Chemotherapy-Related Change in Cognitive Function: A Conceptual Model

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Purpose/Objectives: To develop a conceptual model of chemotherapy-related changes in cognitive function.

Data Sources: MEDLINE®, CINAHL®, HealthStar, and PsycINFO® databases.

Data Synthesis: Patients undergoing chemotherapy often complain of forgetfulness, absentmindedness, and an inability to focus when performing a variety of daily tasks. Changes in cognitive function have been referred to by the colloquial term "chemo-brain." The authors conducted an examination of the literature to investigate relationships among concepts and to synthesize current knowledge.

Conclusions: Cognitive function, defined as higher-order mental processes, may be altered along two distinct and interacting pathways: (a) the cancer diagnosis, which can lead to anxiety, stress, distress, and depression; and (b) the direct physiologic effects of cancer treatment. The Chemotherapy-Related Change in Cognitive Function conceptual model is informed by a review of literature that illustrates antecedents, moderators, mediators, and consequences that may be relevant to this issue.

Implications for Nursing: When a patient presents with cognitive complaints, the problems can be evaluated for intervention when an overall understanding exists of chemotherapy-related cognitive changes based on a conceptual model that continues to be informed through well-conceptualized and well-designed research.

Key Points . . .

- Changes in cognitive function during chemotherapy are a common complaint and are not well understood.
- Chemotherapy-related changes in cognitive function may be influenced by two distinct yet interacting pathways: the psychosocial impact of cancer diagnosis and the physiologic effects of cancer treatment.
- A conceptual model of Chemotherapy-Related Change in Cognitive Function provides a structure on which future research may be based.
- Research that investigates the mechanisms by which cognition is affected following cancer diagnosis can lead to appropriate interventions that can be used in clinics to improve mental functioning as well as patients' quality of life and overall well-being.

Patients receiving chemotherapy often complain of changes in cognitive function, colloquially referred to as "chemo-brain." The condition encompasses a variety of complaints, such as forgetfulness, absentmindedness, and an inability to focus when performing daily tasks. Cognitive function, in general, refers to mental processes. More specifically, cognitive function is defined as the higher-order mental processes that involve information processing and that require integrated activity of several areas of the brain. Higher-order mental processes include memory, psychomotor speed, and executive functioning (e.g., planning, concentration, attention, decision making, initiation, task persistence, abstract reasoning) (Matlin, 2003; Mitchell & Phillips, 2007; Sjogren, Olsen, Thomsen, & Dalberg, 2000). Cognitive function does not include lower-order mental processes (e.g., perception, sensation) that are biologically based rather than based on cognitive information processing (Davidson & Downing, 2000). Although lower-order mental processes are required to complete higher-order processes (e.g., the brain must be able to send a signal to the hand to rearrange blocks), the biologic processes are not cognitive function as defined here (Davidson & Downing).

Changes in cognitive function have been identified as a likely consequence of cancer treatment since the 1980s (Silberfarb, 1983; Silberfarb, Philibert, & Levine, 1980). Chemotherapy also is known to result in a number of adverse effects such as nausea, vomiting, diarrhea, asthenia, fatigue, anorexia, cachexia, and immunosuppression (Aziz & Krouse, 2005); research has only recently begun to acknowledge the impact of cancer therapy beyond those parameters. A number of known psychological and social effects are related to the challenges of confronting potentially terminal illness, sometimes referred to as "the meaning of cancer" based on the meaning of illness (Degner, Hack, O'Neil, & Kristjanson, 2003; Wallberg et al., 2003). The effects include anxiety, depression, and stress and increasingly are being identified and treated. Physiologic and psychosocial factors have been implicated in cognitive function (Cimprich & Ronis, 2001; McCracken & Iverson, 2001; Smith, Redd, Peyser, & Vogl, 1999; van Dam et al., 1998). However, no current standard exists for measurement or assessment of cognitive function in patients with cancer. Because patients experience many physiologic and psychosocial changes following cancer

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diagnosis, a variety of factors may contribute to changes in cognitive function. Because of the confounded nature of the problem (e.g., often co-occurring factors), determining the precise cause of possible cognitive decline may be difficult. Despite potentially contributing factors, chemotherapy has long been implicated as the prime suspect in cognitive decline among patients (Schagen et al., 1999; Silberfarb et al., 1980; Tchen et al., 2003). Furthermore, changes in cognitive function may be dependent on chemotherapy dose or duration (Ahles & Saykin, 2002; Jacobsen et al., 2004; Schagen, Muller, Boogerd, Mellenbergh, & van Dam, 2006; Wieneke & Dienst, 1995).

Generally, individuals with a cancer diagnosis who undergo treatment and experience cognitive decline continue to be assessed within the normal range of functioning (Bender, Paraska, Sereika, Ryan, & Berga, 2001; Tannock, Ahles, Ganz, & van Dam, 2004). Patients receiving chemotherapy perform only slightly lower on specific cognitive measures compared to age-matched, healthy counterparts (Brezden, Phillips, Abdolell, Bunston, & Tannock, 2000; Meyers & Wefel, 2003; Tannock et al.; Wieneke & Dienst, 1995). Although mild to moderate declines in cognitive function may not meet the criteria for a clinical definition of cognitive impairment, the changes may reflect decline from premorbid levels of cognitive functioning and affect quality of life and functional ability (Cull et al., 1996; Degl'Innocenti et al., 2002; Kiessling & Henriksson, 2004; Tchen et al., 2003).

The purpose of this article is to develop a model of cognitive decline experienced by individuals with cancer who have undergone chemotherapy, knowing that the changes may be related to more than the exclusive impact of chemotherapy. However, explaining cognitive changes that take place in the absence of chemotherapy treatment is beyond the scope of the proposed model. A systematic review of the literature was conducted to investigate the relationships among concepts and to synthesize current knowledge of cognitive changes related to chemotherapy treatment. The process was used to develop a conceptual model that would provide a foundation to examine changes in cognitive function experienced by individuals receiving chemotherapy and thereby provide a rational approach for future research.

