest • Wechsler Adult Intelligence Scale (WAIS): arithmetic and digit span subtests
Executive function	• Booklet Category Test • HSCS: self-regulation and planning subtest • Halstead-Reitan Neuropsychological Test Battery (HRNB): categories and Trail Making Test (TMT)- Part B subtests • Stroop Test • WAIS: similarities subtest
Speed of information processing	• Fepsy: binary choice, visual reaction, and visual searching subtests • HRNB: TMT-Part A subtest • Paced Auditory Serial Addition Test • WAIS: digit symbol subtest
Language	• Boston Naming Test • Dutch Adult Reading Test • Dutch Aphasia Society Test: word fluency subtest • Groninger Intelligence Test: word fluency subtest • HSCS: language subtest • Multilingual Aphasia Examination: controlled oral word association subtest • RBANS: language subtest • S.A.N.: word fluency subtest • WAIS: vocabulary subtest • Wide Range Achievement Test: reading subtest
Motor function	• Fepsy: fingertapping test • Grooved pegboard • HSCS: visual motor subtest • HRNB: fingertapping subtest • Thumb-finger sequencing
Visuospatial skill	• Rey Complex Figure Test (RCFT): copy • HSCS: spatial subtest • RBANS: visual construction subtest • WAIS: block design subtest
Verbal memory	• Buschke Verbal Selective Reminding Test • California Verbal Learning Test • HSCS: memory subtest • Hopkins Verbal Learning Test • RBANS: memory subtest • Rey Auditory Verbal Learning Test • Wechsler Memory Scale (WMS): logical memory subscale
Visual memory	• Buschke NonVerbal Selective Reminding Test • RCFT: recall • WMS: facial recognition and visual reproduction subtests

Abbreviations: HRNB = Halstead-Reitan Neuropsychological Test Battery; HSCS = High Sensitivity Cognitive Screen; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; RCFT = Rey Complex Figure Test; TMT = Trail Making Test; WAIS = Wechsler Adult Intelligence Scale; WMS = Wechsler Memory Scale

Chapter 2.

Potential Mechanisms For Chemotherapy-Induced Impairments

In Cognitive Function

Jansen, C., Miaskowski, C., Dodd, M., Dowling, G., & Kramer, J. (2005).

Oncology Nursing Forum, 32(6), 1151-1163.

Abstract

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 a 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.

Introduction

Chemotherapy (CTX) is one of the primary treatments for cancer and has been used successfully to extend patients' lives. Although the occurrence of cognitive impairments following CTX 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. CTX does not appear to cross the blood-brain barrier when given in standard doses; however, recent studies have substantiated CTX-induced impairments in various domains of cognitive function (Ahles et al., 2002; Brezden, Phillips, Abdolell, 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 CTX agents as well as potential mechanisms for CTX-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 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 direction 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, acetycholine, 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 (Spreen & 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 area. 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 were things are in space (Spreen & 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 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, CTX must gain entry into the brain before any cognitive impairment can occur. An understanding of the neurotoxicity of CTX 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 epithelial cells (Laterra & 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).

Neurotoxcity of CTX

CTX is a systemic treatment that has the greatest impact on rapidly dividing tumor cells. Toxicities emerge because of CTX's deleterious effects on rapidly dividing normal cells in areas of the body such the bone marrow or gastrointestinal tract. Therefore, neurotoxicity is surprising as a major side effect because the nervous system consists of cells (e.g., gilia) 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 CTX 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 metabolite 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/m^2 (Nieto et al., 1999; Verstappen 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; Verstappen 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 CTX drugs to cross the blood-brain barrier, the brain appears to be a site for CTX-induced toxicity. Once CTX drugs enter the CNS, the exact mechanism or mechanisms responsible for producing changes in cognitive function are not understood completely.

Potential Mechanisms for CTX-Induced Impairments in Cognitive Function

Many CTX drugs are known to be irritants or have the potential to cause necrosis if tissues are infiltrated. Some professionals have speculated that CTX 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 CTX-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 CTX-induced impairments in cognitive function still is unknown. Impairments in cognitive function resulting from CTX may occur along a continuum from subtle changes to profound neurologic impairment. One of the most acute types of neurologic impairment associated with CTX 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, CTX-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 CTX agents (Filley & Kleinschmidt-DeMasters, 2001). CTX-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 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 CTX 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.; Cossart, 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

CTX 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)-1α, IL-1β, 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 CTX causes injury to normal tissues, the plausibility exists that it could induce the release of cytokines. Proinflammatory cytokines have been implicated directly in the endoneural swelling that produces peripheral neuropathic pain associated with vinca alkaloids, taxanes, and cisplatin in rats (Aley, Reichling, & Levine, 1996; Authier, Fialip, Eschalier, & 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 CTX (Cleeland et al.; Maier & Watkins, 2003). CTX agents that have been shown to induce the production of proinflammatory cytokines in human or murine 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, 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).

CTX-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.).

CTX 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 CTX that occurs in more than 50% of patients (Glaspy, 1997). The incidence of CTX-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 CTX regimens occur in less than 1% to 30% of patients who receive standard doses and

in as many of 80% of patients who receive high-dose regimens (Groopman & Itri, 1999). Specific CTX 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). CTX-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.).

CTX-Induced Menopause

In women, CTX-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 acetycholine, 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.).

CTX 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 in women older than age 50, whereas 25% occur in premenopausal women (Poniatowski, Grimm, & Cohen, 2001). Menopausal symptoms may start in as few as six to twelve weeks after beginning CTX treatment in premenopausal women (Dnistrian et al., 1983). Amenorrhea generally occurs within six to twelve months of treatment; however, the frequency varies and depends on the type, dose, and duration of the CTX 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 CTX (Knobf; Meirow, 2000; Padmanabhan et al.; Saarto et al. 1997). CTX drugs most commonly associated with decreased ovarian function include alkylating agents and doxorubicin (Kaplan, 1992; Meirow; 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 CTX 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 CTX-related mechanisms, a number of patient factors may be protective against cognitive impairments or place individuals at a 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 CTX 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) ε4 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 ε4 allele of APOE (Ahles et al., 2003).

Implications for Clinical Practice

The prevalence, severity, and duration of CTX-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 CTX. Oncology nurses need to be aware of this potential effect of CTX and conduct ongoing assessments of patients. Although no valid and reliable clinical tools exist to assess for CTX-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 CTX-induced impairments in cognitive function most likely are multi-factorial, some patients may be at higher risk. As more information becomes available about the mechanism or mechanisms of CTX-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 CTX-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 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 CTX. 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 CTX 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 CTX (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 CTX 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 CTX-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 CTX agents. In addition, longitudinal studies are needed to further describe the phenomenon of "chemo brain" and elucidate the mechanism or mechanisms responsible for the CTX-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 CTX-induced impairments in cognitive function is crucial to the development of preventive strategies to lessen or eliminate their occurrence.

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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
Speed of information processing	
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

TABLE 2

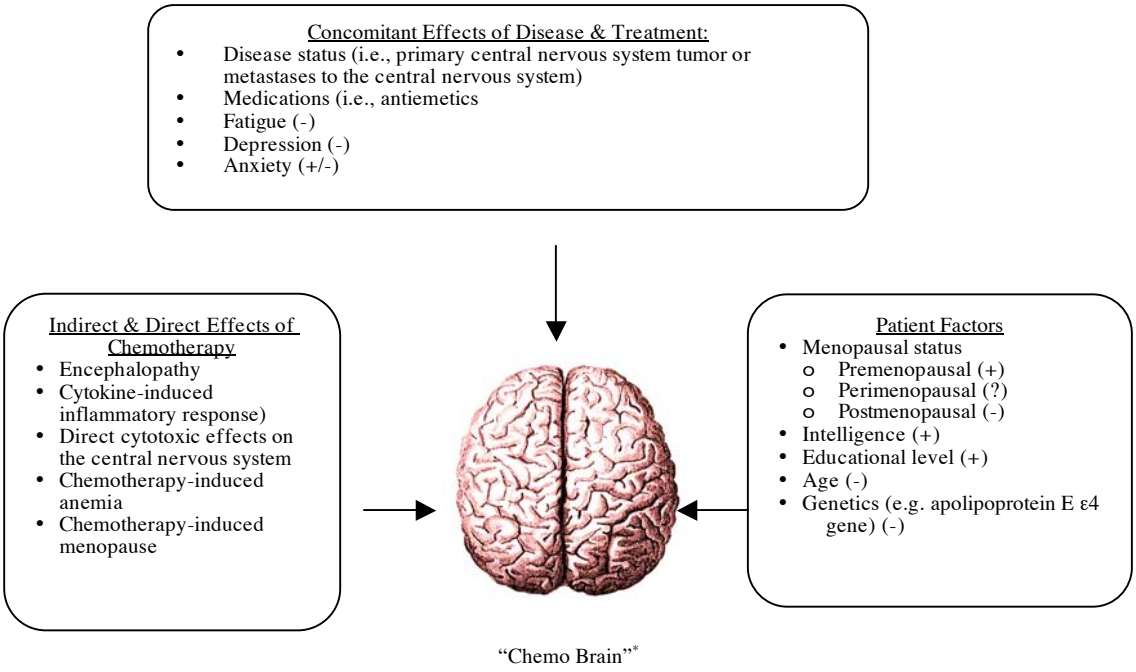
Potential Mechanisms for Chemotherapy-Induced Impairments in Cognitive Function

Mechanism	Domains 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

Figure 1

Potential Contributing Factors for Chemotherapy-Induced Impairments



Symbol Key:

(-) Negatively impacts cognitive function; may contribute to "chemo brain"
(+) Enhances cognitive function; may have protective effect against "chemo brain"
(?) Unknown impact

* *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

Chapter 3.

A Meta-Analysis of Studies of The Effects of Cancer Chemotherapy

On Various Domains of Cognitive Function

Jansen, C.E., Miaskowski, C., Dodd, M., Dowling, G., & Kramer, J. (2005).

Cancer, 104(10), 2222-2233.

Abstract

Background: Little is know about the effects of chemotherapy on cognitive function. The purposes of this meta-analysis were to estimate the effect sizes for the effect of chemotherapy on each domain of cognitive function and to differentiate effect sizes by each method of comparison of effects (i.e., normative data, control group, or baseline data).

Methods: Sixteen studies that evaluated cognitive function in chemotherapy patients were included in the study. DSTAT meta-analysis software was used to calculate an effect size and confidence intervals for each neuropsychologic test. Tests were assigned to a specific cognitive domain, and an average effect size was determined for each domain.

Results: Only one domain of cognitive function (i.e., visual memory) had significant chemotherapy-induced impairment across all comparison types. However, when the neuropsychologic test scores of chemotherapy patients were compared with normative data, significant effect sizes were found for four domains of cognitive function (i.e., executive function, information processing speed, verbal memory, visual memory). In addition, significant, albeit small, effect sizes were found for language and verbal memory when chemotherapy patients' test scores were compared with test scores of healthy matched controls. All significant averaged effect sizes were in the negative direction, indicating that mean scores on neuropsychological tests for patients who had received chemotherapy were on average lower than comparison scores.

Conclusion: Data from this meta-analysis supported the hypothesis that chemotherapy can have a negative impact on cognitive function. However, most deficits in this study ranged from small to moderate and were nonsignificant.

Introduction

Although great strides have been made to decrease the side effects of chemotherapy (CTX), current studies consistently confirm that adverse effects (e.g., fatigue, infection, nausea, vomiting, diarrhea, stomatitis, alopecia, and neuropathy) continue to adversely affect quality of life (Cowley, Heyman, Stanton, & Milner, 2000; Fairclough, Fetting, Cella, Wonson, & Moinpour, 1999; Ganz, 2000). More recently, cancer patients have reported difficulties in their abilities to remember, think, and concentrate (Bender, Paraska, Sereika, Ryan, & Berga, 2001; Brezden, Phillips, Abdolell, Bunston, & Tannock, 2000; Cole, Scialla, & Bednarz, 2000; Cull et al., 1996; Ganz, 1998). However, little is known about the effects of CTX on cognitive function.

Several reviews on CTX-induced impairments in cognitive function have been published in recent years (Ahles & Saykin, 2001; Ahles & Saykin, 2002; Ferguson & Ahles, 2003; Ganz, 1998; Minisini et al., 2004; Morse, Rodgers, Verrill, & Kendell, 2003; Olin, 2001; Peterson & Popkin, 1980; Rugo & Ahles, 2003; Schagen, Muller, Boogerd, van Dam, 2002; Silberfarb, 1983; Troy et al., 2000; Wefel, Kayl, & Meyers, 2004). However, explanations for the disparate findings among studies have not been forthcoming. Because these reviews are either conceptual (Ahles & Saykin, 2001; Ferguson & Ahles, 2003; Minisini et al., 2004; Peterson & Popkin, 1980; Schagen et al., 2002; Silberfarb, 1983), disease specific (Ahles & Saykin, 2002; Ganz, 1998; Morse et al., 2003; Olin, 2001; Rugo & Ahles, 2003), CTX drug specific (Troy et al., 2000), or inclusive of all systemic cancer treatments (Wefel, Kayl, & Meyers, 2004), the specific effects of CTX on the various domains of cognitive function are not readily available. In

addition, none of these reviews determined the effect size of CTX on specific domains of cognitive function.

Meta-analysis is a quantitative approach that is used to combine results from several studies, with various sample sizes, in an attempt to determine an effect size for a specific intervention or procedure (Glass, 1976; Lipsey & Wilson, 2001). A benefit of this approach is that pooling of findings across studies increases the power to detect significant effects if they exist. The standardized mean difference effect size (ES_{sm}, also known as Cohen *d*) is a scale-free measure that contrasts results between groups (Cohen, 1988). Effect sizes are essential for power calculations to determine appropriate sample size and to provide information on direction and magnitude of a relation.

