Chemotherapy-Related Cognitive Change: A Principle-Based Concept Analysis

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Purpose/Objectives: To present the results of a principle-based concept analysis of cognitive change in patients with cancer following chemotherapy treatment.

Data Sources: 86 English-language articles retrieved through OVID, PubMed, CINAHL®, and Web of Knowledge searches through June 2010. No time limits were imposed.

Data Synthesis: Analysis was based on the philosophical principles: epistemologic, pragmatic, linguistic, and logical. Conceptual components were identified and a theoretical definition of chemotherapy-related cognitive change emerged; the term was not clearly defined or well differentiated in the scientific literature. Implicit meanings are found in patients' subjective accounts, descriptions of the cognitive domains studied, and the choice of neuropsychological assessment instruments. Antecedents relative to chemotherapy-related cognitive change include disease and treatment factors. Moderators may include anxiety, depression, and fatigue. Consequences or outcomes of the experience of chemotherapy-related cognitive change include adjustment to illness, impact on quality of life, and potential for emotional distress.

Conclusions: The principle-based concept analysis generated conceptual insights about chemotherapy-related cognitive change that are based on sound scientific evidence. The product of this method of analysis is a theoretical definition that reflects the state of the science.

Implications for Nursing: When the impact of cognitive change following chemotherapy is better understood, meaningful and timely interventions can be developed to improve quality of life for cancer survivors.

Chemotherapy agents used in the treatment of malignant diseases cause a variety of side effects, some debilitating and others life threatening. Change in cognitive function, a side effect of chemotherapy, is not well understood (Schagen, Muller, Boogerd, Mellenbergh, & van Dam, 2006) and is seldom discussed with patients prior to treatment. Although the symptoms are subtle, patients who report those changes are very aware of the differences in their abilities to think clearly (Boehmke & Dickerson, 2005) and commonly use the phrase chemobrain to describe this phenomenon (Staat & Segatore, 2005). Ongoing research suggests that the symptoms of cognitive change make it difficult to carry out normal daily activities in personal and professional life (Boykoff, Moieni, & Subramanian, 2009; Castellon & Ganz, 2009; Jansen, Miaskowski, Dodd, & Dowling, 2005; Mitchell, 2007; Taillibert, Voillery, & Bernard-Marty, 2007).

A clear understanding of cognitive changes following chemotherapy can guide the development of reliable instruments to identify and measure the changes. Understanding the state of the science also is necessary to determine the long-term consequences of cognitive change and its impact on quality of life (QOL). Theoretical insights are needed to identify appropriate research methods for additional scientific inquiry.

Methods

Penrod and Hupcey (2005a) described a principle-based concept analysis to determine the state of the science concerning chemotherapy-related cognitive change. The method is based on four philosophical principles: epistemologic, pragmatic, linguistic, and logical, and includes analysis of the scientific literature to derive a theoretical definition that is closest to the probable truth. The approach enables the researcher to identify gaps and inconsistencies in the state of the science and, subsequently, will lead to advancement of the concept through selection of appropriate research questions and methodologies (Hupcey & Penrod, 2005).

Data Sources

A systematic review of the literature was conducted in June 2010 to determine the use of the concept "chemotherapy-related change in cognitive function."

The search included a systematic process using OVID, PubMed, CINAHL®, and Web of Knowledge, which includes searches of three databases: Science Citation Index–Expanded, Social Science Citation Index, and Arts and Humanities Citation Index. Key words *chemotherapy, chemotherapy adjuvant,* or *chemotherapy side effects* were used and limited to the focus on cognition or cognitive. No time limits were imposed and results were limited to literature written in English. The initial search yielded 235 articles; however, articles related to children, brain cancer, nonmalignant disease states, and animal models were removed. The remaining 115 articles were reviewed for duplicative content, and the final data set totaled 86 items including 2 meta-analysis, 29 review articles, 47 research articles, 3 short commentaries, 1 editorial, 2 newspaper scientific report articles, and 2 book chapters. The search revealed that psychiatrists had documented cognitive change related to chemotherapy as early as 1980; however, increased publication did not occur until the 1990s. In all of the databases described, published literature related to adult patients with cancer and standard chemotherapy did not appear until 1995.