Literature Search

A systematic review of the literature was performed to investigate the use of the concept of changes in cognitive function as applied to oncology research, the various ways that cognitive decline has been conceptualized in the setting of cancer, and current assumptions associated with the concept. A search strategy was employed using MEDLINE®, CINAHL®, and HealthStar (1996–2006), using the keywords "cognition" or "cognitive," limited to a focus on physiology or drug effects, and "cancer" or "chemotherapy." Reviews that were identified through that strategy were scanned for potentially relevant citations. A search in PsycINFO® during the same time period for the terms "cognitive" and "cancer" was added to the strategy. Relevant results included any work with a primary focus on cognitive function related to cancer. Results were limited to adults with cancer because effects of cancer treatment on cognitive function may differ considerably in the developing brains and bodies of children diagnosed with cancer.

Application of the criteria resulted in 70 full-text articles that were included in the review. The articles included 34 research trials, 22 review articles, 2 meta-analyses, and 12 short communications or editorials that focused on chemotherapy-related cognitive function. A complete list of the articles is available from the authors.

Development of a Conceptual Model

The information obtained from the systematic review was summarized to provide a global assessment of the current state of knowledge. The articles then were culled for themes in the following five categories: conceptual definitions, antecedents, consequences, moderators, and mediators. The themes were selected based on foundations of theory of human thought and cognition, which hold that events (in this case, changes in cognitive function) are the result of certain inputs (antecedents) leading to outcomes (consequences) following a set of processes (moderators and mediators) (Miller, 1909). The data within the five themes then were synthesized to develop a conceptual model of chemotherapy-related change in cognitive function.

The assumption underlying the development of the conceptual model is that to best develop effective strategies to prevent, care for, and minimize cognitive decline, healthcare professionals must have a clear understanding of the concept of chemotherapy-related change in cognitive function. Clarity is needed with regard to the aspects of cognitive function that are affected, the outcomes that make a difference to patients, and the causes and mechanisms of cognitive changes associated with chemotherapy. A better understanding is accomplished best through the development of a conceptual model on which a framework for future research can be based. The conceptual model must be tested and refined prior to its use in the development and implementation of interventions to prevent or treat changes in cognitive function.

Results

State of the Knowledge

Changes in cognitive function have been established as an outcome of cancer treatment. However, the evidence is not consistent among all patients or disease sites (see Table 1). None of the ovarian cancer studies detected changes in cognitive function during therapy, whereas all of the studies of breast cancer found significant declines in a variety of cognitive domains. It is unclear what differences exist related to specific chemotherapeutic agents, physiologic changes, or cancer diagnoses that may contribute to the discrepancy. One hypothesis is related to the fact that patients with breast cancer often are treated with medications that cross the blood-brain barrier because of the risk of metastases to the brain associated with advanced breast cancer (Chang & Lo, 2003). Ovarian cancer carries little risk of brain metastases and often is treated with agents that have no central nervous system (CNS) toxicity (Hensley et al., 2006; Mayerhofer et al., 2000). This has yet to be explored fully.

The inconsistency in findings also may be related to the lack of validated instruments to assess cognitive domains in cancer populations. In a comparison study of four cognitive function instruments, the self-report Functional Assessment of Cancer Therapy Cognitive Function Scale (FACT-Cog) and objective

Table 1. Clinical Evidence of Chemotherapy-Related Changes in Cognitive Function

Study	Purpose	Study Population	Primary Findings	Cognitive Domains
Ahles et al., 1998	To compare pretreatment versus post-treatment	Patients with small cell lung cancer	No differences between treatment groups. Post-treatment scores were significantly lower than pretreatment scores.	Cognitive function (general)
Ahles et al., 2002	To compare differences in long-term cancer survivors treated with systemic versus local therapy	Survivors of breast cancer or lymphoma > 5 years after diagnosis	Only one subgroup experienced long-term cognitive deficits associated with chemotherapy. Systemic therapy was associated with greater declines than local therapy.	Verbal memory Psychomotor function Self-reported working memory
Ahles et al., 2003	To compare long-term survivors with the presence versus absence of the ε4 alelle of apolipoprotein E (APOE)	Survivors of breast cancer or lymphoma > 5 years after diagnosis	Patients carrying at least one ε4 alelle of APOE scored lower than noncarriers.	Visual memory Spatial ability Psychomotor function
Brezden et al., 2000	To compare differences between patients with breast cancer and healthy controls	Patients with breast cancer and healthy controls	Patients receiving chemotherapy had poorer function than healthy controls. More moderate to severe cognitive impairment was found among patients.	Cognitive function (general) Memory Language Visual-motor skills
Cull et al., 1996	To compare subjective and objective test performance	Patients with lymphoma	Subjective complaints were not correlated with standard tests. Higher cognitive function scores were associated with higher quality of life.	Cognitive function (general)
Gottschalk et al., 2003	To examine short-term effects of chemotherapy	Patients with breast cancer	Significant impairment scores were found during but not three weeks after the completion of chemotherapy for 58% of patients assessed.	Verbal skills
Hensley et al., 2006	Longitudinal assessment during chemotherapy	Patients with ovarian cancer	No change was found in objective measurements over time. Subjective measurements demonstrated a decline among highly educated women.	Self-reported memory Self-reported concentration
Hurria et al., 2006	Longitudinal assessment during chemotherapy	Patients with breast cancer aged 65 or older	A subset of patients demonstrated decline.	Visual memory Spatial function Psychomotor function Attention
Joly et al., 2006	To assess cognitive function during androgen deprivation therapy	Patients with prostate cancer	No differences were found in cognitive function between patients and controls.	Not specified
Kaplan et al., 1998	To assess the relevance of a subscale of the Symptom Checklist (SCL 90R) to assess cognition	Patients with malignant brain tumors	SCL 90R was associated with psychosocial variables and subjective complaints of cognitive problems but not with objective measures.	Not specified
Klepstad et al., 2002	To investigate whether self-reported cognitive complaints were associated with objective assessments	Patients with cancer at multiple sites	No correlation existed between self-reported and objective assessments of cognitive function; self-reported complaints were associated with fatigue.	Not specified

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Table 1. Clinical Evidence of Chemotherapy-Related Changes in Cognitive Function *(Continued)*