Only one meta-analysis has been performed on cognitive impairments associated with cancer treatments (Anderson-Hanley, Sherman, Riggs, Agocha, & Compas, 2003). The investigators calculated an effect size for mean differences between the cognitive function of patients who were currently receiving or had received cancer treatment, compared with a control group, normative data, or their own baseline data. Effect sizes were calculated for seven domains of cognitive function (i.e., attention, executive function, information processing, motor function, spatial skill, verbal memory, visual memory). When patients' neuropsychological test scores were compared with control group scores, significant effect sizes were found for each of the seven domains of cognitive function. However, when tests scores were compared with normative data, significant effect sizes were found for only three cognitive domains (i.e., executive function, motor function, verbal memory). In addition, when patients' test scores were compared with their own baseline data, significant effect sizes were not found.

Although this meta-analysis (Anderson-Hanley et al., 2003) revealed significant negative effect sizes (i.e., cancer treatment produced deficits in cognitive function) in two sets of comparisons, it did not provide specific data on effects of CTX compared with other cancer treatments. Another limitation of this meta-analysis was that information was not provided on how various neuropsychologic tests were categorized in terms of domains of cognitive function. Because some tests are known to measure more than one cognitive domain, inconsistent designation of test results could lead to differences in effect size calculations for treatment effects on the various domains of cognitive function. In addition, several neuropsychologic tests, used in the 30 studies evaluated, were excluded from analysis without any explanation. Therefore, the purposes of this meta-analysis were to estimate the effect sizes for the effect of CTX on each domain of cognitive function and to differentiate effect sizes by each method of comparison of effects (i.e., normative data, control group data, or CTX patients to their baseline data).

Materials and Methods

Literature Search and Selection of Studies

A preliminary search was performed for original research reports, published in English from 1966 to December 2004, on the association between CTX and cognitive impairments. Five computerized databases were used: PubMed (National Library of Medicine, Bethesda, MD), Psychinfo (American Psychological Association, Washington, DC), CogNet (Massachusetts Institute of Technology [MIT] Press and the Cognitive Neuroscience Institute, Cambridge, MA), CINAHL (Cinahl Information Systems, Glendale, CA) and the Cochrane Database of Systematic Reviews (Oxford, UK). Unpublished sources were not considered. Keywords used for the search included:

"CTX", "cognitive impairment", "cognitive deficits", "cancer", "antineoplastic agents", and "neuropsychologic tests".

While several articles were listed in more than one database, a total of 383 citations were obtained (Figure 1). Abstracts from all of these research studies were reviewed to determine whether they met the following criteria: 1) original study data, 2) adult sample, 3) neuropsychologic testing of cancer patients who had or were currently receiving CTX, 4) valid, reliable, and sensitive neuropsychologic tests with published standardized administration procedures, and 5) sufficient information reported (either by quantitative measurement or inferential statistics) on at least one domain of cognitive function to estimate effect size. The following types of articles were excluded: reviews, commentaries, case reports, and meta-analyses. In addition, if cognitive function was not included as an outcome variable, the article was not included in the current meta-analysis.

Studies were excluded if samples were not exclusively adult participants, because treatment effects would be different in developing brains of children. Studies were also excluded if they were limited to patients with either primary or metastatic central nervous system (CNS) tumors, or other cancer treatments known to cause cognitive deficits (e.g., brain irradiation or biologics). The search was supplemented by manual review of bibliographies of each relevant study and review. Three additional studies were found by using this approach. Table 1 provides information on 16 studies that met all eligibility criteria (Ahles, Tope, Fursetenberg, Hann, & Mills, 1996; Ahles et al., 2002; Andrykowski et al., 1992; Brezden et al., 2000; Freeman & Broshek, 2002; Harder et al., 2002; Kaasa, Olsnes, & Mastekaasa, 1987; Meyers, Byrne, & Komaki, 1995; Meyers et al., 1994; Oxman & Silberfarb, 1980; Schagen et al., 1999; Silberfarb, Philibert, &

Levine, 1980; Tchen et al., 2003; van Dam et al., 1998; Wefel, Lenzi, Theriault, Davis, & Meyers, 2004; Wieneke & Dienst, 1995).

Study Quality Scoring Tool

A study quality scoring tool was developed based on work by Smith and Stullenbarger (1991). A total of 15 study elements were critically appraised to determine a study's quality score. Elements reviewed included the problem statement, study design, sample selection, instruments, description of neuropsychologic test findings, data analysis, and results. The highest possible score was 30, and each item had a possible score of zero to two (0 = absent, 1 = partially met, 2 = completely met). Although the quality of each study was evaluated, studies were not eliminated from meta-analysis because of poor quality.

Classification of Tests by Cognitive Domain

To measure the effect of CTX on each domain of cognitive function, each neuropsychologic test was assigned to a specific cognitive domain. Whereas in some studies, a neuropsychologic test was used to measure more than one domain of cognitive function, for purposes of this meta-analysis, the test was coded for a single domain to avoid over-weighting a particular effect and to provide consistency in evaluations across studies.

As shown in Table 2, each neuropsychologic test was categorized into one of eight cognitive domains: attention or concentration, executive function, speed of information processing, language, motor function, visuospatial skill, verbal memory, and visual memory. Although most categorizations were performed by using neuropsychologic assessment references (Lezak, Howieson, & Loring, 2004; Spreen &

Strauss, 1998), some tests were categorized by using recent meta-analyses of neuropsychologic tests in cancer and human immunodeficiency virus (HIV) populations (Anderson-Hanley et al., 2003; Reger, Welsh, Razani, Martin & Boone, 2002).

Procedure

By using the data abstraction form developed for the current meta-analysis, information from 16 studies was abstracted to record study sample characteristics, neuropsychologic test(s) used, statistical methods, and results. Johnson (1993) DSTAT 1.10 meta-analysis software was used to calculate ES_{sm} and 95% confidence intervals (CI). Because small studies can overestimate an effect size, the potential for bias was corrected by weighting the ES_{sm} for each test by the sample size and pooled variance (Hedges & Olkin, 1985). For studies that used more than one neuropsychologic test to measure a specific cognitive domain, an average effect size was calculated for that domain. In addition, because some tests yield several scores, an average effect size was calculated for that test. Effect sizes were calculated from the standardized mean differences by using means and standard deviations reported for each neuropsychological test result. Approximately 72% of effect sizes (n = 162) were calculated from standardized means and standard deviations. When means and standard deviations were not available, effect sizes were calculated from other reported statistics, such as proportions (10%, n = 22), P values (9%, n = 20), t-tests (7%, n = 16), and F values (2%, n = 4). Effect sizes were coded, so that positive scores indicated better cognitive function, and negative scores indicated poorer cognitive function in the CTX groups.

RESULTS

Study Characteristics

As shown in Table 1, the 16 studies included in this analysis were published between 1980 and June 2004. Only 3 studies were published in the 1980s (19%), 7 were published in the 1990s (43%), and 6 were published in the 2000s (38%). Seventy-five percent (n = 12) of studies were cross-sectional, and 25% (n = 4) were longitudinal. Study quality ranged from 19 to 30 (mean = 23.50, standard deviation [SD] = 3.03).

The total sample consisted of 996 participants, 653 of whom were CTX patients (survivors [n = 425] or patients currently receiving CTX [n = 228], whereas the remaining 343 participants formed the control groups. Control groups consisted of either cancer patients who had received local therapy only [n = 207] or healthy individuals matched for age and education (n = 136). Total sample sizes per study ranged from 10 to 200 (mean = 92.79, SD = 59.40). Sample sizes for CTX patients ranged from 8 to 100 (mean = 55.36, SD = 27.67). The age of CTX patients ranged from 35 to 62 years, with a mean age of 47.64 years (SD 7.54). The age of participants in control groups ranged from 41 to 61 years, with a mean age of 50.89 (SD 6.60). The majority (84%) of participants were female, and in 44% of studies, the entire sample was female. Only three studies reported information on ethnicity. The education level of participants could not be quantified because of differences in education systems across countries and differences in reporting methods.

Some studies had more than one treatment group, differentiated by diagnosis, CTX regimen, or time since completion of CTX. The most common type of cancer in these studies was breast cancer (58%), followed by hematologic malignancies (18%),

mixed diagnoses (10%), lung cancer (9%), and lymphoma (5%). Types of treatment comprised standard-dose CTX (80%), high-dose CTX (5%), or bone marrow transplant (15%). Twenty-four percent of studies included patients who were currently receiving CTX. In the remainder of the studies, the time since treatment was: less than a year (20%), one to two years (31%), two to five years (14%), greater than five years (11%).

Outcome Characteristics

Effect sizes were interpreted as negligible if they were less than 0.20, small if they were 0.20 to 0.50, medium if they were 0.50 to 0.80, and large if they were greater than 0.80 (Cohen, 1988). A significance level of 0.05 was inferred when the 95% confidence interval did not cross zero (Shadish & Haddock, 1994). A total of 224 effect sizes were calculated for test results from 16 studies (see Table 3). When the mean effect size was calculated for all samples by cognitive domain, effect sizes ranged from negligible to moderate. All averaged weighted effect sizes across various domains of cognitive function were in the negative direction, indicating a general trend toward decreased cognitive function in CTX patients. However, only a moderate effect size in visual memory was significant (see Table 4).

Neuropsychologic test results for CTX patients were compared with a control group in 56% of studies (n = 9), within CTX patients in 25% (n = 4), and to published normative test data in 19% (n = 3). In nine studies that used a control group, 67% (n = 6) were of cancer patients who had received only local therapy, 22% (n = 2) were healthy participants, and the remaining 11% (n = 1) were survivors who had received CTX.

As shown in Figure 2, when mean effect sizes were differentiated by the method of comparison (i.e., controls, normative, or baseline data), effect sizes ranged from

negligible to moderate. Twenty of the 23 effect sizes were in the negative direction. As shown in Table 5, for studies that compared neuropsychologic test scores of CTX patients to normative data, significant moderate effect sizes were found in four domains of cognitive function (i.e., executive function, information processing speed, verbal memory, visual memory).

In contrast, when the method of comparison was either neuropsychological test scores from a control group or CTX patients' baseline test scores, effect sizes ranged from negligible to small and were not significant. Because different types of control groups were used (i.e., cancer patients who received only local treatment versus healthy matched participants), the two groups were reanalyzed for each domain. Effect sizes continued to range from negligible to small and nonsignificant when CTX patients neuropsychologic tests scores were compared with test scores of cancer patients who received local treatment. However, small significant effect sizes were found in cognitive domains of language and verbal memory when CTX patient test scores were compared with healthy matched participants.

Discussion

The current meta-analysis is the first to evaluate the effect of CTX on various domains of cognitive function. The absolute magnitude of averaged effect sizes ranged from negligible to moderate in size. Results of this meta-analysis demonstrated that one domain of cognitive function (i.e., visual memory) had significant CTX-induced impairment across all comparison types. However, when neuropsychologic test scores of CTX patients were compared with normative data, significant effect sizes were found for four domains of cognitive function (i.e., executive function, information processing

speed, verbal memory, visual memory). In addition, significant, albeit small, effect sizes were found for language and verbal memory when CTX patient test scores were compared with test scores of healthy matched controls. All significant averaged effect sizes were in the negative direction, indicating that mean scores on neuropsychologic test scores for patients who had received CTX were, on average, lower than comparison scores.

The results of any meta-analysis are limited by studies that are available. The type of CTX regimen varies by cancer diagnosis and stage of disease. In addition, CTX regimens may vary in intensity and frequency of administration. The current meta-analysis included studies whose patients received CTX regimens that may be considered more intense (i.e., high dose CTX, bone marrow transplant). Therefore, the decrements noted in various cognitive domains may related, in part, to dosing regimens. However, when these studies were excluded from analysis, the findings did not change. In addition, because breast cancer was the common diagnosis in this sample, analysis was repeated excluding all other diagnoses. Similar results (i.e., effect size, significance) were found for all cognitive domains, with one exception. A small significant negative effect size was found for language, which remained even when the sample that received high-dose CTX was excluded. However, when only breast cancer patients who received a standard-dose of CTX were evaluated, the small negative effect size for visual memory became nonsignificant. The ability to conduct subanalyses by diagnosis, CTX regimen, and comparison groups is limited because of the paucity of research studies in this area.

The finding that all significant effect sizes were in the negative direction is consistent with the previous meta-analysis (Anderson-Hanley et al., 2003). This finding

supports the hypothesis that cancer treatments, including CTX, negatively influence cognitive function. Both meta-analyses found significant effect sizes when patients' neuropsychologic test scores were compared with normative data in two domains of cognitive function (i.e., executive function, verbal memory), and nonsignificant findings in one domain (i.e., attention and concentration). In contrast, findings differed for other domains of cognitive function (i.e., information processing speed, motor function, and visual memory).

Although the earlier meta-analysis found significant effect sizes for every domain of cognitive function when CTX patients' test scores were compared with a neuropsychologic test scores from a control group (Anderson-Hanley et al., 2003), these findings were not supported by the current meta-analysis. In contrast, small significant effect sizes were found in language and verbal memory but only when test scores were compared with those of healthy matched controls. However, the lack of significant findings when patients' neuropsychologic test scores were compared with their own baseline test scores is consistent between the two meta-analyses. One potential explanation for this finding may be the relatively small number of studies that used this comparative approach. In addition, these studies generally had the smallest sample sizes. Another explanation for the lack of significant findings may be because of the presence of cognitive impairments before the initiation of CTX or practice effects related to repeated testing with the same neuropsychologic tests, resulting in an underestimation of effect sizes.

Differences in findings between the current and previously published meta-analyses may be explained in several ways. The most obvious explanation is different

study populations (various cancer treatments versus CTX only). Each of these cancer treatments may contribute to changes in cognitive function. Differences also existed in the assignment of various neuropsychologic tests to a specific domain of cognitive function. For example, while the Trail Making Test (TMT)-Part A, (S.G. Armitage, 1946), Stroop Test (Steeling Wood Dale, IL), and Paced Auditory Serial Addition Test (PASAT, BrainMetric Software, Drexel Hill, PA) were assigned to information processing speed in the current meta-analysis, the previous meta-analysis designated the PASAT as a test of executive function and the other two neuropsychologic tests (TMT-Part A, Stroop) as measures of attention and concentration. In addition, although the Dementia Rating Scale (DRS, PAR Inc, Lutz, FL) construction subtest was designated as a measure of visuospatial skill in the current meta-analysis, it was designated as a test of motor function in the previous meta-analysis. Finally, the Controlled Oral Word Association (Spreen and Benton, 1977) was designated as a test of executive function in the earlier meta-analysis and as a test of language in the current meta-analysis.