Findings

The findings from the data are presented as they relate to each of the four philosophical principles described in the principle-based concept analysis method.

Epistemologic Principle

For this analysis, the epistemologic principle focuses on how well the concept is defined and differentiated from other concepts. Both explicit and implicit meanings of the concept, as well as common attributes, are identified to differentiate it.

Chemotherapy-related cognitive change is not clearly defined or well differentiated from the other concepts within the scientific literature. Lack of a clear definition is, in part, caused by a lack of understanding about the exact mechanism that brings about cognitive changes (Kannarkat, Lasher, & Schiff, 2007). Advancements in neuroimaging tests offer hope for useful objective measures concerning structural and functional changes in the brain following chemotherapy treatment (Myers, 2009b); however, to date, studies are not conclusive.

Early reports of cognitive change in patients with cancer were described as changes in mental status reflected in behavioral abnormalities (Silberfarb, Philibert, & Levine, 1980). The behavioral changes were not associated with chemotherapy, but rather the emotional distress of a cancer diagnosis. Silberfarb et al. (1980) were among the first to recognize that cognitive change may be related to chemotherapy in some patients with cancer, and a follow-up study concluded that the incidence of this was higher than previously suspected (Oxman & Silberfarb, 1980).

In an article linking chemotherapy to cognitive change, Schagen et al. (1999) described cognitive deficits as "neuropsychological symptoms, in particular memory and concentration problems, frequently reported by patients with cancer treated with chemotherapy, even years after completion of treatment" (p. 641). Ahles et al. (2003) described changes in cognitive function following chemotherapy as being "relatively subtle changes in memory, concentration, and executive function" (p. 612). Others have substantiated those claims, describing cognitive change related to chemotherapy as involving difficulty with memory as well as some higher order processes that include psychomotor speed and executive functioning (Hess & Insel, 2007). Specifically, executive functioning includes such activities as planning, decision-making, judgment, and the ability to shift between activities in a flexible way (Schagen et al., 2006). Although symptoms associated with cognitive change (e.g., memory, difficulty concentrating, planning, decision-making) describe aspects of the phenomenon, they do not provide a clear definition of the concept.

The literature contains several examples of implicit meaning related to the concept. Jansen, Miaskowski, Dodd, and Dowling (2005) provided a definition of normal cognitive function, rather than cognitive impairment, as a method of thinking about possible changes in function. The definition of cognitive function identifies domains routinely included in assessment and measurement of cognitive abilities. That definition poses several important questions that, if answered, would derive a clearer conceptual meaning: Does cognitive change related to chemotherapy affect all domains of cognition? To what extent are changes seen in each of the domains? How is that change manifested?

Related concepts have been explored in the scientific literature in attempts to increase the understanding of the concept. The problem of attentional fatigue and its impact on a person's concentration has been considered an attribute of cognitive dysfunction. Cimprich (1993) studied patients following breast cancer surgery and reported that attentional fatigue made it difficult for patients to conduct everyday activities, maintain clarity of mind, take effective action, and regulate interpersonal behaviors. In addition, the capacity to direct attention is important to other cognitive functioning (von Ah, Russell, Storniolo, & Carpenter, 2009). Those behaviors, also described as social functioning, require attentive listening, exercising patience, and delaying when responses are appropriate. Comparisons have been made between the capacity to direct attention and the clinical features of adult attention deficit disorder (Simmons, 2009; Staat & Segatore, 2005). The findings

are consistent with reports of individuals appearing to be disoriented, inattentive, and having difficulty learning new tasks (Louiselle & Rockhill, 2009).

Implicit meaning of chemotherapy-related cognitive change also can be found in the description of the cognitive domains likely affected. In general, cognitive function refers to mental processes typically assessed by a person's performance of tasks using a series of neuropsychological tests related to established cognitive domains. However, a lack of standard identification and description of the cognitive domains remains. For example, some studies identify nine domains although others use only eight (see Figure 1).