Study	Purpose	Study Population	Primary Findings	Cognitive Domains
Mayerhofer et al., 2000	To investigate the effects of paclitaxel on various neuropsychological parameters	Patients with ovarian cancer	Cognitive assessments at enrollment were below normal range, but scores were significantly higher after chemotherapy treatment. No changes were noted from before to during treatment.	Attention Concentration
Paganini-Hill et al., 2000	To assess the impact of tamoxifen on cognitive function	Patients with breast cancer	Tamoxifen users were more likely to report seeing a physician for memory problems and to make errors in objective assessments than nonusers.	Memory Visuospatial ability
Paraska & Bender, 2003	To describe cognitive dysfunction after chemotherapy in a longitudinal case study of two patients	Patients with breast cancer	Cognitive dysfunction was documented by a neuropsychological battery of tests as well as via self-report. Patients reported complaints before objective assessments were able to detect declines.	Attention Concentration Memory Psychomotor ability Visuospatial ability
Salminen et al., 2003	To assess whether cognitive function was impaired during androgen deprivation therapy	Patients with prostate cancer	Androgen deprivation therapy was associated with improved cognitive function despite impaired physical and sexual function.	Memory Recall
Salminen et al., 2005	To assess the association of androgen deprivation–induced estradiol decline with cognitive function	Patients with prostate cancer	Changes in cognitive function were associated with estradiol decline; but, in general, cognitive function was preserved during androgen deprivation therapy.	Verbal fluency Visual recognition Visual memory
Schagen et al., 1999	To assess differences in cognitive function among patients with cancer treated with systemic therapy versus those treated with surgery and radiation	Patients with breast cancer	Patients treated with systemic chemotherapy had significantly greater declines in cognitive function than those not treated with chemotherapy.	Attention and concentration Processing Memory Verbal function Psychomotor function
Schagen et al., 2002	To assess the persistence of cognitive declines four years post-treatment	Patients with breast cancer	Changes in cognitive function that were identified during chemotherapy treatment may have been transient.	Not specified
Schagen et al., 2006	To assess the impact of high-dose versus standard-dose chemotherapy on cognitive function	Patients with breast cancer	More patients receiving high-dose chemotherapy experienced cognitive decline than those treated with standard-dose chemotherapy.	Not specified
Shilling et al., 2003	To determine whether hormone therapy is associated with changes in cognitive function	Patients with breast cancer	Patient group significantly differed from control group.	Verbal memory Processing
Taylor et al., 1998	To assess cognitive function among patients receiving radiation in addition to chemotherapy treatment	Patients with glioma	No evidence was found of decline in cognitive function among patients with high-grade brain tumors treated with chemotherapy and radiation, but progression of brain tumors may contribute to decline.	Not applicable

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Table 1. Clinical Evidence of Chemotherapy-Related Changes in Cognitive Function *(Continued)*

Study	Purpose	Study Population	Primary Findings	Cognitive Domains
Tchen et al., 2003	To investigate incidence and severity of cognitive function, fatigue, and menopausal symptoms to explore interrelationships	Patients with breast cancer	Chemotherapy was identified as the cause of cognitive decline but was not associated with fatigue, menopausal symptoms, or quality of life; this may have been because of the small sample size (N = 16).	Language Attention Concentration Self regulation and planning (executive functioning)
van Dam et al., 1998	To assess the impact of high-dose versus standard-dose chemotherapy on cognitive function	Patients with breast cancer	More patients receiving high-dose chemotherapy experienced cognitive decline than did patients treated with standard-dose chemotherapy.	Attention and concentration Processing Memory Psychomotor ability
Vardy et al., 2006	To compare screening instruments for cognitive function	Patients with breast cancer or colorectal cancer	30%, 55%, 26%, and 47% of patients on chemotherapy demonstrated cognitive impairment via the High Sensitivity Cognitive Screen, Headminder, CogHealth, and Functional Assessment of Cancer Therapy (FACT)–Cog tools, respectively. No correlation was found between objective measures and the self-report FACT-Cog. Poor correlations existed among the objective measures (Spearman correlation < 0.20).	Not specified
Walker et al., 1996	To assess the impact of chemotherapy with or without recombinant interleukin-2 (rIL-2) on cognitive function	Patients with colorectal cancer	A progressive decline in cognitive performance occurred during and immediately after rIL-2 administration, with a return to baseline after approximately 15 days.	Vigilance Concentration Psychomotor ability Visuomotor ability
Wefel et al., 2004	To assess cognitive function prior to the initiation of chemotherapy	Patients with breast cancer	35% of women tested exhibited cognitive impairment in at least one domain prior to the initiation of adjuvant therapy.	Memory Verbal learning

measures CogHealth and HeadMinder Cognitive Stability Index were able to detect subtle changes in cancer populations to different degrees (e.g., cognitive problems ranged from 30%–55% of the sample population depending on the instrument used). Furthermore, the self-report and objective instruments were not correlated (Vardy et al., 2006). The literature shows no correlation between self-reported cognitive change and formal assessments of cognitive function among individuals who have experienced cancer (Ahles et al., 2002; Klepstad et al., 2002; Schagen, Hamburger, Muller, Boogerd, & van Dam, 2001; Schagen et al., 1999; Tannock et al., 2004; van Dam et al., 1998). An additional concern is that instruments validated for the assessment of cognitive function in other settings (e.g., Alzheimer disease) may not be sensitive to the subtle changes experienced as a result of cancer treatment (Bender et al., 2001; Meyers & Wefel, 2003; Tchen et al., 2003). Furthermore, selection of instruments in research studies is inconsistent; for example, self-reported cognitive changes have been measured via the Chronic Illness Problem Inventory Cognitive Subscale (Kaplan & Miner, 1998), the Cognitive Problems in Daily Life Checklist (van Dam et al., 1998), the FACT-Cog (Joly et al., 2006; Vardy et al.), and the Patient's Assessment of Own Functioning Scale (Paraska & Bender, 2003). Whether the instruments are correlated, or whether each measures a unique set of underlying constructs, is unclear.