Language was not included as one of the domains of cognitive function in the first meta-analysis. Therefore, several tests that were used to measure language (i.e., Boston Naming Test [Veterans Administration Hospital, Boston, MA], Dutch Adult Reading Test [Swets and Zeitlanger, Netherlands], Dutch Aphasia Society Test word fluency subtest, High Sensitivity Cognitive Screen language subtest [Faust and Fogel, 1989], S.A.N. word fluency subtest [Swets and Zeitlanger, Netherlands], Wechsler Adult Intelligence Scale vocabulary subtest [{WAIS} Manual: Wechsler Memory Scale. Psychological Corporation, New York, NY], Wide Range Achievement Test reading subtest [Wide Range Inc., now at Psychological Assessment Resources Inc., Lutz, FL])

were not included in the first meta-analysis, although they were used in studies that were included in the meta-analysis. In contrast, although attention, executive function, information processing speed, motor function, and verbal memory were included as domains of cognitive function in the first meta-analysis, several tests used to measure these domains were excluded (i.e., Continuous Performance Test distractibility and vigilance subtests, d2 test (PAR, Inc., Lutz, FL], Ruff 2 & 7, WAIS arithmetic subtest to measure attention; Booklet Category Test [PAR, Inc., Lutz, FL], DRS conceptualization and initiation or preservation subtest to measure executive function [PAR, Inc., Lutz, FL]; Fepsy binary choice, visual reaction, and visual searching subtests to measure information processing speed [WCJ Alpherts & APA/der Kamp, 1994]; finger-thumb sequencing, grip strength [PAR, Inc., Lutz, FL], HSCS psychomotor subtest to measure motor function; and verbal learning test to measure verbal memory).

Given the limited number of studies of CTX-induced impairments in cognitive function, these results need to be interpreted with caution. One explanation for the limited number of significant findings may be that the neuropsychologic tests used in these studies are not sufficiently sensitive to detect subtle changes in cognitive function induced by CTX. The combining of neuropsychologic tests with various degrees of sensitivity to detect subtle changes in cognitive function induced by CTX, may have also limited the findings. Another explanation for these findings is that test sensitivity was found only for domains that are actually impaired by CTX. Little is known about CTX-induced impairment in cognitive function, whether it is acute, chronic, persistent, or transient. Therefore, combining studies that measured cognitive function at various time

periods (e.g., during treatment to as many as 10 years after CTX is completed) may have influenced effect sizes.

Conclusion

Findings from this meta-analysis fill a gap in the literature and highlight potential CTX-induced impairment in various domains of cognitive function. The current meta-analysis included a total of 16 studies, for which over half compared patients with controls. It is likely that small samples in some of these studies, especially those that compared patients' neuropsychologic test scores to the patients' own baseline, had insufficient power to detect significant differences. However, this meta-analysis provides some early information concerning the effects of CTX on cognitive function. Although the degree of impairment in cognitive function appears higher in those who are treated with CTX, most deficits ranged from small to moderate and were nonsignificant.

Although evidence of CTX-induced impairments in cognitive function exists, there is still much to be discovered. More studies are needed to further elucidate the phenomenon of CTX-induced impairment in cognitive function and to describe its characteristics (e.g., onset, duration). In addition, studies need to be performed to identify tests that are the most valid, reliable, sensitive, and specific for detecting short-term and persistent CTX-induced cognitive impairments. Regardless of the size of the effect, it is still not clear how clinically significant these impairments in cognition may be to an individual's everyday functioning. Future studies will be necessary to determine the clinical significance of cognitive deficits and how these deficits relate to patient complaints.

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*Indicates articles included in the current meta-analysis.

TABLE 1

Characteristics of Studies Included in the Meta-Analysis

Primary author, year published	Study quality score	Comparison group	Treatment	Diagnosis	Treatment/ total no.	Age in years	Education	Time since treatment in months
Ahles, 1996	25	Within subjects	BMT	Breast, Hematologic	34/34	39.2	Not reported	1
Ahles, 2002	27	Control Norms	SD	Breast, Lymphoma	71/128	Survivors: Breast 60.6 Lymphoma 48.7 Control: Breast 59.1 NHL 55.9	Survivors: Breast 15.2 years NHL 48.7 years Control: Breast 59.1 years NHL 55.9 years	Breast 112.8 Lymphoma 118.8
Andrykowski, 1992	21	Norms	SD	Hematologic	55/55	35.9	15% less than high school; 29% high school; 9% vocational or trade school; 36% some college or a degree; 11% some graduate or professional training	24.9
Brezden, 2000	28	Control	SD	Breast	71/107	Control: 41.5; Current CTX: 49; Survivors: 46	Control: 36% secondary; 64% post-secondary; Current CTX group: 48% secondary; 52% post-secondary. Survivor group: 37.5% secondary; 62.5% post-secondary	Current CTX: 0 Survivors: 12
Freeman, 2002	19	Control (survivors)	SD	Breast	17/17	Current CTX: 52.6 Survivors: 51.1	Current: 16 years; Survivors: 17.3 years	Current CTX: 0 Survivors: 9
Harder, 2002	22	Norms	BMT	Hematologic	40/40	40.8	7.5% less than high school; 35% high school; 25% vocational or trade school; 17.5% some college or degree; 15% some graduate or professional training	15.1
Kaasa, 1988	23	Control (XRT)	SD	Lung	31/65	Control: 61 Current CTX: 62	Not reported	0
Meyers, 1994	23	Within subjects	BMT	Hematologic lung	21/21	37.5	13.2 years	8
Meyers, 1995	24	Control	SD	Lung	25/46	Control: 54.7 Survivors: 47.1	Control: 12.7 years; Current CTX: 13.2 years	0

TABLE 1

Characteristics of Studies Included in the Meta-Analysis (cont.,)

Primary author, year	Study quality score	Comparison group	Treatment	Diagnosis	Treatment/ total no.	Age in years	Education	Time since treatment in months
Oxman, 1980	20	Within subjects	SD	Various solid tumors	10/10	52.8	80% high school; 20% some college	0
Schagen, 1999	25	Control	SD	Breast	39/73	Control: 46.1; Survivors: 47.1	Control: 41% primary school; 41% secondary school; 18% university and graduate Survivors: 33% primary school; 18% secondary school; 49% university and graduate	Survivors: 22.8
Silberfarb, 1980	21	Control	SD	Varied	23/50	59.4	Not reported	0
Tchen, 2003	30	Control	SD	Breast	100/200	Control: median 47; Current CTX: median 48	Control: 30% secondary; 70% post-secondary Current CTX: 38% secondary; 62% post-secondary	0
Van Dam, 1998	25	Control	SD & HD	Breast	70/104	Control: 46.1; Survivors (SD): 48.1 Survivors (HD): 45.5	Control: 41% primary; 41% secondary school; 18% university and graduate Survivors (SD CTX): 31% primary school; 25% secondary school; 44% university and graduate; (HD CTX): 32% primary school; 32% secondary school; 36% university and graduate	Survivors (SD): 22.8 Survivors (HD): 19.2
Wefel, 2004	21	Within subjects	SD	Breast	18/18	45.4	14.0	12
Wieneke, 1995	22	Norms	SD	Breast	28/28	42	16	6.6

Abbreviations: BMT = bone marrow transplant; CTX = chemotherapy; HD = high dose; SD = standard dose

TABLE 2

Assignment of Neuropsychological Tests to a Specific Domain of Cognitive Function

Cognitive Domain	Tests Used
Attention and concentration	• Continuous Performance Test (CPT) ~ distractibility and vigilance tests • D2 Test • Dementia Rating Scale (DRS) ~ attention subtest • High Sensitivity Cognitive Screen (HSCS) ~ attention subtest • Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) ~ attention subtest • Ruff 2 & 7 test • Wechsler Adult Intelligence Scale (WAIS) ~ arithmetic and digit span subtests
Executive function	• Booklet Category Test • DRS ~ conceptualization and initiation and preservation subtests • Halstead-Reitan Neuropsychological Test Battery (HRNB) ~ categories and Trail Making Test (TMT)- Part B subtests • HSCS ~ self-regulation and planning subtest • Stroop Test • WAIS ~ similarities subtest
Speed of information processing	• Complex Reaction Time Test • Fepsy binary choice, visual reaction, and visual searching subtests • HRNB ~ TMT-Part A subtest • Paced Auditory Serial Addition Test • WAIS ~ digit symbol subtest
Language	• Boston Naming Test • Controlled Oral Word Association • Dutch Adult Reading Test • Dutch Aphasia Society Test: word fluency subtest • Groninger Intelligence Test: word fluency subtest • HSCS ~ language subtest • RBANS ~ language subtest • S.A.N. ~ word fluency subtest • WAIS ~ vocabulary subtest • Wide Range Achievement Test ~ reading subtest
Motor function	• Fepsy fingertapping test • Finger-thumb sequencing • Grooved pegboard • HSCS ~ visual motor subtest • HRNB ~ fingertapping subtest
Visuospatial skill	• DRS ~ construction subtest • HSCS ~ spatial subtest • RBANS ~ visuospatial/construction subtest • Rey-Osterrieth Complex Figure Test (RCFT) ~ copy • WAIS ~ block design subtest • Wechsler Memory Scale (WMS) ~ facial recognition subtest
Verbal memory	• Buschke Verbal Selective Reminding Test • California Verbal Learning Test • DRS ~ memory subtest • HSCS ~ memory subtest • Hopkins Verbal Learning Test • Rey Auditory Verbal Learning Test • WMS ~ logical memory subscale
Visual memory	• RCFT ~ recall • WMS ~ visual reproduction subtests

Abbreviations: CPT: Continuous Performance Test; DRS: Dementia Rating Scale; HRNB: Halstein-Reitan Neuropsychologic Battery; HSCS: High Sensitivity Cognitive Screen; RBANS: Repeatable Battery for the Assessment of Neuropsychologic Status; RCFT: Rey-Osterrieth Complex Figure Test; TMT: Trail Making Test; WAIS: Wechsler Adult Intelligence Scale; WMS: Wechsler Memory Scale

TABLE 3

Unweighted Effect Sizes (Cohen's D) for the Individual Studies by Type of Comparisons and Cognitive Domain

Norm Comparison								
First author, yr	AC	EF	I	L	MF	VS	VERM	VISM
Andrykowski,1980	-0.32	**-0.99**	-0.35		**-0.52**		**-1.18**	**-1.01**
Harder, 2002	-0.40	-0.21	**-1.15**	+0.91	-0.00	**+1.50**	-0.18	0.001
Wieneke, 1995	**-0.72**	-0.05	**-0.64**	**-0.67**	**-0.89**	**-0.95**	-0.45	**-1.47**
Control Comparison								
First author, yr	AC	EF	I	L	MF	VS	VERM	VISM
Ahles, 2002								
Breast	-0.12	-0.24	-0.34	-0.34	+0.05	+0.00	-0.22	-0.32
Lymphoma	-0.17	-0.48	-0.42	-0.08	**-0.54**	-0.15	-0.37	-1.08
Brezden, 2000	-0.05	-0.37		-0.49	-0.48	-0.23	-0.34	
Freeman, 2002		+1.12		-0.77	-0.70	**-1.68**	-0.68	
Kaasa, 1988		-0.39	-0.26				-0.10	-0.37
Meyers, 1995	+0.12	-0.19	-0.23	+0.06	-0.28	+0.20	-0.13	+0.02
Schagen, 1999	-0.12	-0.14	-0.38	-0.41	-0.44	-0.24	-0.26	-0.46
Silverfarb, 1980		**-0.71**	**-1.03**					
Tchen, 2003	**-0.28**	-0.17		**-0.43**	-0.14	-0.03	**-0.53**	
Van Dam, 1998	-0.35	-0.03	-0.28	**-0.69**	-0.43	-0.24	-0.45	
Baseline Comparison								
First author, yr	AC	EF	I	L	MF	VS	VERM	VISM
Ahles, 1996		**-0.54**		-0.44				-0.25
Meyers, 1994	-0.15	-0.36				+0.32	+0.09	
Oxman, 1980	-0.21	-0.11	+0.29					
Wefel, 2004	-0.07	-0.22	-0.54	-0.59	-0.02	-0.36	-0.44	-0.43

Abbreviations: AC: attention/concentration; EF: executive function; I: information processing speed; L: language; MF: motor function; VS: visuospatial skill; VerM: verbal memory; VisM: visual memory.

Bolded figures represent significant results ($P \leq 0.05$)

TABLE 4

Overall Mean Effects Sizes and Confidence Intervals for the Effect of Chemotherapy on Domains of Cognitive Function

Cognitive domain	AC	EF	I	L	MF	VS	VERM	VISM
No. studies	12	16	11	11	11	11	13	10
No. combined samples	830	996	617	795	816	782	902	591
Weighted d	-0.17	-0.26	-0.44	-0.33	-0.36	-0.11	-0.37	**-0.51**
99% CI-lower	-0.62	-0.74	-0.96	-0.78	-0.80	-0.57	-0.83	**-1.01**
99% CI-upper	+0.27	+0.20	+0.07	+0.13	+0.10	+0.34	+0.09	**-0.01**

Abbreviations: AC: attention/concentration; EF: executive function; I: information processing speed; L: language; MF: motor function; VS: visuospatial skill; VerM: verbal memory; VisM: visual memory.