In addition, the selection of neuropsychological tests used to measure cognitive change related to chemotherapy lacks consistency (Jansen, Miaskowski, Dodd, & Dowling, 2007), and whether the tests provide reliable measures of chemotherapy-related cognitive changes is unknown. The shortcomings of the current neuropsychological tests have been clearly documented (Rugo & Ahles, 2003; Vardy, Rourke, & Tannock, 2007; Wefel et al., 2004; Weiss, 2008); however, little progress has been made toward standardization. In several studies, patients showed little or no change in cognitive ability on standard assessment instruments; however, the same patients reported perceived cognitive changes (Castellon et al., 2004; Galantino, Brown, Stricker, & Farrar, 2006; Hermelink et al., 2006; Tannock, Ahles, Ganz, & van Dam, 2004).

The concept of chemotherapy-related cognitive change has not been defined explicitly in the literature. Although subjective accounts of individuals experiencing chemotherapy-related cognitive change provide some insight into the specific symptoms associated with the phenomenon, the accounts describe the attributes of the concept and do not provide a definition.

Ahles et. al., 2003		Castellon et al., 2004
Verbal ability	⟷	Verbal fluency
Verbal learning	⟷	Verbal learning
Verbal memory	⟷	Verbal memory
Visual memory	⟷	Visual memory
Spatial ability	⟷	Visuospatial function
Psychomotor function	⟷	Psychomotor speed
Motor function	⟷	Reaction time
Attention accuracy	⟷	Executive function
Attention reaction time		–

Figure 1. Example of Contrast in Labels of Cognitive Domains in the Literature

Therefore, the lack of a clear and consistent definition of chemotherapy-related cognitive change makes it difficult to differentiate its conceptual boundaries.

Pragmatic Principle

The pragmatic principle determines the usefulness of the concept for understanding its importance to nursing (Penrod & Hupcey, 2005b). The data were analyzed from an evolutionary perspective to determine the concept's pragmatic use to nursing and how it has been operationalized in nursing.

Cognitive change relative to cancer treatment first appeared in the nursing literature with the recognition of the problem of attention fatigue observed in patients with cancer following breast cancer surgery (Cimprich, 1992). Subsequent interventions to restore attention in patients with cancer and descriptions of loss of concentration following cancer treatment were documented (Cimprich, 1993, 1995). The next published nursing accounts of treatment-related cognitive change appeared in 2003 with the presentation of two case studies relating cognitive dysfunction following chemotherapy for breast cancer (Paraska & Bender, 2003).

Nurses' contributions to the scientific literature concerning chemotherapy-related cognitive change have increased, demonstrated by a variety of publications including review articles documenting the state of the knowledge (Evens & Eschiti, 2009; Hafner, 2009; Jansen, Miaskowski, Dodd, & Dowling, 2005; Jansen, Miaskowski, Dodd, Dowling, & Kramer, 2005; Mulrooney, 2008; Myers, 2009b; Myers, Pierce, & Pazdernik, 2008; Nail, 2006), book chapters (Cohen & Armstrong, 2004; Skinner, 2009), meta-analyses (Jansen et al., 2007), literature critiques (Jansen, Miaskowski, Dodd, & Dowling, 2005), research articles (Boehmke & Dickerson, 2005; Byar, Berger, Bakken, & Cetak, 2006; Fitch, Armstrong, & Tsang, 2008; Jansen, Dodd, Miaskowski, Dowling, & Kramer, 2008; Myers & Teel, 2008; von Ah et al., 2009), and development of conceptual models (Hess & Insel, 2007; Myers, 2009a).

Although limited to only a few studies, nurse researchers have focused on the impact of cognitive change on QOL (Byar et al., 2006; von Ah et al., 2009) and the impact of cognitive changes on a person's ability to meet responsibilities and to maintain personal and professional relationships (Paraska & Bender, 2003). Others have focused on the patient's perspective of the emotional toll of chemotherapy-related side effects (Mitchell, 2007) and the identification of successful strategies used by patients to cope with cognitive changes (Fitch et al., 2008).