Two meta-analyses were conducted of 29 trials (838 patients) and 16 trials (653 patients), respectively (Anderson-Hanley, Sherman, Riggs, Agocha, & Compas, 2003; Jansen, Miaskowski, Dodd, Dowling, & Kramer, 2005a). Significant declines have been found for executive function, verbal memory, and motor function (Anderson-Hanley et al.), whereas significant declines were limited to visual memory when analyses included all comparisons (e.g., normative data, controls, baseline data) (Jansen et al., 2005a). Executive function and verbal memory were identified as cognitive domains affected by cancer treatment in meta-analyses when using normative data. However, the findings may underestimate the

impact among specific cancer populations. The trials included were heterogeneous, that is, studies included all cancer disease sites and treatment regimens and encompassed patients actively undergoing treatment as well as long-term survivors. Similarly, research trial designs varied (e.g., longitudinal, cross-sectional, cohort studies), and the inconsistent use of controls or standardized norms as controls also was evident, perhaps biasing the true treatment effects in unknown directions. Furthermore, among the trials included in the meta-analyses, an average number of six instruments was used to assess each cognitive domain (range = 3–10). The same instruments also were used to assess different cognitive domains; for example, the Rey Auditory Verbal Learning Test measured the ability to learn and remember new verbal information in one study (Paraska & Bender, 2003), whereas another study used the same test to measure immediate memory span (van Dam et al., 1998). Unfortunately, neither meta-analysis conducted statistical tests to assess or account for heterogeneity nor followed standard guidelines for meta-analyses (Moher et al., 2000; Moher, Schulz, & Altman, 2005), limiting the usefulness of the findings.

Future work should address the development and validation of instruments that have demonstrated sensitivity to assess cognitive function among patients with cancer. Additional work also is needed on the mechanisms underlying the impact of cancer treatment on cognitive function, the domains of cognitive function being assessed, and the impact of cognitive change on patient outcomes. A rational, model-driven approach to identifying and conceptualizing the problem is needed. Knowledge can be advanced and appropriate interventions developed only if an overall understanding exists of the phenomenon based on a conceptual model that continues to be informed through well-conceptualized and well-designed research.

Conceptual Definitions

One of the greatest challenges in the evaluation of chemotherapy-related changes in cognitive function is that researchers have investigated the concept in the absence of a working definition of cognitive function. Definitions of cognitive function in the literature generally are nonexistent or limited to nonspecific definitions such as "brain function" (Meyers, 2000; Meyers & Wefel, 2003; Miller, 2001). This limits not only the ability to use empirical findings, but also the use of data to guide future research and potential clinical interventions. The lack of standardized terminology and instrument selection requires that research trials provide details regarding the domains of cognitive function investigated. Based on the systemic review of the literature and the standard terminology used in the field of cognitive science, Table 2 proposes a set of definitions that may be applied to future research.

Studies of cognitive function more frequently have defined what constitutes "impairment"; however, the definitions are highly variable, ranging from subjective determinations (Frytak et al., 1988) to a variety of z-scores (Ahles et al., 2002) to standard deviation changes (Schagen et al., 2001; Wieneke & Dienst, 1995; van Dam et al., 1998) on various cognitive tests. Standardized diagnostic criteria exist for a number of cognitive disorders, such as delirium and dementia, but no corresponding criteria exist to diagnose clinically meaningful declines in cognitive function. Once the nature and extent of chemotherapy-related changes in cognitive function are understood, researchers will be able to develop diagnostic criteria to identify declines that are clinically meaningful (e.g., associated with patient complaints or declines in quality of life or functional ability).

Antecedents

Antecedents are preconditions of chemotherapy-related changes in cognitive function. Two general categories of antecedents exist: psychological and social factors resulting from the diagnosis of cancer (the meaning of cancer) and physiologic factors as a consequence of treatment. They differ from educational or genetic features (which are not required preconditions but moderators, as discussed later) because the phenomenon of chemotherapy-related changes in cognitive function is unique to individuals who have been diagnosed with cancer and treated with chemotherapeutic agents. Although psychosocial and physiologic factors interact a great deal, subjective instruments (e.g., patient self-report) that measure cognitive declines may capture consequences related to psychosocial factors, whereas more formal assessment instruments may better capture the effects of physiologic factors (Cimprich, So, Ronis, & Trask, 2005).

Moderators

Moderating variables affect either the strength or direction of the relationship between an independent variable (e.g., chemotherapy) and a dependent variable (e.g., cognitive function) (Baron & Kenny, 1986; Schagen et al., 2006). Moderators are unrelated to cancer diagnosis and may include age, education, and general intelligence. Co-occurring with cancer diagnosis may be age-related cognitive declines (Ahles & Saykin, 2002; Smith et al., 1996; Vas, Rajkumar, Tanyakitpisal, & Chandra, 2002). The process may be accelerated in the setting of disease. Education has been shown to moderate the effects of disease-related cognitive declines (Bennett et al., 2003; Wight, Aneshensel, & Seeman, 2002) and therefore may moderate the relationship between chemotherapy and decline in that population. Performance on measures of cognitive function is influenced by education and general intelligence (Ahles & Saykin, 2002). Changes in cognitive function do not occur among all patients with cancer or all those receiving chemotherapy, even among those treated with identical therapeutic regimens (Schagen et al., 1999; van Dam et al., 1998; Wieneke & Dienst, 1995). Some investigators in the field, such as Ahles et al. (2003), have worked to identify specific genetic factors that may make some patients more prone to declines in cognitive function during cancer treatment. Table 3 provides a summary of the primary moderators identified. Thus, cognitive function assessments must take into account patient-specific independent variables that could affect chemotherapy-related cognitive changes.

Mediators

Mediating variables may explain how or why antecedent factors lead to the outcomes (consequences) of changes in cognitive function (MacKinnon, 2002), in that variations in mediators exists, so subsequent variations in outcomes exist. Mediators may include drugs administered, dose intensity, duration of treatment, concomitant medications, use of radiation therapy, and toxicities that patients may be experiencing. Each variable places patients in a fairly complicated context that may affect cognitive function and its assessment. Specific