Bolded figures represent significant results ($P \leq 0.05$)

TABLE 5

Results for Cognitive Domains by Method of Comparison

Overall Mean Effects Sizes and Confidence Intervals for the Effect of Chemotherapy on Domains of Cognitive Function

Method		AC	EF	IPS	L	MF	VS	VerM	VisM
Normative	# studies	3	3	3	2	3	2	3	3
	# combined samples	123	123	123	68	123	68	123	123
	weighted d	-0.18	**-0.52**	**-0.58**	+0.26	-0.44	+0.49	**-0.69**	**-0.78**
	99% CI –lower	-0.63	**-0.96**	**-1.12**	-0.23	-0.88	-0.03	**-1.14**	**-1.24**
	99% CI - upper	+0.25	**-0.10**	**-0.22**	+0.75	+0.00	+1.01	**-0.25**	**-0.32**
Control	# studies	6	9	6	7	7	7	8	5
	# combined samples	658	790	466	675	675	675	740	416
	weighted d	-0.18	-0.23	-0.40	-0.37	-0.35	-0.18	-0.33	-0.46
	99% CI –lower	-0.60	-0.69	-0.91	-0.81	-0.79	-0.62	-0.78	-0.95
	99% CI – upper	+0.13	+0.23	+0.12	+0.08	+0.11	+0.25	+0.12	+0.05
Baseline	# studies	3	4	2	2	b	2	2	2
	# combined samples	49	83	28	52		39	39	52
	weighted d	-0.05	-0.19	-0.25	-0.49		+0.01	-0.15	-0.31
	99% CI –lower	-0.76	-0.81	-1.03	-1.06		-0.67	-0.81	-0.87
	99% CI - upper	+0.66	+0.40	+0.54	+0.08		+0.68	+0.51	+0.25

Abbreviations: AC: attention/concentration; EF: executive function; I: information processing speed; L: language; MF: motor function; VS: visuospatial skill; VerM: verbal memory; VisM: visual memory.

Bolded figures represent significant results ($p \leq 0.05$).

[b] Only one baseline study measured motor function

FIGURE 1

Literature Search and Selection of Studies

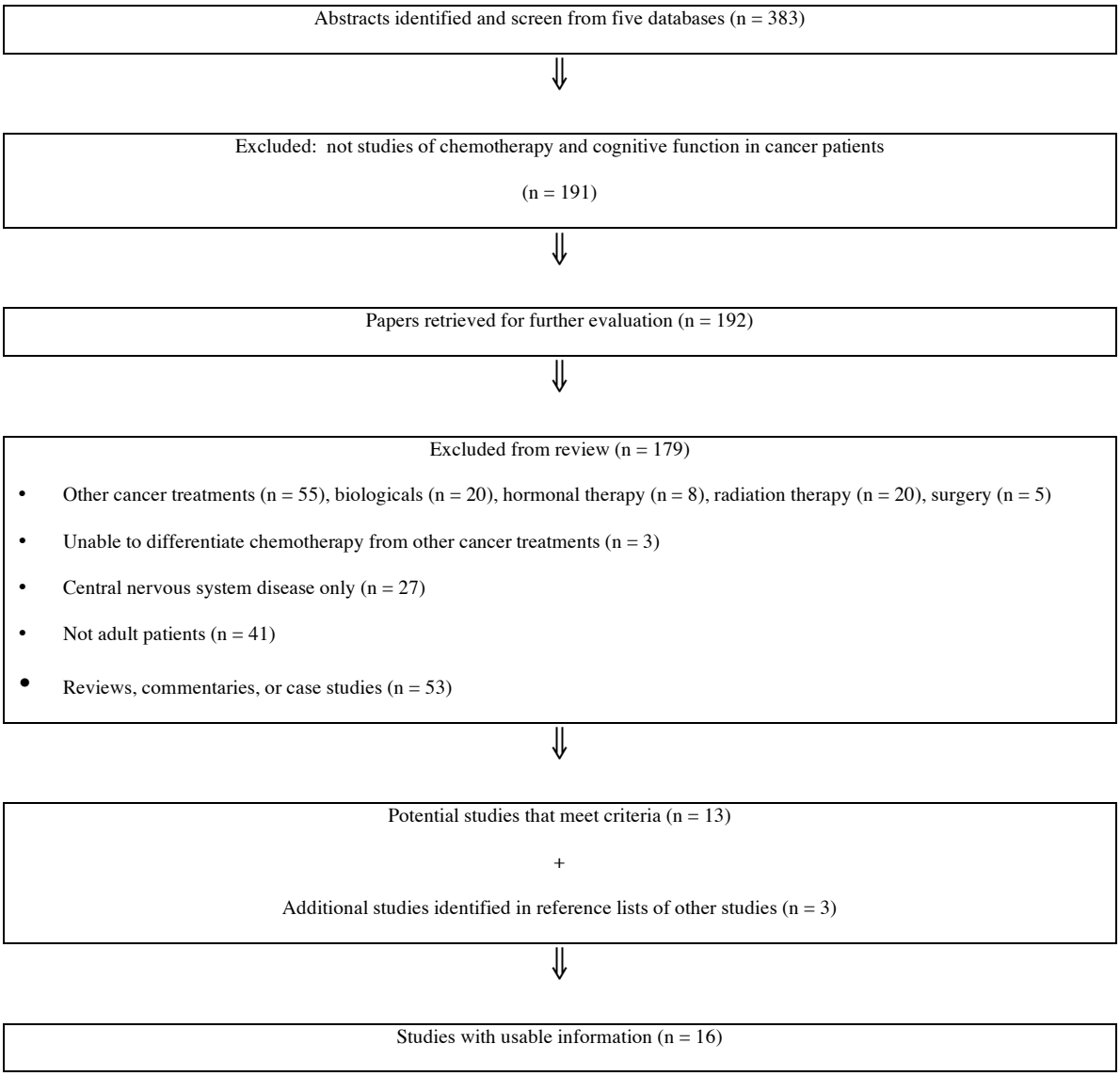
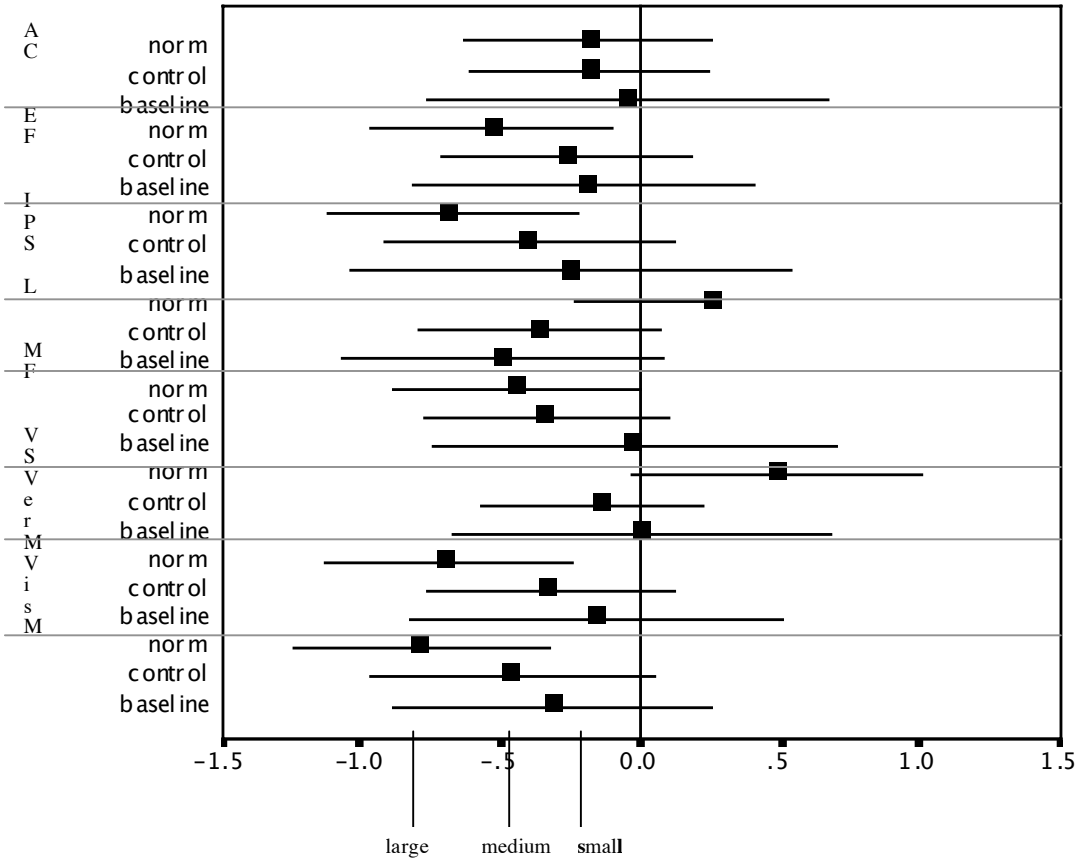


Figure 2

Effect Sizes For Each Domain Of Cognitive Function By Method Of Comparison (With 99% Confidence Interval)



Abbreviations: AC: attention and concentration; EF: executive function; IPS: information processing speed; L: language; MF: motor function; VS: visuospatial skill; VerM: verbal memory; VisM: visual memory

Chapter 4.

A Meta-Analysis of the Sensitivity of Various Neuropsychological Tests Used To Detect Chemotherapy-Induced Cognitive Impairments In Patients With Breast Cancer

Jansen, C. E., Miaskowski, C. A., Dodd, M. J., & Dowling, G. (2007).

Oncology Nursing Forum, 34(5).

Abstract

Purpose/Objectives: To identify which neuropsychological tests have been used to evaluate chemotherapy-induced impairment in various domains of cognitive function in breast cancer patients and to determine the sensitivity of each of these tests through the estimation of an effect size.

Data Sources: Original studies published from 1966-June 2006.

Data Synthesis: Although an array of neuropsychological tests is available to measure the various domains of cognitive function, information regarding the sensitivity and specificity of neuropsychological tests to detect changes in cognitive function from chemotherapy is lacking.

Methods: Thirteen original studies were found that reported sufficient information on neuropsychological testing of breast cancer patients who had or were currently receiving chemotherapy. Meta-analysis was used to calculate the effect sizes for the various neuropsychological testes used to measure attention and concentration, executive function, information processing speed, language, visuospatial skill, motor function, and memory.

Findings: While thirty neuropsychological tests were evaluated, only six tests were found to be sensitive in only four of the eight domains of cognitive function (i.e., language, motor function, visuospatial skill, and verbal memory).

Conclusion: This meta-analysis provides initial data on the sensitivity of some neuropsychological tests to determine chemotherapy-induced changes in cognitive function in patients with breast cancer.

Implications for Nursing/Interpretation: Nurses need to increase their knowledge of assessment for chemotherapy-induced cognitive impairments.

Introduction

Impairment in cognitive function as a side effect of chemotherapy (CTX), is a growing area of research as the numbers of cancer patients who complain of difficulties in their abilities to remember, think, and concentrate increases (Brezden, Phillips, Abdolell, Bunston, & Tannock, 2000; Cole, Scialla, & Bednarz, 2000; Cull et al., 1996). Impairment in cognitive function may adversely impact patients' return to normal life when treatment is completed. Survivors have complained about difficulties with multi-tasking at home and decreased performance at work. An increased awareness among cancer survivors and clinicians about this toxicity of CTX has resulted in a limited number of studies and points to the need for additional research on the acute and chronic effects of CTX on cognitive function.

An array of neuropsychological tests is available to measure the various domains of cognitive function. Numerous factors should be considered when selecting tests to measure each domain of cognitive function, including: 1) the specific cognitive domain to be measured; 2) the appropriateness of the test for the domain being studied; 3) the reliability and validity of the test and the availability of normative data for comparison; 4) the sensitivity and specificity of the test for a particular condition; 5) the availability of parallel forms when repeated measures are used; and 6) the feasibility of the instrument for clinical use (Lezak, Howieson, & Loring, 2004).

Although thirteen studies have evaluated CTX-induced cognitive impairments in patients with breast cancer (Ahles et al., 2002; Ahles, Tope, Furstenberg, Hann, & Mills, 1996; Bender et al., 2005; Brezden et al., 2000; Castellon et al., 2004; Donovan et al., 2005; Schagen et al., 1999; Scherwath et al., 2006; Shilling et al., 2005; Tchen et al.,

2003; van Dam et al., 1998; Wefel, Lenzi, Theriault, Davis, & Meyers, 2004; Wieneke & Dienst, 1995), often it is not clear how the specific neuropsychological tests used in these studies were chosen. Most studies state that tests were chosen for their ability to measure a specific domain, evidence of reliability and validity, availability of parallel forms for longitudinal studies, and/or feasibility. However, a great deal of variability exists in the tests that were chosen to measure various domains of cognitive function. In addition, discrepancies exist in which cognitive domain specific tests were purported to measure.

Specific information on the purpose, description, administration time, scoring, reliability, validity, normative data, and availability of parallel forms is readily available for most neuropsychological tests. However, information regarding the sensitivity and specificity of neuropsychological tests to detect changes in cognitive function from CTX is lacking. Lezak and colleagues (2004) defined sensitivity of a neuropsychological test as "the probability of correctly detecting abnormal functioning in an impaired individual" and specificity as "the probability of correctly identifying a normal individual or an individual from another clinical population intact with respect to the test under consideration (i.e., correct rejection of abnormality)".

Only one pilot study has evaluated the relative sensitivity of a number of neuropsychological tests to detect CTX-induced cognitive impairments in patients with cancer (Freeman & Broshek, 2002). Fifteen neuropsychological tests and subtests were chosen for evaluation based on their sensitivity to detect mild cognitive impairments in patients following a head injury. The sample in this cross-sectional study consisted of seventeen breast cancer patients, eight of whom were currently receiving standard-dose CTX and nine survivors who had completed standard-dose CTX treatment six to twelve

months earlier. The authors hypothesized that patients who were currently receiving CTX would have significantly poorer test scores than the survivors. Significant differences between the two groups were found for only two of the fifteen neuropsychological tests. However, the findings were not in the hypothesized direction for both of these tests. Patients undergoing active cancer treatment demonstrated poorer performance on the visual construction subtest of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), while survivors demonstrated poorer performance on the Stroop test. Since impairments in cognitive function have been found in survivors up to ten years following CTX (Ahles et al., 2002), a major limitation of this study was the use of a comparison group with potentially similar cognitive deficits to determine the sensitivity of the various neuropsychological tests. In addition, cognitive impairment was found in some patients at baseline, prior to the initiation of CTX (Shilling et al., 2005; Wefel et al., 2004). Another limitation of this study was the lack of baseline or pre-chemotherapy testing.