Efforts to increase nurses' awareness and understanding of chemotherapy-related cognitive change are increasingly evident. The Oncology Nursing Society (ONS) 2009–2013 Research Agenda emphasizes

studies in cognitive function as a research priority (ONS, 2009). Specifically, future research should focus on the description of long-term effects, identification of sensitive measures, physiologic mechanisms underlying cognitive changes, and the development and testing of interventions. In a descriptive pilot study of oncology nurses' awareness of cognitive impairment secondary to chemotherapy, Myers and Teel (2008) found that, generally, oncology nurses were aware of an association. However, only 38% of participants assessed patients for cognitive changes and 44% provided education to patients and families on the topic.

The concept of chemotherapy-related cognitive change is important to nursing because it relates to understanding the experience of the phenomenon and the exploration of strategies to manage the changes in cognitive abilities. Although growing research exists in nursing that is relative to chemotherapy-related cognitive change, the concept is not well defined and its pragmatic use is limited.

Linguistic Principle

The linguistic principle evaluates whether the concept has been used consistently and appropriately within context. Chemotherapy-related cognitive change is not referred to with consistent meaning in the scientific literature. In fact, the concept has many different labels such as cognitive impairment, cognitive decline, neurobehavioral disorders, and neuropsychological performance, among others, and phrases such as chemobrain, chemofog (Jansen, 2006; Nelson & Roth, 2006), chemo malaise, and memory lock (Mitchell, 2007). Those are just a few to have been used by cancer survivors to describe these changes.

The lack of consistent terminology leads to further confusion in identifying characteristics of the observed side effects. When patients undergoing chemotherapy report symptoms of cognitive change, they are commonly referring to their perceptions of mental slowness, decreased attention and concentration, and difficulty with short-term memory (Silverman et al., 2007). When healthcare professionals address the topic, they often use terms that refer to a variety of cognitive abilities based on one's performance on neuropsychological tests directed to specific domains of cognition.

Chemotherapy-related cognitive change has been studied in several treatment contexts including adjuvant therapy that consists of standard and high-dose chemotherapy and anti-estrogen therapy. The effect of hormone therapy in the treatment of breast cancer is an issue of increasing importance to patients and healthcare providers. Anti-estrogen therapy often is prescribed following surgery and chemotherapy for patients with breast cancer whose tumors are hormone-receptor positive to prevent disease recurrence and prolong survival. Although the number of young breast cancer survivors requiring adjuvant anti-estrogen therapy is increasing, little is known currently about the long-term effects of these agents on cognitive function (Pandya & Morris, 2006). Importantly, the literature is expanding with studies involving the effects on cognitive change of chemotherapy alone compared to chemotherapy combined with anti-estrogen therapy (Bender, Paraska, Sereika, Ryan, & Berga, 2001; Collins, Mackenzie, Stewart, Bielajew, & Verma, 2009; Jim et al., 2009; Phillips & Bernhard, 2003; Rugo & Ahles, 2003; Stewart et al., 2008). As a result, the contextual scope of the concept is generally expanded to include cognitive change related to adjuvant chemotherapy in combination with anti-estrogen therapy.

The concept of chemotherapy-related cognitive change has been applied in several contexts related to cancer diagnoses and time post-treatment. Although most studies have focused only on individuals with breast cancer, some studies have included the occurrence of cognitive change following chemotherapy treatment for other solid tumors and hematologic malignancies (Ahles et al., 2002; Eberhardt et al., 2006; Fitch et al., 2008; Kohli et al., 2007; Myers et al., 2008; Staat & Segatore, 2005; Tannock et al., 2004; Vardy et al., 2006; Vardy, Wefel, Ahles, Tannock, & Schagen, 2008). However, insufficient studies exist to adequately determine whether cognitive change manifests differently across cancer diagnoses. In addition, a lack of clarity remains about the timing of cognitive changes following chemotherapy. Changes in cognition may include acute changes occurring during the treatment cycle alone or long-term effects noticeable for years beyond treatment (Ferguson et al., 2007; Kreukels, van Dam, Ridderinkhof, Boogerd, & Schagen, 2008; Schagen & van Dam, 2006).