Table 2. Working Definitions and Measures

Term	Definition	Instruments That Have Been Used for Assessment
Cognitive Function[a]	Global term for higher-order mental functions and processes. The functions encompass many domains, including, but not limited to, comprehension, inferencing, decision making, planning, learning, attention, reasoning, memory, language processing, and mental imagery (Bender et al., 2001). Assessments of individual domains are used as indicators of overall cognitive function (Miyake et al., 2001).	High Sensitivity Cognitive Screen (Brezden, 2000; Joly et al., 2006; Tchen et al., 2003) Mini Mental Status Examination (Cimprich & Ronis, 2001; Joly et al., 2006; Klepstad et al., 2002; Massa et al., 2006; Taylor et al., 1998; Tchen et al.; Walker et al., 1996) Cognitive Capacity Screening Test (Silberfarb et al., 1980) Cognitive Drug Research System (Walker et al., 1996) Sickness Impact Profile (SIP) Alertness Behavior Subscale (McCracken & Iverson, 2001)
Domains of Cognitive Function[b]		
Executive function	Global term for the capacity to control and apply one's mental abilities. Executive function is believed to be regulated by the cortical lobe. The domains that fall into this category of cognitive function include planning, sustained attention, and selection among problem-solving strategies (Wikipedia, 2007b).	Stroop Test (Schagen et al., 1999; van Dam et al., 1998) Cognitive Stability Index (Erlanger, 2000) Trailmaking Test B, Category Test, and Wechsler Adult Intelligence Test–Similarities (Wefel et al., 2004)
Attention	The process of selectively concentrating on one thing while ignoring other things (Wikipedia, 2007a)	Continuous Performance Test (Ahles et al., 2002, 2003; Tchen et al., 2003) D2 Test (Schagen et al., 1999; van Dam et al., 1998) Necker Cube Pattern Control Test (Cimprich & Ronis, 2001) SIP–Alertness Behavior subscale (McCracken & Iverson, 2001) Symbol Digit Modalities Test (Cimprich & Ronis, 2001) Digit Span/Digit Symbol (Wieneke & Dienst, 1995) CogHealth (Vardy et al., 2006) CogniSpeed Attentional Domain and Vigilance Test (Salminen et al., 2005) Weschler Adult Intelligence Scale (WAIS) and Trailmaking Test A (Wefel et al., 2004)
Concentration	The process of focusing one's efforts; often used interchangeably with attention, the more commonly used term	Digit Vigilance (Paraska & Bender, 2003) WAIS–Digit Span Subtest (Ahles et al., 2003; Cimprich & Ronis, 2001; Paraska & Bender, 2003; Schagen et al., 1999) Alphabetic Crossout Test (Mayerhofer et al., 2000) Trailmaking Test B (Paraska & Bender, 2003) Subtraction test (Salminen et al., 2005)
Intelligence	Indicator of overall mental capabilities (Miyake et al., 2001), whereas cognitive function relates to the processes underlying mental capacity.	–
Memory and recall	A global term referring to the ability to retain information and reconstruct past experiences (Sutton, 2004). This term includes implicit, explicit, short-term, and long-term memory.	Complex Figure Test (Schagen et al., 1999; van Dam et al., 1998) Rey 15 Words Test/Weschler Memory Scale (WMS) Recall (Schagen et al., 1999) Rey Verbal Learning Test/Rivermead Behavioral Memory Test–Paragraph Recall Subtest (Paraska & Bender, 2003) Squire Memory Self-Rating Questionnaire (Ahles et al., 2002) WMS (Ahles et al., 2002; Shilling et al., 2003) Cognitive Stability Index (Erlanger, 2000) CogHealth (Vardy et al., 2006) Mattis Dementia Rating Scale (Kaplan & Miner, 1998) Numerical memory test (Mayerhofer et al., 2000)

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[a] Instruments designed to measure this global term must identify the domains assessed. No measure exists that can encompass the whole of cognitive function, although some domains are thought to be representative of the whole.

[b] List is not comprehensive; limited to those domains investigated in the results of the literature search for this work

Table 2. Working Definitions and Measures *(Continued)*

Term	Definition	Instruments That Have Been Used for Assessment
		Digit span forward/backward (Salminen et al., 2005) Paced Auditory Serial Addition Task (PASAT) (Sjogren et al., 2000) Hopkins Verbal Learning Test, Verbal Selective Reminding Test, and Rey-Osterreith Complex Figure Test (Wefel et al., 2004) California Verbal Learning Test (CVLT) and Rey Complex Figure Test (Wieneke & Dienst, 1995)
Psychomotor ability	Global term encompassing purposeful movement; has been found to be dependent on other cognitive domains, such as working memory (Chaiken et al., 2000)	Trailmaking Tests A and B (Ahles et al., 1998; Paraska & Bender, 2003; Schagen et al., 1999; Tchen et al., 2003; van Dam et al., 1998) WAIS–Digit Symbol Subtest (Schagen et al., 1999; van Dam et al., 1998) Fine-Motoric Test (Mayerhofer et al., 2000) Grooved Pegboard Test (Paraska & Bender, 2003; Wefel et al., 2004; Wieneke & Dienst, 1995) Digit symbol/block design (Salminen et al., 2005) Fepsy Finger-Tapping Test (Schagen et al., 1999; Sjogren et al., 2000).
Processing	Cognitive processing refers to the time needed to complete cognitive tasks. Specific domains within processing (e.g., mathematical processing) refer to specific functional tasks.	Cognitive Stability Index (Erlanger, 2000) CogniSpeed (Salminen et al., 2003) Recognition thresholds (Salminen et al., 2005) Fepsy Visual Reaction (Schagen et al., 1999) Kendrick Assessment of Cognitive Ageing Battery (Shilling et al., 2003) PASAT and Trailmaking Tests A and B (Wieneke & Dienst, 1995)
Verbal ability	Global term encompassing all aspects of spoken language, including, but not limited to, vocabulary, grammar, and language processing (e.g., reorganizing sentences, paraphrasing)	CVLT (Ahles et al., 2002, 2003; Kaplan & Miner, 1998) Dutch Adult Reading Test (Schagen et al., 1999; van Dam et al., 1998) Dutch Aphasia Society Test-Word Fluency Subtest (van Dam et al., 1998) SAN Test–word fluency subtest (Schagen et al., 1999) Rey Auditory Verbal Learning Test (Paraska & Bender, 2003; Schagen et al., 1999; van Dam et al., 1998) Multilingual Aphasia Examination/Boston Naming Test (Wefel et al., 2004) Controlled Oral Word Association Test (Wieneke & Dienst, 1995)
Vigilance	The ability to attend to and respond rapidly to external stimuli for an extended period of time (Sjogren et al., 2000)	Continuous Reaction Time Test (Sjogren et al., 2000)
Visuospatial and visuomotor ability	Global term for a variety of independent factors such as spatial visualization, visuomotor skills, spatial relations, and visuospatial perceptual speed (Miyake et al., 2001)	Clock Drawing Task (O'Shaughnessy, 2002; Paganini-Hill & Clark, 2000) WAIS–Visual Reproduction Subtest (Schagen et al., 1999) WAIS Block Design (Wefel et al., 2004; Wieneke & Dienst, 1995) Judgment of Line Orientation and Rey-Osterreith Complex Figure Test-Copy (Wefel et al., 2004) Rey Complex Figure Test (Paraska & Bender, 2003; Wieneke & Dienst, 1995) Benton Visual Retention Test (Salminen et al., 2005) Digit Symbol Test (Silberfarb et al., 1980; Wieneke & Dienst, 1995)

[a] Instruments designed to measure this global term must identify the domains assessed. No measure exists that can encompass the whole of cognitive function, although some domains are thought to be representative of the whole.