Another method that has been used to determine the sensitivity of neuropsychological tests is meta-analysis (Irwig et al., 1994; Zakzanis, 2001). Meta-analysis is a quantitative approach that is used to combine the results from several studies, with various sample sizes, in an attempt to determine an effect size for a specific intervention or procedure (Glass, 1976; Lipsey & Wilson, 2001). A benefit of this approach is that the pooling of findings across studies increases the power to detect significant effects if they exist. An effect size is defined as the standardized index of the magnitude of the difference, in the results across studies between the treatment and the comparison groups (Cohen, 1988). In addition, effect sizes provide information on the

direction of the relationship. Meta-analysis has been suggested as a potentially useful tool for assessing the diagnostic accuracy of tests (Irwig et al.).

Only one meta-analysis was found that evaluated the sensitivity of various neuropsychological tests to detect diffuse brain damage in multiple patient populations (Chouinard & Braun, 1993). The sample consisted of sixty-seven studies that used at least two neuropsychological tests to measure the same cognitive domain and provided evidence of a statistically significant difference in test scores between the clinical and control groups for at least one test.

Twenty-two neuropsychological tests were assigned to a specific domain of cognitive function (i.e., attention and concentration; problem solving; speed of information processing; motor abilities; complex visual perception; constructional abilities; memory; language; executive function). Tests were then ranked within each study, based on their ability to detect group differences. For tests that had several scores, only the score that found the greatest difference was used in the meta-analysis. Test rankings were then summed and divided by the total number of study comparisons to provide a mean proportional ranking. Rankings were done, so that smaller proportions indicated increased test sensitivity, and larger proportions indicated decreased sensitivity. Although this meta-analysis (Chouinard & Braun, 1993) found differences in the sensitivity of several neuropsychological tests within specific domains of cognitive function, an effect size was not calculated for each test. Since few studies provided means and standard deviations, the authors calculated z scores from the control group and used them to rank tests in terms of sensitivity. Therefore, the rankings may be biased because sample sizes were not accounted for in the calculations.

While the findings from this meta-analysis represent an initial first step in determining the sensitivity of various neuropsychological tests to detect changes in cognitive function, they are not readily transferable to patients who are receiving cancer CTX for several reasons. First, many of the neuropsychological tests used in studies of CTX-induced cognitive impairment were not included in this meta-analysis. In addition, the patient samples included in this meta-analysis were heterogeneous (e.g., normal aging, alcoholism, multiple sclerosis, Parkinson's disease, human immunodeficiency virus, Alzheimer's disease, schizophrenia) and did not include cancer patients. The focus of this meta-analysis was on patients with diffuse brain injury, which may induce changes in cognitive function by different mechanisms than cancer CTX and result in impairments in different domains of cognitive function.

Two meta-analyses have examined the nature and severity of the cognitive impairments induced by CTX in patients with breast cancer (Falletti et al., 2005; Stewart et al., 2006). Falleti's analysis (2005) consisted of six studies that used a total of fifty-five different neuropsychological tests to measure various domains of cognitive function. Tests were assigned to one of six cognitive domains (i.e., attention; memory; motor function; executive function; spatial ability; language). Negative effect sizes (i.e., CTX resulted in deficits in cognitive function), ranging from negligible to moderate, were found in each domain. Stewart's analysis (2006) consisted of seven studies that used a total of fifty-five neuropsychological tests or subtests. Tests were conceptually grouped into eight cognitive domains (i.e., simple attention; working memory; short-term memory; long-term memory; speed of information processing; language; spatial; motor abilities). Significant small negative effects sizes were found for every cognitive domain

except attention. Since the effect size for each neuropsychological test that was used to measure the various domains of cognitive function was not provided in either of these meta-analyses, it is not clear which tests were more sensitive to detect changes in cognitive function associated with cancer CTX. Therefore, the purposes of this meta-analysis were to identify which neuropsychological tests were used to evaluate CTX-induced impairment in various domains of cognitive function in patients with breast cancer and to determine the sensitivity of each of these tests, that were used in at least two studies, through an estimation of an effect size.

Methods

Literature Search and Selection of Studies

A preliminary search was done for original research reports, published in English, from 1966 to June 2006, on the association between CTX and cognitive impairments in patients with breast cancer. Five computerized databases were used: PubMed®, Psychinfo, CogNet, CINAHL, and the Cochrane Database of Systematic Reviews. Unpublished sources were not considered. Key words used for the search included: "breast cancer", "CTX", "cognitive impairment", "cognitive deficits", "cognitive function", "antineoplastic agents", and "neuropsychological tests".

While several articles were listed in more than one database, over 150 citations were obtained. Abstracts from all of these research studies were reviewed to determine if they met the following eligibility criteria: 1) original study data; 2) neuropsychological testing of patients with breast cancer who had or were currently receiving CTX; 3) valid and reliable neuropsychological tests with published standardized administration procedures; and 4) sufficient information reported (either by quantitative measurement or

inferential statistics) on at least one test of cognitive function, to allow for the estimation of an effect size. The following types of articles were excluded: reviews, commentaries, case reports, and meta-analyses.

Heterogeneous studies were excluded if they did not distinguish patients with breast cancer from other cancer diagnoses. The search was supplemented by a manual review of the bibliographies of each of the relevant studies and reviews. One additional study was found using this approach. Table 1 provides a summary of the thirteen studies that met all of the eligibility criteria and their sample characteristics. Although each study used numerous tests to measure cognitive function, some of these tests were not used in two or more studies or information was not available on a specific test to calculate an effect size. Only tests that were used in at least two studies were included in the meta-analyses and are listed in Table 2.

Classification of Tests by Cognitive Domain

Prior to determining the effect sizes for each of the neuropsychological tests, each of the neuropsychological tests was assigned to a specific cognitive domain. While in some of the studies, several neuropsychological tests were used to measure more than one domain of cognitive function, for the purposes of this meta-analysis, each test was assigned to a single domain to provide consistency in the evaluations. Although most of the domain assignments were done using neuropsychological assessment references (e.g., Lezak et al., 2004; Spreen & Strauss, 1998), some were made using the guidance of the meta-analyses of CTX-induced cognitive impairments in cancer patients (Anderson-Hanley, Sherman, Riggs, Agocha, & Compass, 2003; Falletti et al., 2005; Stewart et al., 2006).

Procedure

Johnson's (1993) DSTAT 1.10 meta-analysis software was used to calculate the standardized mean difference effect size (ES_{sm}) and the 95% confidence intervals. Since small studies can overestimate an effect size, the potential for bias was corrected by weighting the ES_{sm} for each test by the sample size and pooled variance (Hedges & Olkin, 1985). In addition, since some tests yielded several scores, an average effect size was calculated for that test (Lipsey & Wilson, 2001; Wolf, 1986). Effect sizes were calculated from the standardized mean differences using the means and standard deviations reported for each neuropsychological test result. Approximately 79% of the effect sizes (n = 131) were determined using means and standard deviations. When means and standard deviations were not available, effect sizes were calculated from other reported statistics, such as p values (11%, n = 18), or t-tests (10%, n = 17). Effect sizes were coded, so that positive scores indicated better cognitive function and negative scores indicated poorer cognitive function for each of the neuropsychological tests.

Results

Effect sizes are interpreted as negligible if they are less than 0.20, small if they are between 0.20 and 0.50, medium if they are between 0.50 and 0.80, and large if they are greater than 0.80 (Cohen, 1988). A significance level of 0.05 is inferred when the 95% confidence interval does not cross zero (Shadish & Haddock, 1994). A total of 166 effect sizes were calculated from test results in the 13 studies, that ranged from negligible to large. However, the averaged effect sizes for each test ranged from negligible to moderate and are summarized in Table 3.

Attention/concentration

Attention is a cognitive function of the brain that enables a person to triage relevant inputs, thoughts, and actions, while ignoring those that distract or are irrelevant (Gazzaniga, Ivry, & Mangun, 2002; Grober, 2002; Heilman, Valenstein, & Watson, 1997). Concentration is the ability to focus and sustain attention (Lezak et al., 2004). Four neuropsychological tests were used in at least two studies to measure CTX-induced impairments in attention and concentration (i.e., d2 test, High Sensitivity Cognitive Screen (HSCS) ~ attention subtest, Wechsler Adult Intelligence Scale (WAIS) ~ digit and spatial span subtests). While the digit span backwards test produced the largest effect size, none of the tests of attention and concentration produced significant effect sizes.

Executive function

Executive function refers to higher-order cognitive processes, which include initiation, planning, hypothesis generation, cognitive flexibility, decision-making, regulation, judgment, feedback utilization, and self-perception (Spreen & Strauss, 1998). Five neuropsychological tests were used in at least two studies to measure CTX-induced impairments in executive function (i.e., Booklet Categories Test, Trail Making Test (TMT)-Part B, HSCS-self regulation and planning subtest, Stroop Test, WAIS-similarities subtest). Although the Booklet Category test produced the largest effect size, none of the tests of executive function produced a significant effect size.

Information processing speed

Information processing speed refers to the brain's ability to rapidly process simple and complex information (Freeman & Broshek, 2002). Because the input of information may be tactile, auditory, verbal, or visual, this domain is inter-related with all of the other

domains of cognitive function and may have a direct influence on one's ability to store such information into memory. Six neuropsychological tests were used in at least two studies to measure CTX-induced impairments in information processing speed (i.e., Fepsy-binary choice, visual reaction, and visual searching subtests, Paced Auditory Serial Addition Test (PASAT), TMT-Part A, WAIS- digit symbol subtest). Although the largest effect size was found with the PASAT and the visual reaction test subtest of the Fepsy, none of the tests of information processing speed produced a significant effect size.

Language

Language incorporates both verbal and written communication when used to express thoughts. Impairments in language inhibit one's ability to communicate with others, or to follow directions without needing repetitions and explanations. Language processing involves representing, comprehending, and communicating symbolic information, either written or spoken (Gazzangia et al., 2002). Only two neuropsychological tests were used in at least two studies to measure CTX-induced impairments in language (i.e., HSCS-language subtest, Controlled Oral Word Association (COWA)). Only the language subtest of the HSCS produced a small, but significant effect size (-.43, $p = .05$).

Motor function

Motor function relates to motor performance, such as speed, strength, and coordination. Four neuropsychological tests were used in at least two studies to measure CTX-induced impairments in motor function (i.e., Fepsy finger tapping test, grooved pegboard, HSCS-psychomotor subtest, Halstein-Reitan Neuropsychological Battery

(HRNB) ~ finger tapping subtest). Significant effect sizes were found for two of the tests of motor function. The grooved pegboard produced a large effect size (-.90, p = .05) and the Fepsy finger tapping test produced a moderate effect size (-.60, p = .05).

Visuospatial skill

Visuospatial skill refers to the ability to process and interpret visual information regarding where things are situated in space (Spreen & Strauss, 1998). Three neuropsychological tests were used in at least two studies to measure CTX-induced impairments in visuospatial skill (i.e., HSCS-spatial subtest, Rey-Osterrieth Complex Figure Test (RCFT) ~ copy, WAIS- block design subtest). Significant effect sizes were found for two of the tests of visuospatial skill. Both tests produced a moderate effect size (RCFT ~ copy -.51, p = .05; block design subtest of the WAIS -.55, p = .05).

Verbal memory

Memory is an outcome of learning that is created and strengthened by repetition (Gazzangia et al., 2002). Memory infers the ability to acquire, store, and use new information (Grober, 2002). The most common types of memory are visual or verbal. Four neuropsychological tests were used in at least two studies to measure CTX-induced cognitive impairments in verbal memory (i.e., California Verbal Learning Test (CVLT), HSCS-memory subtest, Rey Auditory Verbal Learning Test (RAVLT), Wechsler Memory Scale (WMS) ~ logical memory test). Significant effect sizes were found for two tests of verbal memory. Only the memory subtest of the HSCS produced a small, but significant effect size (-45, p = .05).

Visual Memory

Two neuropsychological tests were used in at least two studies to measure CTX-induced impairments in visual memory (e.g., RCFT ~ delayed, WMS ~ visual reproduction subtest). Although the largest effect size was found with the delayed recall of the RCFT, neither of the tests of visual memory produced a significant effect size.

Discussion

This meta-analysis is the first to evaluate the sensitivity of several neuropsychological tests to detect impairments in various domains of cognitive function induced by cancer CTX in patients with breast cancer. Results of this meta-analysis demonstrate that only six neuropsychological tests were sensitive to CTX-induced impairment in four of the eight domains of cognitive function (i.e., language, motor function, visuospatial skill, and verbal memory). The most sensitive test was the grooved pegboard test, used to measure motor function. In addition, the Fepsy finger tapping test was found to be a sensitive measure in the same cognitive domain. Similarly, two tests used to measure visuospatial skill were found to be sensitive (i.e., RCFT ~ copy, block design subtest of WAIS). In contrast, only one neuropsychological test was found to be sensitive to detect impairments in language (i.e., language subtest of the HSCS) and verbal memory (i.e., memory subtest of the HSCS).

Although some of the specific neuropsychological tests that were identified as sensitive in this study differed from those identified in the Chouinard and Braun study (1993), both studies provide some evidence for tests sensitive to impairment in the cognitive domains of language, motor function, and visuospatial skill in patients with diffuse brain injury and in those who received cancer CTX. Although the mechanisms of

CTX-induced cognitive impairments remain to be determined, some of the cognitive impairments identified in patients with diffuse brain injury from congestive heart failure and chronic obstructive pulmonary disease are similar to those identified in patients with CTX-induced cognitive impairments (Raffa et al., 2006). Because these two meta-analyses identified different tests to measure most of these domains, one cannot determine if the tests that were found to be sensitive in the analysis by Chouinard and Braun (1993) might be sensitive enough to detect changes induced by CTX.