Many terms and labels are used in reference to the concept of chemotherapy-related cognitive change. Although the terms vary, the implied meaning consistently focuses on characteristic symptoms of problems with memory, attention, concentration, and executive function. Although clinically important, the inclusion of hormone therapies contributes to lack of conceptual clarity. Lastly, variation in cancer diagnoses, as well as the timing of cognitive effects, are contextual variations that have not been adequately studied.

Logical Principle

The logical principle guided the analysis of chemotherapy-related cognitive change to determine its integration with related concepts and, then, to determine if the concept remains clear and holds its boundaries when positioned theoretically with other concepts (Penrod & Hupcey, 2005b).

Normal cognitive function is a multidimensional concept involving mental processes that span multiple

domains of cognition (Bender et al., 2001; O'Shaughnessy, 2003; Phillips & Bernhard, 2003; Wieneke & Dienst, 1995). Chemotherapy-related cognitive impairment may be generalized across several cognitive domains such as language, verbal and nonverbal memory, spatial ability, and motor function (Bower, 2008; Falletti, Sanfilippo, Maruff, Weih, & Phillips, 2005). Jansen et al. (2007) proposed that the domains of cognition may be so closely linked and interdependent that a change in one domain may affect another. Through the conceptual analysis, other phenomena emerge such as fatigue, depression, anxiety, and sickness behavior. Since the earliest studies, researchers have questioned the relationship among psychological and behavioral variables and the incidence of chemotherapy-related cognitive change (Cull et al., 1995; Oxman & Silberfarb, 1980; Schagen et al., 1999; Silberfarb et al., 1980). Paraska and Bender (2003) recognized that although not all patients with breast cancer experience depression, it could be a confounding symptom. In addition, individuals with depression commonly experience decline in the following cognitive dimensions: attention and concentration, learning and memory, and psychomotor efficiency. However, studies have not yet demonstrated a relationship between chemotherapy-related cognitive change and emotional states (Brezden, Phillips, Abdolell, Bunston, & Tannock, 2000; Eberhardt et al., 2006; Hermelink et al., 2006; Mehlsen, Pedersen, Jensen, & Zachariae, 2009; Tchen et al., 2003; Weineke & Dienst, 1995).

Some difficulty results from the blurring of boundaries of the behavioral phenomena themselves. Several have identified common and confounding issues concerning fatigue and emotional distress. Taillibert et al. (2007) identified a potential link to stress-response symptoms (different from depression) that may impact performance during cognitive testing. In addition, difficulties in cognition may create stress that weakens performance with high level cognitive tasks (Stewart et al., 2008). Fatigue, recognized as a common side effect of cancer treatments, may lead to difficulty performing cognitive tasks; however, the impact of fatigue on cognitive impairment still remains unclear (Downie, Mar Fan, Houede-Tchen, Yi, & Tannock, 2006; Falleti et al., 2005).

The identification of sickness behavior offers new information that blurs the conceptual boundaries. Sickness behavior is associated with cytokine release related to inflammatory processes associated with the body's response to the cancer disease process and includes a group of symptoms that appear in cluster and include fever, fatigue, lethargy, muscle aches, anorexia, decreased ability to concentrate, and loss of pleasure (Barsevick, 2007; Myers, 2009b; Myers et al., 2008). In addition, the role of chronic disease, in general, and its impact on cognitive change has been studied. Raffa et al. (2006) compared cognitive impairment among individuals with other chronic diseases where similar association of cognitive impairment had been reported.

Although a lack of conceptual definition of cognitive change related to chemotherapy exists, the concept has given rise to two attempts at theoretical integration. Hess and Insel (2007) developed the Conceptual Model of Chemotherapy-Related Changes in Cognitive Function that suggests that two distinct pathways influence cognitive function changes. Those distinct, but interacting, pathways include the physiologic effects of cancer treatments and the psychosocial impact of cancer diagnoses. In the model, the psychosocial impact of a cancer diagnosis is theorized as leading to anxiety, stress, and depression.