[b] List is not comprehensive; limited to those domains investigated in the results of the literature search for this work

agents that are implicated in cognitive changes are chemotherapies associated with CNS neurotoxicity and those that cross the blood-brain barrier (e.g., 5-fluorouracil, cytarabine, methotrexate, ifosfamide, cisplatin), concomitant medications used with chemotherapy (e.g., glucocorticosteroids, dexamethasone), and certain biologic (e.g., interferon) and hormonal therapies (e.g., tamoxifen) (Jansen et al., 2005b; Staat & Segatore, 2005). The impact of the drugs on cognitive function may be dose dependent, with patients who are exposed to higher doses or treated for longer periods of time having greater declines in cognitive function (Keime-Guibert, Napolitano, & Delattre, 1998; Schagen et al., 2001, 2006; van Dam et al., 1998). Many other aspects of normal physiology are disrupted during cancer treatment, which, in turn, may affect cognitive function. Cytokines are known to play a role in cognitive function and may be affected by treatment (e.g., interferon-α) or inflammatory response (Jansen et al., 2005b; Licinio, Kling, & Hauser, 1998). Anemia can result in reduced brain oxygenation and is a common side effect of chemotherapy treatment (Groopman & Itri, 1999). Chemotherapy-induced

Table 3. Evidence of Mediating and Moderating Factors Influencing Chemotherapy-Related Cognitive Function

Study	Mediator/Moderator	Level of Evidence[a]	Findings
Mediators			
Jacobsen et al., 2004	Anemia	Secondary	Changes in hemoglobin levels were associated with changes in cognitive function.
Massa et al., 2006	Anemia	Secondary	The cognitive function of older anemic patients improved following erythropoietin treatment to elevate hemoglobin levels.
McCracken et al., 2001	Anxiety	Secondary	Anxiety was a predictor of cognitive complaints.
Gottschalk et al., 2003	Concomitant medications	Quinary	Patients often are prescribed antidepressents and pain medications, which may contribute to cognitive changes.
McCracken et al., 2001	Concomitant medications	Secondary	Use of depressants or narcotics was a predictor of self-reported declines in cognitive function.
Sjogren et al., 2000	Concomitant medications	Secondary	Patients with cancer may take medications for pain that have the potential to impact cognitive function.
McCracken et al., 2001	Depression	Secondary	Depression was correlated with changes in self-reported but not objective assessments of cognitive function.
Paraska & Bender, 2003	Depression	Quaternary	Depression can accompany cognitive decline, and improvements in depression can accompany improved cognitive function.
Hensley et al., 2006	Distress	Quinary	Distress may have accounted for lower pretreatment cognitive scores.
Wefel et al., 2004	Distress	Quaternary	Distress was related to lower cognitive function.
Ahles et al., 1998	Distress	Secondary	Distress was associated with cancer.
Schagen et al., 2001, 2006	Dose intensity	Primary	Patients randomized to high-dose chemotherapy experienced greater changes in cognitive function than patients receiving standard-dose chemotherapy.
van Dam et al., 1998	Dose intensity	Primary	Patients randomized to high-dose chemotherapy experienced greater changes in cognitive function than patients receiving standard-dose chemotherapy or controls.
Barton et al., 2002	Hormonal changes	Primary	Citation was provided of clinical trial that demonstrated that progestins were associated with fewer cognitive symptoms.
Paganini-Hill et al., 2000	Hormonal status	Secondary	Use of tamoxifen may have a negative impact on cognitve function.
Paraska & Bender, 2003	Hormonal status	Quaternary	Changes in reproductive status may occur with cancer treatment and can accompany cognitive changes.
Salminen et al., 2003	Hormonal status	Secondary	Androgen deprivation is associated with cognitive function.
Salminen et al., 2005	Hormonal status	Secondary	Cognitive changes are associated with estrodiol decline.
Shilling et al., 2003	Hormone therapy	Tertiary	Cognitive deficits were more evident among patients treated with hormone therapy than among controls.
Walker et al., 1996	Immune function	Primary	Patients randomized to immunochemotherapy had reduced cognitive function.
Barton & Loprinzi, 2002	Immune response	Quinary	Immune response may cause neuronal damage via cytokine release or microglia activation.
Barton & Loprinzi, 2002	Neuronal damage	Quinary	Neuronal protection or injury prevention may preserve cognitive function.
Fleissbach et al., 2003	Neurotoxicity	Secondary	White matter lesions were detected but were not associated with results of neuropsychologic testing.
McCracken et al., 2001	Pain	Secondary	Patients in pain reported impaired cognitive function.
Sjogren et al., 2000	Pain	Secondary	Pain may interfere with cognitive function but in this finding may have been confounded by opioid use.
Ahles et al., 1998	Radiation therapy	Secondary	Declines were reported after radiation therapy.
Barton & Loprinzi, 2002	Vascular injury	Quinary	Oxidative damage may decrease blood perfusion and flow, leading to changes in cognitive function.
Moderators			
Cimprich et al., 2005	Age and education	Tertiary	Age and education are individual factors that may be associated with cognitive function prior to treatment.
Mayerhofer et al., 2000	Age	Secondary	A weak negative association was found between age and cognitive function.
Hensley et al., 2006	Education	Secondary	Highly educated people had self-reported declines during therapy.
McCracken et al., 2001	Education	Secondary	Education was a predictor of cognitive complaints.
Ahles et al., 1998	Gender	Secondary	Women experienced greater distress associated with cancer than men.
Ahles et al., 2003	Genetics	Secondary	Presence of apolipoprotein E ε4 allele was associated with lower cognitive function scores.
Schagen et al., 1999	Intelligence	Secondary	Intelligence quotient was significantly associated with risk of cognitive impairment.