One limitation of this study was the exclusion of unpublished studies, that may have been published because of negative findings, which would result in an overestimation of the effect sizes reported in this analysis. Given the limited number of studies on the effects of cancer CTX on cognitive function in patients with breast cancer, the results of this meta-analysis need to be interpreted with caution. Most of the neuropsychological tests used in the studies done to date do not appear to be sensitive to detect changes in cognitive function. One explanation for the lack of significant findings is the relatively small number of patients studied to date, as well as the hetereogeneity of the study samples (e.g., various CTX regimens, patients undergoing active treatment, cancer survivors at variable times post treatment). Another equally plausible explanation is that CTX-induced changes in the various domains of cognitive function are time-dependent or acute or chronic in nature. The detection of time-dependent and/or acute versus chronic changes, while dependent on the sensitivity of the neuropsychological test, is more dependent on the timing of test administration. Another possibility that needs to be considered is that certain domains of cognitive function are not affected by cancer

CTX. Lastly, CTX-induced impairments in cognitive function may be so subtle that none of the currently used tests are sensitive enough to detect changes.

Conclusion

While this meta-analysis provides initial data on the sensitivity of some neuropsychological tests to determine CTX-induced changes in cognitive function in breast cancer patients, the limited number of studies makes it difficult to draw any definitive conclusions. Further investigation is needed to identify the instruments that are the most valid, reliable, sensitive, and specific for detecting CTX-induced cognitive impairments, whether they are short-term or persistent. In addition, carefully designed, longitudinal studies with baseline measurements are needed to evaluate this potentially deleterious and devastating consequence of cancer treatment. The identification of sensitive neuropsychological tests is crucial to further our understanding of CTX-induced cognitive impairments. Increased awareness of this side effect of CTX can guide nurses to monitor for its occurrence, as well as provide support to and advocate for patients.

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*Indicates articles included in the meta-analysis

Table 1

Characteristics of Studies Included In The Meta-Analysis

Study	Comparison (Total N)	Age (SD); Range	Staging/Chemotherapy (CTX) Treatment	Time since treatment (SD)
Ahles, 1996	Within subjects (20)	Not reported.	Staging not reported. High-dose CTX: 90% CTC 10% cyclophosphamide/cisplatin/carmustine	Prior to BMT, 1-3 days post BMT, 1 month post BMT)
Ahles, 2002	Control: patients treated with local therapy; Norms (70)	Survivors: 60.6 (10.5) Control: 59.1 (10.7)	Survivors: Staging: 37% Stage I; 54% Stage II; 3% Stage III; 3% Stage IV; 3% Regional Standard-dose CTX: 40% CMF 40% CAF 9% AC 6% CMF plus vincristine/prednisone 3% cyclophosphamide/carboplatin 2% other Control Group Staging: 20% Stage 0; 60% Stage I; 14% Stage II; 3% Stage III; 3% Unknown	Survivors: 9.4 (4.5) years Control: 9.9 (5.8) years
Bender, 2005	Within subjects; Control: patients with DCIS (46)	CTX only: 40.1 (6.5) CTX + HRT: 44.1 (3.5) Control: 44.5 (4.2)	CTX only: Staging: 32% Stage I; 68% Stage II Standard-dose CTX: 20% CMF 40% AC 40% AC plus a taxane CTX + HRT: Staging: 32% Stage I; 68% Stage II Standard-dose CTX: 25% doxorubicin and a taxane 33% AC 42% AC plus a taxane Control Group Staging: 100% DCIS	CTX only: Within a week and one year after CTX completed CTX + HRT: Within a week and one year after CTX completed

Table 1

Characteristics of Studies Included In The Meta-Analysis (cont.,)

Study	Comparison (Total N)	Age (SD); Range	Staging/Chemotherapy (CTX) Treatment	Time since treatment (SD)
Brezden, 2000	Control: healthy females (107)	Current CTX: median 49; 34-70 Survivors: median 46; 26-61 Control: median 41.5; 24-61	Current CTX Stage I or II (exact percentages not reported) Standard-dose CTX: 39% CMF 51% FEC Survivors Stage I or II (exact percentages not reported) Standard-dose CTX: 52.5% CMF 42.5% FEC 5% other	Current CTX: median 3 cycles CTX; range 2-8 cycles of CTX Survivors: median 25; range 12–36+ months
Castellon, 2004	Control: local tx (53)	Survivors: 46.8 (6.3) Control: 48.3 (4.0)	CTX Survivors Stage I or II (exact percentages not reported) Standard-dose CTX: 41% CMF 38% AC or doxorubicin added to CMF 9% AC plus a taxane	2-5 years after diagnosis, exact time since CTX not reported
Donovan, 2005	Control: local tx (143)	CTX Survivors: 52.3 (8.1) Control: 57.7 (9.1)	CTX Survivors: 18.3% Stage 0 or I, 81.7% Stage II Standard-dose CTX: 56.7% AC 16.7% AC plus paclitaxel 13.3% CMF 10% AC plus a docetaxel 3.3% doxorubicin and docetaxel Control: 95.2% Stage 0 or I, 4.8% Stage II	CTX survivors: 213.3 days after completion of XRT, exact time since CTX not reported
Schagen, 1999	Control: Stage I (73)	Survivors: 47.1 (6.5) Control: 46.1 (5.2)	Node positive (greater than stage I, exact staging not reported) Standard-dose CTX: CMF	Survivors: 1.9 (1.0) years Control: 2.4 (1.0) years

Table 1

Characteristics of Studies Included In The Meta-Analysis (cont.,)

Study	Comparison (Total N)	Age (SD); Range	Staging/Chemotherapy (CTX) Treatment	Time since treatment (SD)
Scherwath, 2006	Control: local tx only (76)	Standard dose ctx survivors: 51.8 (8.6) High dose ctx survivors: 53.3 (7.1) Control: 54.6 (8.0)	High risk, greater than 10 nodes positive (exact staging not reported) Standard-Dose CTX: EC followed by CMF High-Dose CTX: EC followed by CTM with stem cell support	Standard dose: 62.2 (22.7) months High dose: 61.6 (21.7)
Shilling, 2005	Within and Control: healthy females (93)	Survivors: 51.1 (8.6) Control: 52.3 (5.8)	Early Stage (exact staging not reported) Standard-dose CTX: 82% FEC 3% CMF 3% AC 12% FEC followed by docetaxel or additional FEC	4 weeks after final CTX treatment
Tchen, 2003	Control: healthy females (200)	Current CTX: median 48; 27-60 Control: median 47; 26-62	Staging not reported Standard-dose CTX: 64% FEC 11% CMF 17% AC 8% Other	36% after 3rd, 28% after 4th, 14% after 5th, 20% after 6th, and 2% after 7th cycle of CTX
Van Dam, 1998	Control: stage I patients (104)	Standard dose CTX: 48.1 (6.8) High dose CTX: 45.5 (6.2) Control: 46.1 (5.2)	Stage II Standard-dose CTX: FEC High-dose CTX: FEC followed by CTC	Standard-dose: 1.9 (1.1) years High-dose: 1.6 (0.8) years Control: 2.4 (1.0) years
Wefel, 2004	Within subjects (18)	45.4 (6.7); 34-63	28% Stage I and 72% Stage II Standard-dose CTX: CAF	Prior to CTX, 3 weeks and 1 year post CTX
Wieneke, 1995	Norms (28)	42 (6.7); 28-54	Stage I and II (% of each not reported) Standard-dose CTX: 57% CMF 29% CMF plus CAF 14% CAF	6.6 (4); 0.5-12 months

Abbreviations: AC = doxorubicin/cyclophosphamide; CAF = cyclophosphamide/doxorubicin/5-fluorouracil; CMF = cyclophosphamide/methotrexate/5-fluorouracil; CTC = cyclophosphamide/thiotepa/carboplatin; CTM = cyclophosphamide/thiotepa/mitoxantrone; EC = epirubicin/cyclophosphamide; FEC = cyclophosphamide/epirubicin/5-fluorouracil

Table 2

Neuropsychological Tests Included in the Meta-Analysis and Assignment to a Specific Domain

Neuropsychological Tests by Cognitive Domain	Assignment References
Attention	
d2 test	F, S
High Sensitivity Cognitive Screen (HSCS) ~ attention subtest	A
Wechsler Adult Intelligence Scale (WAIS) ~ digit span subtest	A, F, L, St
WAIS ~ spatial span subtest	A, L
Executive Function	
Booklet Category Test	F, L, S
HSCS ~ self regulation subtest	A
Stroop Test	A, F, S
Trail Making Test (TMT)-Part B	A, F, S
WAIS ~ similarities subtest	A, F, L
IPS	
Fepsy ~ binary choice subtest	St
Fepsy ~ visual reaction subtest	St
Fepsy ~ visual searching subtest	St
Paced Auditory Serial Addition Test	S
TMT-Part A	S
WAIS ~ digit symbol subtest	A, St
Language	
Controlled Oral Word Association	L, S, St
HSCS ~ language subtest	St
Motor Function	
Fepsy ~ finger tapping subtest	F, St
Grooved pegboard	A, F, L, S, St
Halstein-Reitan Neuropsychological Battery ~ finger tapping subtest	A, F, L, S, St
HSCS ~ psychomotor subtest	*
Visuospatial Skill	
HSCS ~ spatial subtest	A
Rey-Osterrieth Complex Figure Test (RCFT) ~ copy	A, F, L, S, St
WAIS ~ block design subtest	A, F, L, St

Table 2

Neuropsychological Tests Included in the Meta-Analysis and Assignment to a Specific Domain (cont.,)

Neuropsychological Tests by Cognitive Domain	Assignment References
<u>Verbal Memory</u>	
California Verbal Learning Test	A, F, L, S
HSCS ~ memory subtest	A
Rey Auditory Verbal Learning Test	A, F, L, S
Wechsler Memory Scale (WMS): logical memory subtest	A, F, L, S, St
<u>Visual Memory</u>	
RCFT ~ recall	A, F, L, S, St
WMS ~ visual reproduction subtest	F, L, S, St

Abbreviations: A = Anderson-Hanley et al., 2003; F = Falleti et al., 2005; L = Lezak et al., 2004; S = Spreen and Strauss, 1998; St = Stewart et al., 2006; * = not listed in any of the above references

Table 3

Effect Sizes For Neuropsychological Tests Used In Studies Of Chemotherapy-Induced Impairments

Tests	Number of Studies	Total Sample N	Effect size	LBCI	UBCI
Attention/Concentration					
d2 test	3	316	-0.399192	-0.898373	+0.100013
HSCS ~ attention subtest	2	343	-0.184726	-0.540761	+0.171310
WAIS ~ digit span subtest**	2	222	-0.348107	-0.78188	+0.072237
WAIS ~ digit span forward	4	340	-0.023283	-0.542055	+0.495490
WAIS ~ digit span backward	3	235	-0.448912	-0.961065	+0.063241
WAIS ~ spatial span subtest	2	188	+0.008552	-0.442101	+0.459204
Executive Function					
Booklet Category Test	2	46	-0.456752	-1.084876	+0.171314
HSCS ~ self regulation subtest	2	343	-0.258260	-0.615507	+0.008087
Stroop Test	4	357	-0.021877	-0.492703	+0.448949
TMT-Part B	9	567	-0.125702	-0.606911	+0.370226
WAIS ~ similarities subtest	2	46	+0.188273	-0.422259	+0.798805
Speed of Information Processing					
Fepsy ~ binary choice subtest	2	211	-0.105302	-0.573555	+0.362945
Fepsy ~ visual reaction	2	211	-0.501889	-0.978857	+0.160956
Fepsy ~ visual searching subtest	2	211	-0.055699	-0.523706	+0.412307
PASAT	2	81	-0.538267	-1.107843	+0.031309
TMT-Part A	8	547	-0.299549	-0.766981	+0.191314
WAIS ~ digit symbol subtest	7	523	-0.375823	-0.816644	+0.100617
Language					
COWA	8	557	-0.332899	-0.791787	+0.125989
HSCS ~ language subtest	2	343	**-0.434461**	**-0.816900**	**-0.096861**
Motor Function					
Fepsy ~ finger tapping test	2	211	**-0.599585**	**-1.078915**	**-0.120254**
Grooved pegboard	3	87	**-0.955051**	**-1.684365**	**-0.225752**
HRNB ~ finger tapping	2	213	+0.194945	-0.214320	+0.541522
HSCS ~ psychomotor subtest	2	343	-0.282503	-0.640663	+0.107783

Table 3

Effect Sizes For Neuropsychological Tests Used In Studies Of Chemotherapy-Induced Impairments (cont.,)

Tests	Number of Studies	Total Sample N	Effect size	LBCI	UBCI
<u>Visuospatial Skill</u>					
HSCS ~ spatial subtest	2	343	-0.114439	-0.470401	+0.177954
RCFT ~ copy	4	292	**-0.512445**	**-1.017514**	**-0.007376**
WAIS ~ block design subtest	4	169	**-0.554656**	**-1.106400**	**-0.002912**
<u>Verbal Memory</u>					
CVLT	4	216	-0.409361	-0.883348	+0.065488
HSCS ~ memory subtest	2	343	**-0.453015**	**-0.813005**	**-0.093025**
RAVLT	4	328	-0.269487	-0.750206	+0.211232
WMS ~ logical memory	3	216	-0.409361	-0.883348	+0.344564
<u>Visual Memory</u>					
RCFT ~ recall	7	514	-0.373973	-0.886677	+0.138735
WMS ~ visual reproduction	4	339	-0.194879	-0.625094	+0.235345
<u>Visuospatial Skill</u>					
HSCS ~ spatial subtest	2	343	-0.114439	-0.470401	+0.177954
RCFT ~ copy	4	292	**-0.512445**	**-1.017514**	**-0.007376**
WAIS ~ block design subtest	4	169	**-0.554656**	**-1.106400**	**-0.002912**
<u>Verbal Memory</u>					
CVLT	4	216	-0.409361	-0.883348	+0.065488
HSCS ~ memory subtest	2	343	**-0.453015**	**-0.813005**	**-0.093025**
RAVLT	4	328	-0.269487	-0.750206	+0.211232

*****Values that are **bolded** indicate significant effect sizes (p = .05)

Abbreviations: COWA = Controlled Oral Word Association; CVLT = California Verbal Learning Test; HSCS = High Sensitivity Cognitive Scale; HRNB = Halstead-Reitan Neuropsychological Test Battery; LBCI = lower 95% confidence interval; RAVLT = Ray Auditory Verbal Learning Test; RCFT = Rey-Osterrieth Complex Figure Test; TMT- Trail Making Test; UBCI = upper 95% confidence interval; WAIS = Wechsler Adult Intelligence Scale; WMS = Wechsler Memory Scale

Chapter 5.