Myers (2009a) proposed a blending of the Theory of Unpleasant Symptoms (TUS) (Lenz, Pugh, Milligan, Gift, & Suppe, 1997) with the Conceptual Model of Chemotherapy-Related Changes in Cognitive Function (Hess & Insel, 2007). The TUS focuses on symptoms and their interactions. It asserts that multiple symptoms can occur at one time leading to interaction among symptoms and influencing factors that affect the individual's performance of physical, cognitive, and social activities. The blended model proposed by Myers (2009a) provides a clear description of the symptoms related to cognitive change and recognizes the components of the cancer diagnosis and treatment, which are potential antecedents to the experience of cognitive change.

Those examples provide effective frameworks for future research; however, the lack of a clear definition of chemotherapy-related cognitive change continues to make the development of accurate theoretical models challenging. Important issues emerge for nursing research and practice that focus on the potential outcomes and serious consequences of cognitive change and its impact on QOL for cancer survivors.

Conceptual Components

Conceptual components of chemotherapy-related cognitive change include antecedents and consequences. Antecedents relative to chemotherapy-related cognitive change include individual, disease, and treatment factors. Individual factors, particularly age and gender, may play a role in the experience of chemotherapy-related cognitive change. Disease factors encompass the specific cancer diagnosis and also may include preexisting cognitive impairment and experiences of depression, anxiety, and other behavioral disorders. Treatment factors include the specific treatment, either chemotherapy or hormone therapy, or a combination

of the two, as well as the dose and duration of therapy. In some cases, mood disorders such as depression and anxiety may present as antecedents and, in other cases, serve as moderators.

Consequences or outcomes of chemotherapy-related cognitive change include adjustment to illness, impact on QOL, and potential for emotional distress. Adjustment to illness may include reassigning family roles and responsibilities, which can lead to subsequent strain. In addition, common symptoms of cognitive change (e.g., poor concentration, inability to focus) make it difficult to carry out normal daily activities in personal and professional life. Emotional distress, resulting from the impact of cognitive change on everyday activities, also may contribute to additional fear, anxiety, or depression.

Theoretical Definition

A theoretical definition is presented as the final product of a principle-based concept analysis. Chemotherapy-related cognitive change is a multidimensional phenomenon that follows cancer diagnosis and chemotherapy treatment and involves the patient's perception of change in his or her cognitive abilities. Symptoms of cognitive change may last for the duration of treatment or may persist for months or years. Changes in cognition following chemotherapy treatment often are subtle but clearly recognized by the individual experiencing them. An individual may perceive changes in cognition that do not correlate with objective measures of cognitive impairment. Factors such as fatigue, depression and anxiety may be moderators of the symptom experience. The exact relationship of those factors to cognitive change is unclear; however, evidence exists that individuals still experience cognitive change when the factors are controlled. In addition, some of the symptoms of cognitive change may be frightening and lead to emotional distress. The resulting physical and psychological consequences can significantly impact QOL.

Discussion

The principle-based concept analysis served as an appropriate method for identifying what is known about the concept of chemotherapy-related cognitive change. Importantly, the analysis of each philosophical principle identified gaps in understanding and generated questions concerning limitations. The lack of a clear conceptual definition became evident in the epistemologic analysis and continued to create limitations as the concept was evaluated on the pragmatic, linguistic, and logical principles. In addition, the method generated meaningful conceptual insights about chemotherapy-related cognitive change that are based on sound, scientific evidence. The product is a theoretical definition that reflects the current state of the science.

Implications for Nursing Practice

Analyzing chemotherapy-related cognitive change and its impact on cancer survivors is important to nursing because it may guide research in the development of reliable assessment tools that can determine the long-term consequences of cognitive impairment and develop successful strategies to manage living with cognitive deficits. This concept analysis also may help to direct efforts in patient and family counseling and to inform healthcare policy related to cancer survivors' QOL, establishing standards for routine assessment and follow-up evaluations of cognitive changes after treatment.

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