[a] Based on Centre for Evidence-Based Medicine (2001) levels

anemia has been implicated as a factor contributing to changes in cognitive function (Cunningham, 2003; Jacobsen et al., 2004; Jansen et al., 2005b). Cancer treatment also frequently affects hormonal status (e.g., early menopause, estrogen deficiency) among women. Although decreases in estrogen have been associated with cognitive changes in other settings, the relationship in the cancer population is not clear (Bender et al., 2001; Phillips & Bernhard, 2003). Vascular injury is a side effect of chemotherapy that also has been implicated in cognitive function (Abayomi, 2002; Saykin, Ahles, & McDonald, 2003; Staat & Segatore). Furthermore, radiation therapy has been suggested to cause additive effects on chemotherapy-related

cognitive decline (Frytak et al., 1988; Keime-Guibert et al.) but has not demonstrated negative effects on cognitive function independent of chemotherapy (Komaki et al., 1995; Lilja, Portin, Hamalainen, & Salminen, 2001). Table 3 provides a summary of the primary mediators identified.

Mediators associated with cancer diagnosis may be largely independent of treatment. They include psychosocial factors such as stress, depression, anxiety, and distress (Foster & McLellan, 2000). The factors have been associated with self-reported, but not formally assessed, changes in cognitive function (Cimprich et al., 2005; van Dam et al., 1998) and have been found to be associated with lower prechemotherapy cognitive function assessment scores (Wefel, Lenzi, et al., 2004). This suggests independent effects of physiologic and psychosocial mediators with regard to cognitive function. When controlling for psychosocial factors such as anxiety and depression, patients continue to demonstrate cognitive decline (Ahles et al., 2002; Schagen et al., 1999; Silberfarb et al., 1980; van Dam et al., 1998; Wefel, Kayl, & Meyers, 2004; Wieneke & Dienst, 1995).

Consequences

Consequences refer to the outcomes of chemotherapy-related changes in cognitive function. They are the measurable effects of changes in cognitive function, such as quality of life and functional ability. To date, most studies have not identified, evaluated, or quantified the specific outcomes that are affected by chemotherapy-related changes in cognitive function (Olin, 2001) or the length of time chemotherapy exerts influence on cognition. However, several consequences have been hypothesized in the general categories of health-related quality of life (HRQOL) and functional ability. Patients who self-report better cognitive function also report higher quality of life (Cull et al., 1996). Unlike general quality of life (an individual's overall "subjective well-being, including standard of living, family life, friendships, and job satisfaction" [Coons & Craig, 2005, p. 12]), HRQOL directly concerns the impact of health on well-being. HRQOL has been shown to be associated with changes in cognitive function in a variety of diseases (Cull et al.; Degl'Innocenti et al., 2002; Kiessling & Henriksson, 2004; Sweet, Doninger, Zee, & Wagner, 2004). Changes in functional ability have been implicated as a consequence of cognitive changes in a number of domains: the ability to function in daily life (Meyers, 2000; Phillips & Bernhard, 2003); independence (Meyers); productivity (Meyers); the ability to maintain family, career, and community responsibilities (Paraska & Bender, 2003); and performance at work (Ahles & Saykin, 2001; U.S. Department of Health and Human Services, 2002). In a study of patients with cancer, cognitive function had the greatest impact on several functional abilities, including frequency of minor accidents and difficulty finishing tasks (McCracken & Iverson, 2001). The importance of the consequences of changes in cognitive function should not be understated. Declines in cognitive function become a problem to be addressed only when they result in undesirable consequences for patients. Currently, no treatments are available for patients who present with cognitive complaints. The primary purpose of studying and evaluating cognitive changes among those being treated for cancer is to improve or maintain functional ability and to avoid adverse effects on HRQOL.

Conceptual Model

A simplified descriptive-relational statement (Walker & Avant, 2005) based on the systematic review of the literature is as follows: Cognitive function, defined as an individual's higher-order mental processes, may be altered among individuals diagnosed with cancer along two distinct and interacting pathways: (a) cancer diagnosis (the meaning of cancer), leading to anxiety, stress, distress, and depression; and (b) direct physiologic effects of cancer treatment, both of which may affect cognitive function. The conceptual model of Chemotherapy-Related Change in Cognitive Function (see Figure 1) illustrates the physiologic and psychological antecedents, moderators, mediators, and consequences and provides a rational framework on which future research may be based.

Patients with cancer must confront and deal with the meaning of cancer at the time of diagnosis. This occurs to different degrees depending on the individual and contributes to increased psychosocial factors, including depression, anxiety, stress, and distress. In addition, patients with cancer generally undergo treatment for the disease. Cancer treatment is associated with a number of undesirable side effects. The physiologic factors increase as a direct result of the initiation or continuation of cancer treatment. As doses or duration of chemotherapy increase, physiologic factors increase.

Furthermore, psychosocial and physiologic factors may interact. They may increase or decrease together; however, the relationship is not yet clear and may not be linear.

Psychological and physiologic factors can lead to changes in formal assessment of cognitive function and self-report of cognitive function. As such factors increase, cognitive function declines. Whether the changes occur completely independently of each other or in collaboration with each other is unclear**.**

In the model, HRQOL is the ultimate outcome of interest. As cognitive function undergoes negative changes, HRQOL and functional ability also may be affected negatively. Still unknown are which attributes of HRQOL and which functional abilities are affected, and whether and how the impact of decline in specific attributes of cognitive function through the physiologic pathway differs from that of the psychosocial pathway.