Changes in Cognitive Function in Breast Cancer Patients Undergoing Chemotherapy

Poster presentation at the Oncology Nursing Society's 9th National Conference on Cancer Nursing Research, Hollywood, CA, February 2007.

To be submitted to: CANCER

Abstract

Background: Recent studies suggest that standard dose chemotherapy (CTX) for breast cancer may cross the blood-brain barrier. However, the evidence for CTX-induced cognitive impairments in breast cancer patients is inconsistent. The purposes of this study in a sample of newly diagnosed patients with breast cancer were: (1) to evaluate cognitive function prior to the administration of CTX; (2) to assess changes in cognitive function over time; and (3) to evaluate potential relationships between cognitive function and anxiety, depression, fatigue, hemoglobin level, menopausal status, and perception of cognitive function.

Methods: Thirty women with breast cancer completed neuropsychological testing before the initiation of CTX and after four cycles of doxorubicin and cyclophosphamide. Descriptive statistics were used to summarize sample characteristics and paired t-tests to evaluate for changes in neuropsychological test scores prior to and following completion of CTX. Linear mixed models were used to determine whether significant changes in neuropsychological test scores remained after controlling for anxiety, depression, fatigue, hemoglobin level, menopausal status and perceived cognitive function.

Results: Significant decreases in visuospatial skill ($p < .001$) and total cognitive scores ($p = .001$) were found following CTX. In addition significant improvement was found in executive function ($p = .014$). Of note, these changes remained significant even after controlling for anxiety, depression, fatigue, hemoglobin level, menopausal status and perceived cognitive function.

Conclusion: Data from this study supported the hypothesis that CTX may have a negative impact on select domains of cognitive function.

Introduction

Chemotherapy (CTX) is an essential component of breast cancer treatment because it contributes to significantly increased survival rates (Jemal et al., 2007). In the past, CTX was thought not to cross the blood-brain barrier when given in standard doses. However, two recent meta-analyses of CTX-induced cognitive impairments in women with breast cancer found small, albeit significant, effect sizes for all cognitive domains except attention (Falleti, Sanfilippo, Maruff, Weih, & Phillips, 2005; Stewart, Bielajew, Colins, Parkinson, & Tomiak, 2006). In our review of CTX-induced cognitive impairments in women with breast cancer (Jansen, Miaskowski, Dodd, & Dowling, 2005), deficits were reported most frequently in information processing speed (83%), then motor function (71%), visual memory (67%), language (50%), attention and concentration (43%), executive function (43%), verbal memory (43%) and visuospatial skill (29%).

Definitive conclusions about the effects of CTX on cognitive function cannot be made at the present time, because the studies included in the two meta-analyses (as well as in our review) with one exception (Wefel, Lenzi, Theriault, Davis, & Meyers, 2004) used cross-sectional designs. Since these studies lacked any measures of cognitive function prior to CTX, it is difficult to determine the impact of CTX on cognitive function.

In 2004, Wefel et al. conducted the first longitudinal study of cognitive function in women (n = 18) receiving CTX for breast cancer. Cognitive impairments were identified in 35% of the women prior to the initiation of CTX. Most women had stable or improved cognitive function a year after CTX completion. Although differences in mean

scores over time were not found, within subject analyses revealed that 61% of the women had some degree of cognitive impairment at three weeks post CTX in the cognitive domains of executive function, information processing speed, visuospatial skills, as well as verbal and visual memory.

Findings from subsequent longitudinal studies of cognitive function in women with breast cancer (Bender et al., 2006; Hermelink et al., 2007; Hurria et al., 2006; Jenkins et al., 2006) have been inconsistent. Only one study (Hurria et al.) evaluated women for cognitive impairments prior to the initiation of CTX and found deficits in three patients (11%). In another study (Bender et al.), cognitive impairments in both verbal and visual memory were found in women who received both CTX and hormonal therapy, but only in verbal memory in those who received just CTX. Most of these changes were found one year after the completion of CTX. However, two studies (Hermenlink et al; Jenkins et al.) have shown no differences in cognitive function over time.

In summary, only five longitudinal studies have evaluated the effects of CTX on cognitive function in women with breast cancer. Results from two of these studies (Hurria et al., 2006; Wefel et al., 2004) suggest that some women experience impairments in cognitive function prior to the initiation of CTX. Interpretation of findings regarding CTX-induced cognitive impairments are complicated by the lack of consistency in the timing of the measures, the CTX regimens used, and neuropsychological measures employed. Most of these studies are limited by small sample sizes, the inclusion of multiple CTX regimens, concurrent use of hormonal therapy, and significant attrition over time. Therefore, ascertaining whether deficits might

be limited to a specific period of time after CTX versus associated with a specific CTX regimen or the use of hormonal therapy is difficult.

In addition to CTX, a number of other factors may be protective against cognitive impairments or place individuals at a higher risk for impairments in cognitive function. These factors include concomitant effects of breast cancer and its treatment (e.g., medications, fatigue, depression, anxiety); indirect and direct effects of CTX (e.g., CTX-induced anemia or menopause); as well as individual patient factors (e.g., age, intelligence level, educational level, menopausal status) (Jansen, Miaskowski, Dodd, Dowling, & Kramer, 2005).

Few of the longitudinal studies mentioned earlier evaluated the relationships between cognitive tests and depression (Bender et al., Hermenlink et al., 2007; Hurria et al., 2006; Wefel et al., 2004), anxiety (Bender et al., Hermenlink et al.; Wefel et al.), menopausal status (Bender et al., Hermelink et al., Jenkins et al.), perception of cognitive function (Bender et al., Hermenlink et al.; Jenkins et al.), or fatigue (Bender et al., Jenkins et al.). Of note, none of these studies found significant correlations between any of these factors and cognitive function.

The purposes of this study in a sample of newly diagnosed patients with breast cancer were: (1) to evaluate cognitive function prior to the administration of CTX; (2) to assess changes in cognitive function over time; and (3) to evaluate potential relationships between cognitive function and anxiety, depression, fatigue, hemoglobin level, menopausal status, and perception of cognitive function.

Methods

Study Design, Sample, and Setting

This study used a prospective, longitudinal design to describe changes in cognitive function in women with breast cancer who received a doxorubicin and cyclophosphamide (AC) CTX regimen. Women were recruited from two outpatient oncology clinics of a large Health Maintenance Organization (HMO) in the San Francisco Bay Area. Women who were diagnosed with early-stage breast cancer (i.e., stage I and II) were asked to participate if they were: between 18 and 65 years of age; scheduled to receive AC; and able to read, write, and understand English. Patients were excluded if they had any of the following: a history of head injury with loss of consciousness; evidence of delirium; moderate or severe dementia; aphasia; a previously-diagnosed psychiatric illness; alcohol or drug abuse; central nervous system disease; a previous malignancy; and/or previous exposure to CTX.

Instruments

Demographic and Clinical Characteristics

The Clinical Data Form was used to examine the medical records of patients for inclusion and exclusion criteria, as well as for information on age, tumor type, surgical procedure, nodal status, current medications, hemoglobin level, and treatment plan. The Patient Demographic Questionnaire obtained information on age, ethnicity, marital status, education, employment status, and menopausal status.

Measures of Cognitive Function

The Repeatable Battery of Adult Neuropsychological Status (RBANS, Randolph, 1998) is a neuropsychological screening battery that can detect mild impairments in

cognitive function. It consists of twelve subtests that yield five index scores for immediate memory, visuospatial skill, language, attention, and delayed memory as well as a total score for cognitive function. Higher scores indicate better cognitive function. The RBANS was chosen for this study because of its brevity, ease of administration, and availability of an alternate, equivalent version in order to minimize practice effects during follow-up testing. The test is valid and reliable in individuals between 20 and 89 years of age (Randolph, 1998). In this study, the Cronbach's alpha for the RBANS was 0.88.

The Stroop Test measures executive function by requiring participants to inhibit habitual patterns of responding and attending to atypical stimuli (Stroop, 1935). The Stroop Test consists of three parts. In Part A, the participant is asked to read five columns of 20 color words that are printed in black ink. In Part B, the participant is asked to name the color of the Xs that are printed in red, green, or blue ink. Part C requires the participant to name the ink color that words are printed in, which is different from the actual color of the word that is printed. Scores are based on the participant's age and educational level, with higher scores indicating better executive functioning. The Stroop Test has extensive support for its validity and reliability (Golden & Freshwater, 2002). In the present study, the Cronbach's alpha for the Stroop Test was 0.80.

The Grooved Pegboard (Klove, 1963) is a timed activity that evaluates motor function. The pegboard consists of five columns with five slotted holes angled in different directions. Participants are instructed to pick up 25 small, key-shaped metal pegs with the dominant hand and insert them into matching keyholes. The exercise is then repeated with the non-dominant hand. Normative data are based on age, with lower scores indicating better motor function. The instrument has sufficient reliability and

validity for manual dexterity and visual-motor coordination (Lafayette Instrument Company, 2002). In the present study, the Cronbach's alpha for the Grooved Pegboard was 0.80.

Measures of Potential Covariates

The Attentional Function Index (AFI, Cimprich, 1992) is a 16-item instrument that measures directed attention and is used to assess cognitive distress. In addition, it measures perceived effectiveness of cognitive functioning in daily life activities. Higher scores indicate better attentional function. The AFI has established validity and internal consistency reliability coefficients (Cimprich, 1992; Cimprich, 1999). In the present study, the Cronbach's alpha for the AFI was 0.91.

The Center for Epidemiological Studies-Depression Scale (CES-D) is a 20-item questionnaire that was used to measure the presence of depressive symptoms (Radloff, 1977). Individual items are rated on a 4-point Likert scale that ranges from zero to three. Total scores can range from 0 to 60, with higher scores indicating more depressive symptoms. The CES-D has well-established validity and reliability coefficients (Radloff, 1977). In the present study, the Cronbach's alpha for the CES-D was 0.80.

The State-Trait Anxiety Inventory (STAI) state subscale is a 20-item instrument that was used to measure current levels of anxiety (Speilberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983). Items are rated is a 4-point Likert scale that ranges from one to four. Total scores can range from 20 to 80, with higher scores indicating higher levels of anxiety. The STAI has well established validity and reliability (Speilberger et al., 1983). In the present study, the Cronbach's alpha for the STAI state subscale was 0.92.

The 18-item Lee Fatigue Scale (LFS) was used to measure current fatigue severity

(Lee, Hicks, & Nino-Murcia, 1991). Items are rated on a Likert scale that ranges from zero to ten. A fatigue severity score is calculated from the mean of 13 items with higher scores indicating higher levels of fatigue severity. The LFS has established validity and reliability. In the present study, the Cronbach's alpha for the LFS was 0.80.

Study Procedures

The medical records of newly diagnosed breast cancer patients who were scheduled to see a medical oncologist, were screened for initial eligibility. The medical oncologist initiated a conversation with the patient about the study. If the woman agreed to participate, an investigator explained the study procedures and obtained written informed consent.

Patients underwent neuropsychological testing and completed self-assessment questionnaires at baseline (prior to the start of CTX) and approximately one week after the completion of four cycles of AC. Patients completed the neuropsychological measures and study questionnaires in an office in the outpatient setting or at home if they preferred. The average time for battery administration was sixty minutes. All of the assessments and questionnaires were administered in a set order and were conducted by the same investigator.

Data Analysis

Raw scores for the neuropsychological tests were converted into standardized scores, using published normative data. Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 13. Descriptive statistics and frequency distributions were generated for demographic, disease, and treatment characteristics. Paired t-tests were used to evaluate for differences in cognitive function from baseline to

one week after four cycles of AC. Differences were considered statistically significant at a p value of less than 0.05.

In addition, each individual's baseline level of cognitive function (prior to CTX administration) was compared with normative data for each neuropsychological test. Consistent with other studies (Hermenlink et al., 2007; Wefel et al., 2004) cognitive impairment was defined as a score of 1.5 standard deviations (SDs) below published norms on two or more tests, or two SDs on one test, prior to receiving CTX. In the subsequent measurement, cognitive impairment was defined as a decrease of one or more SDs on two or more tests. Linear mixed models was used to evaluate the effects of CTX on cognitive function over time. Anxiety, depression, fatigue, hemoglobin levels, menopausal status, and patient's perception of cognitive function were controlled as time-dependent covariates across all cognitive function measures.

Results

Sample Characteristics

Between November 2005 and November 2006, 39 women with early-stage breast cancer were identified who met the study's initial eligibility criteria. The most common reasons for ineligibility were age over 65 years, a different CTX regimen, and inadequate knowledge of the English language.

Thirty-nine women were approached for this study before the initiation of CTX. Seven women (18%) declined to participate because they were uninterested or too busy. Thirty-two women consented to participate. At the time of the second testing, one patient declined further participation and another had died, resulting in a 6% dropout rate. The disease and treatment characteristics of the patients who completed testing at both time

periods are listed in Table 1. Although one woman decided to stop CTX after three cycles of AC, the rest of the sample completed four cycles of AC. None of the women were taking hormonal therapy.

The demographics of this multicultural sample are listed in Table 2. The majority of the sample was well-educated, married, and working full time. Although patients who were on antidepressants prior to CTX were excluded from the study, 3 (10%) of the women started taking antidepressants by the time of the second assessment.