Discussion

The conceptual model is limited to the impact of cancer and its treatment on cognitive function in adults. However, it is broad enough to encompass a multidisciplinary approach (e.g., mechanistic, psychosocial, and outcomes research in nursing, medicine, and psychology) and is presented in a manner that enables methodical investigation. Future work on chemotherapy-related cognitive function should include an operational definition of the concepts being tested and must specify the cognitive domains and outcomes being evaluated. To date, such definitions have been assumed but not clarified. As the domains affected during chemotherapy are identified clearly, the concept of cognitive function will be investigated more accurately, thus identifying the specific domains of cognitive function that are affected by cancer treatment and those that affect an individual's ability to function. Furthermore, as methods to assess cognitive domains are developed and understood and as the conceptual model is

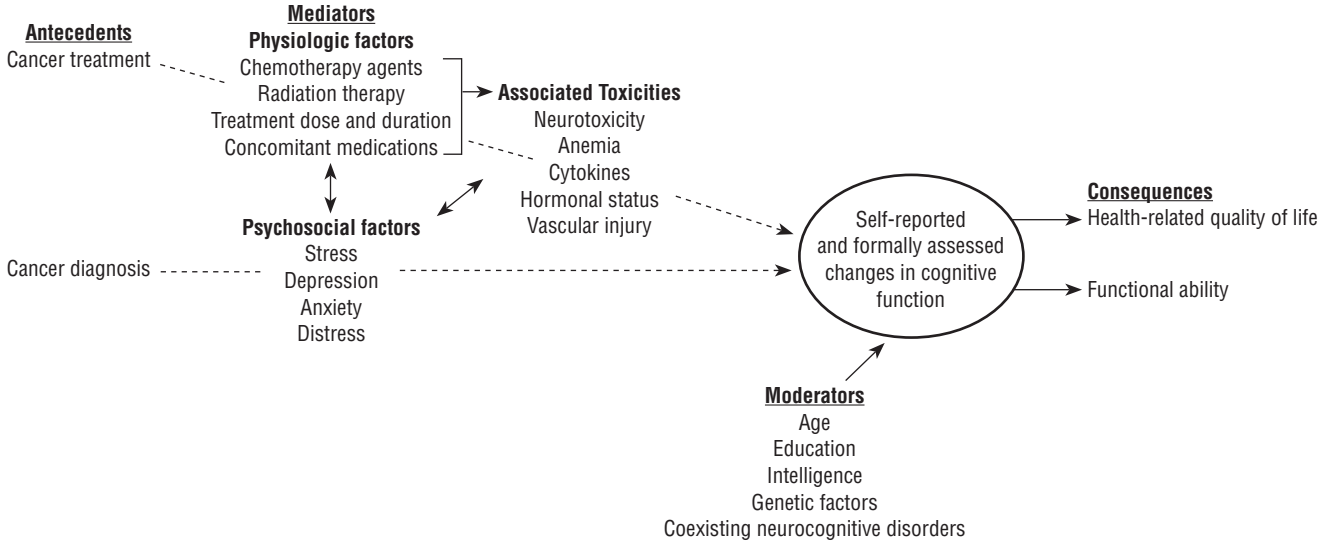

Figure 1. Conceptual Model of Chemotherapy-Related Changes in Cognitive Function

tested, new hypotheses may arise to explain the physiologic and psychosocial impact of cancer on specific cognitive functions. Certainly, the mediators and modifiers identified to date are not comprehensive but are hypothesized and remain to be assessed.

Prospective research trials evaluating cognitive function in patients with cancer have found that self-reports of cognitive decline do not necessarily correlate with formal assessments (Ahles et al., 2002; Klepstad et al., 2002; Schagen et al., 1999, 2001; Tannock et al., 2004; van Dam et al., 1998). In fact, current research demonstrates that patients who report cognitive changes may not be those who demonstrate changes via formal assessment and vice versa (van Dam et al.). Although this does not necessarily mean that self-report and formal assessments are unrelated, it does provide preliminary evidence that self-report measures of cognitive decline may not be valid indicators of changes in cognitive abilities. Current research indicates that self-report measures of cognitive function are related to distress, anxiety, and depression (Cull et al., 1996; McCracken & Iverson, 2001), whereas cognitive function using formal assessments were found to occur independently of mood, anxiety, stress, and depression (Ahles et al., 2002; Schagen et al., 1999; Silberfarb et al., 1980; van Dam et al.; Wefel, Kayl, et al., 2004; Wieneke & Dienst, 1995). This does not eliminate the possibility of an interaction between the physiologic and psychosocial factors but emphasizes the need for further research to understand how the factors interact in relation to cognitive function.

More than 80 instruments have been used to assess various attributes of cognitive function in patients with cancer. The type of instrument chosen to assess cognitive function can influence findings, particularly if different instruments are used to assess the same cognitive processes or if the same instrument is used to assess different cognitive processes. A consistent problem with all research to date of cognitive function among patients with cancer is inconsistency in the use of instruments to measure specific cognitive domains. Until the domains of cognitive function affected by cancer treatment are identified and instruments are used consistently to measure the domains, knowledge will not progress concerning the prevention or treatment of the problem. Future research should make efforts to use standard definitions from the field of cognitive science and to select validated instruments to assess the specific cognitive domains of interest in patients with cancer.

Although the impact of cancer on overall quality of life is receiving more attention and significant progress is being made (Andersen, 2002; Graves, 2003), self-report and formal assessments of cognitive change have yet to be assessed consistently in conjunction with HRQOL or functional ability. The outcomes of cognitive changes are extremely important. Caregivers have an opportunity to provide support at various points along the pathways described in the model to enhance quality of life and daily functioning for patients. Therefore, a need exists to assess the physiologic impact of cancer independently and with the psychosocial impact of cancer, in terms of cognitive changes until the relationship is better understood. Healthcare professionals should listen to patients' reported symptoms and concerns independent of results of formal assessments. Examining the reliability and validity of self-report and formal assessments in the cancer population is important to shed light on the potential reasons for any discrepancies. At present, researchers cannot determine whether discrepancies truly reflect different pathways for cognitive decline or whether they simply are a result of measurement error.

Conclusion

When patients present with cognitive complaints, the problems can be evaluated for intervention only if an overall understanding of chemotherapy-related cognitive changes exists based on a conceptual model that continues to be informed by well-conceptualized and well-designed research. The model presented can be used as a basis for future research efforts, allowing for investigational interventions and evaluations at many points along the model. As research progresses and evolves, the conceptual model can be elaborated and modified. Differences in the causal attribution of cognitive decline

require different intervention strategies. Psychological distress may be approached with counseling and medications, whereas cognitive declines caused by physiologic responses may require dose modifications or supportive care. Hypothesis-driven research is needed specific to chemotherapy-related changes in cognitive function so that rational, knowledge-based preventive and treatment strategies can be developed.

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