Cognitive function measures

Published normative data, adjusted for age and/or education, were used to convert raw neuropsychological test scores into standardized scores. Neuropsychological test scores at baseline and post CTX are presented in Table 3. At baseline, the mean scores for all of the cognitive measures were within normal limits. However, based on our pre-established scoring criteria, three women (10%) were classified as having cognitive impairments prior to CTX. Two women (7%) had visuospatial skill impairment and one woman (3%) had both immediate memory and language impairments.

After the completion of CTX, only mean visuospatial skill ($p \leq 0.001$) and total cognitive scores ($p = .002$) decreased over time. In contrast, mean executive function ($p = .014$) scores improved over time.

On an individual basis, eleven women (37%) had a decrease of one or more SDs for two or more tests after CTX. Decreased scores of at least one SD were found most often in visuospatial skills (40%), followed by motor function (17%), immediate memory (13%), language (13%), delayed memory (10%), attention (7%) and total cognitive score

(7%). Of the three women who had cognitive impairment prior to CTX, none had further declines in cognitive function after the completion of CTX.

Potential covariates

Table 4 provides a summary of the changes over time in patients' ratings of anxiety, depression, fatigue, and perceptions of cognitive function. Prior to CTX, mean scores on these inventories suggest that women were anxious, but generally not depressed or fatigued, and had high levels of perceived cognitive functioning.

After the completion of AC, significant increases were found in depression ($p < 0.001$) and fatigue ($p < 0.001$) scores, and significant decreases were found in perceived cognitive function ($p = 0.003$) and hemoglobin level ($p < 0.001$). Regardless of these changes, after controlling for anxiety, depression, fatigue, hemoglobin level, and perceived cognitive function, the declines in visuospatial skill and total cognitive scores remained significant. Of note, women who were pre- or peri-menopausal had a greater decline in visuospatial test scores ($t = 2.081$, $p = 0.047$) than women who were post-menopausal.

Discussion

This prospective, longitudinal study was initiated to evaluate the effect of CTX on various domains of cognitive function in women with breast cancer. To control for the potential effects of CTX regimens, women who were to receive only AC were included in the study, compared with two to four regimens in previously published longitudinal studies (Bender et al., 2006; Hermelink et al., 2007; Hurria et al., 2006; Jenkins et al., 2006; Wefel et al., 2004). Cognitive impairment was found in 10% of women prior to the initiation of CTX. This finding is consistent with those of Hurria et al. (2006) in

older women, but considerably less than the 32% and 33% found in other longitudinal studies (Hermelink et al., 2007; Wefel et al., 2004). Although comparable in age, our sample was more highly educated than previous studies, which may have been protective against cognitive impairments.

Women in this study experienced cognitive impairments in visuospatial skill and total cognitive scores. Deficits in visuospatial skill impact a woman's ability to process and interpret visual information and are manifested by diminished ability to perform manual tasks. These results contrast with previous studies (Bender et al., 2006; Hermelink et al., 2007; Jenkins et al., 2006; Wefel et al., 2004) that found no differences within a similar time frame (one to four weeks after CTX completion). In addition, women who were pre- or peri-menopausal had a greater decline in visuospatial skill compared to postmenopausal women. AC CTX is known to adversely affect ovarian function by decreasing estrogen levels. However estrogen deficiencies are most often associated with verbal memory and not with visuospatial skill. Therefore, the implication of this difference between pre- or peri-menopausal and postmenopausal women is unclear.

The decreases in cognitive function found in this study may be due in part to the fact that the RBANS is more sensitive than other neuropsychological tests to detect subtle changes in cognitive function after CTX. Another advantage of the neuropsychological battery and subjective tests used in this study was that administration time was approximately one hour, which was considerably less than the two hours required in other studies. The decrease in time may have reduced patient fatigue and produced more reliable results.

Consistent with other longitudinal studies (Bender et al., 2006; Hermelink et al., 2007; Jenkins et al., 2006), no significant correlations were found between subjective perceptions of cognitive function and objective neuropsychological measures. However, similar to these studies (Bender et al.; Hermelink et al.; Jenkins et al.), a significant correlation was found between perceived cognitive function and depression.

Comparable to one study (Wefel et al., 2004), we found that 37% of women experienced a decline in a variety of cognitive domains after the completion of CTX. The most-commonly affected domains were visuospatial skill, motor function, immediate memory and language. Additional research is warranted to identify the risk factors in these women that contributed to the decrease in cognitive function.

Limitations of our study include small sample size, the use of a convenience sample, and the lack of a control group. Although the use of a convenience sample is the most common method to obtain participants, the ability to obtain a representative sample is often a problem (Polit & Hungler, 1999). The use of a control group would help identify differential practice effects. However, an advantage of our study was the low attrition rate of only 6%, which was consistent with two studies (Hermelink et al., 2007; Hurria et al., 2006), but considerably less than the 29% found in another (Bender et al., 2006) at a similar period of time.

Summary

This study provides some preliminary insights into the prevalence of potential covariates for CTX-induced cognitive impairments in women who receive AC for breast cancer. Although these women did not experience significant changes in most of the domains of cognitive function, significant group mean declines did occur in visuospatial

skill and total cognitive scores. These cognitive changes persisted even after controlling for changes in anxiety, depression, fatigue, hemoglobin levels and perceived cognitive function. Although profound cognitive impairments were not found in other cognitive domains a subset of women demonstrated a decline in other domains after treatment with AC.

Patients report experiencing cognitive changes during the immediate treatment experience as well as during their return to normal life after the completion of CTX. Additional longitudinal studies are needed to determine the characteristics of CTX-induced impairment (e.g. prevalence, onset, duration) with homogenous cancer populations and with longer follow-up. In addition, the relationship between cognitive function and sudden premature menopause needs to be evaluated. Future research needs to determine the potential risk factors for CTX-induced impairments in cognitive function so that prevention trials may be initiated.

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Table 1

Disease and Treatment Characteristics

Variable	N	Percentage
Ductal carcinoma		
Yes	27	90.0
No	3	10.0
Estrogen receptor positive		
Yes	19	63.3
No	11	36.7
Progesterone receptor positive		
Yes	16	53.3
No	14	46.7
Her2neu status		
Positive	8	26.7
Negative	15	50.0
Weak/equivocal	7	23.3
Positive lymph nodes		
Yes	12	40.0
No	15	50.0
Unknown	3	10.0

Table 2

Patient Characteristics

Variable	N	Mean	SD
Age (years)	30	49.6	9.0
Education (years)	30	15.7	3.2
Marital status		Percentage	
Single	7	23.3	
Married/partnered	15	50.0	
Divorced	8	26.7	
Ethnicity			
Caucasian	13	43.3	
Asian/Pacific Islander	11	36.7	
African-American	3	10.0	
Hispanic	2	6.7	
Other	1	3.3	
Employment status			
Full time	17	56.7	
Part time	5	16.7	
Disabled	7	23.3	
Retired	1	3.3	
Menopausal status			
Pre-menopausal	15	50.0	
Peri-menopausal	4	13.3	
Post-menopausal	11	36.7	

Table 3

Changes Over Time in Neuropsychological Test Scores

	Baseline		Post-treatment		
Test	Mean ± SD	Range	Mean ± SD	Range	Test and statistical significance*
RBANS 1 ~ immediate memory	103.2 ± 13.9	65.0 – 123.0	105.3 ± 16.7	73.0 – 136.0	t = -.755; p = .456
RBANS 2 ~ visuospatial skill	94.8 ± 14.9	69.0 – 126.0	84.5 ± 16.4	60.0 – 116.0	t = 4.566; p = .000*
RBANS 3 ~ language	97.3 ± 15.0	60.0 – 127.0	94.2 ± 15.0	57.0 – 118.0	t = 1.708; p = .098
RBANS 4 ~ attention	104.6 ± 15.0	79.0 – 135.0	103.2 ± 14.9	72.0 – 132.0	t = 1.784; p = .440
RBANS 5 ~ delayed memory	102.6 ± 10.6	78.0 – 126.0	100.9 ± 9.0	75.0 – 118.0	t = .987; p = .332
RBANS tot ~ total scale	100.9 ± 15.1	72.0 – 139.0	96.5 ± 14.2	68.0 – 128.0	t = 3.523; p = .001*
Stroop ~ interference (executive function)	47.9 ± 8.2	32.0 – 65.0	50.5 ± 9.0	33.0 – 74.0	t = -2.616; p = .014*
Grooved pegboard					
dominant	69.0 ± 10.2	53.3 - 92.6	67.9 ± 13.4	46.8 - 98.1	t = .671; p = .508
non-dominant	75.8 ± 15.3	52.9 - 115.7	72.0 ±16.9	47.8 - 121.8	t = 1.928; p = .064

* Indicates significance ($p \leq 0.05$)

Abbreviations: RBANS = Repeatable Battery for Adult Neuropsychological Status; tot = total

Table 4

Changes Over Time In Measures of Potential Covariates

	Baseline		Post-Treatment		
Test	Mean ± SD	Range	Mean ± SD	Range	Test and statistical significance
State Trait Anxiety Inventory ~ state subscale	33.0 ± 8.9	20.0 – 49.0	32.5 ± 10.9	20.0 – 53.0	t = .320; p = .751
Center for Epidemiological Studies-Depression	12.9 ± 6.6	4.0 – 30.0	18.1 ± 7.9	4.0 – 35.0	t = -4.220; p = .000*
Lee Fatigue Scale - Fatigue	2.3 ± 1.8	0.0 - 6.5	4.1 ± 1.8	0.0 - 6.9	t = -4.963; p = .000*
Attentional Function Index	7.0 ± 1.4	3.4 - 9.8	6.2 ± 1.4	3.9 - 9.9	t = 3.296; p = .003*
Hemoglobin level	13.4 ± 1.1	11.2 – 15.8	11.9 ± 1.0	9.3 – 13.6	t = 6.686 ; p = .000*

*Indicates significance ($p \leq 0.05$)

SUMMARY

CTX-induced cognitive impairments have the potential to adversely impact patients' return to normal life after treatment completion. Therefore, CTX-induced deficits in cognitive function are of increasing interest to the growing numbers of cancer survivors. This research project revealed that although data from published studies suggest that CTX-induced impairments in cognitive function do occur in some women with breast cancer, differences in time since treatment, CTX regimen, menopausal status, and neuropsychological tests used limit comparisons among the various studies.

Our meta-analysis of the effects of cancer CTX on various domains of cognitive function in cancer patients revealed only one domain of cognitive function (i.e., visual memory) had significant CTX-induced impairment across all comparison types (i.e., normative data, control groups, patients' baseline). However, when the neuropsychologic test scores of CTX patients were compared with normative data, significant effect sizes were found for four domains of cognitive function (i.e., executive function, information processing speed, verbal memory, visual memory). In addition, significant, albeit small, effect sizes were found for language and verbal memory when CTX patients' test scores were compared with test scores of healthy matched controls. All significant averaged effect sizes were in the negative direction, indicating that mean scores on neuropsychological tests for patients who had received CTX were on average lower than comparison scores.

When only breast cancer patients were evaluated in the meta-analysis, similar results (i.e., effect size, significance) were found for all cognitive domains, with one exception. A small significant negative effect size was found for language, which

remained even when the sample that received high-dose CTX was excluded. However, when only breast cancer patients who received a standard-dose of CTX were evaluated, the small negative effect size for visual memory became nonsignificant.

We determined the sensitivity of neuropsychological tests that have been used to evaluate CTX-induced impairment in various domains of cognitive function in breast cancer patients. While thirty neuropsychological tests were evaluated, only six tests (i.e., block design subtest of the Wechsler Adult Intelligence Scale, grooved pegboard, Fepsy finger tapping test, language and memory subtests of High Sensitivity Cognitive Screen, Rey-Osterrieth Complex Figure Test) were found to be sensitive in only four of the eight domains of cognitive function (i.e., language, motor function, visuospatial skill, and verbal memory).

While evidence of CTX-induced impairments in cognitive function exists, clinical studies attempting to elucidate the mechanisms for chemotherapy-induced impairments in cognitive function are lacking. From our review of the current evidence on the domains of cognitive function and their corresponding neuroanatomic structures, neurotoxicity associated with specific chemotherapeutic agents as well potential mechanisms we proposed potential contributing factors for CTX-induced impairments in cognitive function. We included as many of the concomitant, direct and indirect effects of CTX, and patient factors (i.e., anemia, anxiety, depression, fatigue, menopause) proposed in our model as was possible in our study.

This research project found cognitive impairments in 10% of women with breast cancer prior to the initiation of CTX. Although this was considerably less than what was seen in Wefel's (2004) study, it confirms that some women have cognitive impairments

prior to the starting treatment. We demonstrated that some women who receive AC for breast cancer do experience cognitive impairments. Significant declines in group mean scores were found in visuospatial skill and total cognitive scores, even after controlling for anxiety, depression, fatigue, hemoglobin levels, menopausal status and perceived cognitive function. In addition, in a subset of women who received AC for breast cancer, cognitive deficits were found in motor function, immediate memory, language, delayed memory and attention.

In conclusion, the study provided significant insights into cognitive impairments in women who receive CTX for breast cancer. It revealed methodological and conceptual issues that hinder the comparison of current studies in the literature. Additionally, it identified potential mechanisms of CTX-induced cognitive impairments as well as individual patient factors that may be protective or place women at a higher risk for changes in cognitive function. Our study was the first to identify neuropsychological tests that may be more sensitive in evaluating cognitive changes in women with breast cancer who receive CTX.

Knowledge is still limited about cognitive impairments in women who receive CTX for breast cancer. However, our findings suggest that regardless of potential covariates, cognitive impairments occur in breast cancer patients receiving AC CTX. Additional longitudinal studies are necessary to determine the characteristics of CTX-induced impairment (e.g. prevalence, onset, duration) with homogenous cancer populations. There is also a further need to evaluate homogenous regimens to determine the differential effects of individual drug regimens on cognitive function. Further research needs to further evaluate the most sensitive and appropriate neuropsychological

tests to determine cognitive changes in this population as well as develop animal models to examine the underlying mechanisms for these changes.

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