Cognitive Dysfunction Following Adjuvant Chemotherapy for Breast Cancer: Two Case Studies

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Purpose/Objectives: To describe the cognitive dysfunction experienced by two women after they received adjuvant chemotherapy for breast cancer and to discuss the potential role of changes in reproductive status and depression in the development of cognitive dysfunction.

Data Sources: Journal articles, research data, and clinical experience.

Data Synthesis: Following chemotherapy, 17%–50% of women with breast cancer experience cognitive dysfunction that may include decrements in memory, attention, and psychomotor efficiency. One mechanism that may contribute to cognitive dysfunction involves changes in reproductive status resulting from chemotherapy. Additionally, the presence of depression may confound the experience of cognitive dysfunction.

Conclusions: A comprehensive description of cognitive dysfunction and improved understanding of the interrelationships among cognitive dysfunction, reproductive hormone levels, and depression in women with breast cancer receiving adjuvant chemotherapy may hasten the development of interventions for the management of cognitive dysfunction.

Implications for Nursing: Nurses should teach women with breast cancer and their families about the potential for cognitive dysfunction after chemotherapy so the problem can be recognized and interventions can be implemented to help women compensate for the dysfunction.

Key Points . . .

- Cognitive dysfunction can persist for years following the completion of adjuvant chemotherapy in women with breast cancer.
- Cognitive dysfunction associated with adjuvant chemotherapy can affect the ability of women with breast cancer to maintain usual family, career, and community responsibilities.
- Women with breast cancer can be taught to integrate strategies into their lives to help compensate for the cognitive dysfunction they experience as a consequence of adjuvant chemotherapy.

Breast cancer is the most common malignancy and the second leading cause of cancer-related death in women in the United States (Jemal et al., 2003). Twenty-five percent of women with breast cancer are premenopausal at the time of diagnosis (Danforth, 1991). Adjuvant chemotherapy has significantly improved the cure rate in premenopausal women with early-stage breast cancer; however, chemotherapy for breast cancer has been associated with deficits in cognitive function (Brezden, Phillips, Abdolell, Bunston, & Tannock, 2000; Paganini-Hill & Clark, 2000; Schagen et al., 1999; van Dam et al., 1998). These deficits may persist for years after the completion of treatment (Berglund, Bolund, Fornander, Rutqvist, & Sjoden, 1991; Cimprich, 1992; Paganini-Hill & Clark; Schagen et al.; van Dam et al.; Wieneke & Dienst, 1995). Cognitive dysfunction occurs in 17%–50% of women who receive chemotherapy for breast cancer (Brezden et al.; van Dam et al.) and may include decrements in verbal and visual memory, mental flexibility, psychomotor efficiency, attention and concentration, and visuospatial ability (Bender, Paraska, Sereika, Ryan, & Berga, 2001).

One mechanism that may contribute to cognitive dysfunction in women who receive chemotherapy for breast cancer involves changes in reproductive hormone levels and consequent change in reproductive status (Bender et al., 2001). Adjuvant chemotherapy results in loss of estrogen and progesterone and ovarian failure in 77% of women who are premenopausal at the time of a breast cancer diagnosis (Bines, Oleske, & Cobleigh, 1996; Mehta, Beattie, & Das Gupta, 1992). Reductions in estrogen and progesterone levels are associated with deficits in learning, memory, attention, and psychomotor efficiency in healthy women who experience natural or surgical menopause (Farrag, Khedr, Abdel-Aleem, & Rageh, 2002; Phillips & Sherwin, 1992; Sherwin, 1996). Improvement in these dimensions of cognitive function occurs with hormone replacement therapy (Grodstein et al., 2000; Henderson, Paganini-Hill, Emanuel, Dunn, & Buckwalter, 1994; Resnick & Maki, 2001; Robinson, Friedman, Marcus, Tinklenberg, & Yesavage, 1994; Sherwin & Gelfand, 1985). However, no studies have examined the extent to which chemotherapy influences the relationship between cognitive function and reproductive hormone status in premenopausal women with breast cancer. Additionally, although not all women with breast cancer experience depression during the course of treatment, the presence of depression may be a confounding factor in the experience of cognitive dysfunction in this population (Cohen, Weingartner, Smallberg, Pickar, & Murphy, 1982; Weingartner & Silberman, 1982).

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Therefore, a prospective study currently is being conducted to determine the short- and long-term effects of adjuvant chemotherapy on cognitive function and reproductive hormone status in three groups of premenopausal women with breast cancer. Women in groups 1 and 2 have stage I or II breast cancer, and those in group 3 have ductal carcinoma in situ. Women in group 1 receive chemotherapy alone, women in group 2 receive chemotherapy plus tamoxifen, and women in group 3 receive no chemotherapy or tamoxifen. Cognitive function and reproductive hormone levels are measured prior to chemotherapy (time 1) and one week (time 2) and 12 months (time 3) after the completion of chemotherapy. Reproductive hormone levels are used to determine each woman's reproductive status. Additionally, depression is measured at each time point as a potential covariate of cognitive function.

This article profiles two of the prospective study's participants who experienced cognitive dysfunction during and after treatment with chemotherapy and tamoxifen for breast cancer. A case study approach is used to describe each participant's results from a neuropsychological test battery (objective measures of cognitive function) and measures of perceived cognitive function, depression, and reproductive status (see Table 1). The authors' intent is to illustrate the cognitive difficulties experienced by two women being treated for breast cancer to enhance the understanding of healthcare professionals who care for women with breast cancer.

Procedures

The institutional review board approved the prospective study. After completion of informed consent procedures, participants provided demographic information and completed a menstrual history questionnaire. Blood samples were drawn for reproductive hormone levels, including estradiol, estrone, progesterone, follicle-stimulating hormone, luteinizing hormone, total testosterone, and androstenedione. Reproductive hormone levels and menstrual history data were used to characterize women as premenopausal, perimenopausal, or menopausal before and after chemotherapy. A neuropsychological battery of tests assessed the dimensions of cognitive function in attention and concentration, learning and memory, and psychomotor efficiency and visuospatial ability. General intelligence was estimated at time 1 only to standardize the results of the remaining tests in the neuropsychological battery. Depression and perceived cognitive function also were measured.

Case Study 1

Participant one was a 46-year-old, married, Caucasian woman with 12 years of education who resided with her husband and two school-aged children. She had been employed as a bookkeeper outside the home until her breast cancer surgery. She had undergone a lumpectomy with axillary node dissection for stage II infiltrating ductal carcinoma of the breast. At the initial meeting (time 1), she revealed that menarche had occurred at age 13 and she had experienced no changes in her menstrual cycle in the previous year. She reported memory problems manifested by forgetting things and the names of people in the past day or two, as well as in the year prior to her diagnosis of breast cancer. She was not depressed at time 1, as measured by the Beck Depression Inventory-Second Edition (BDI-II) (Beck, Steer, & Brown, 1996).

Participant one began chemotherapy one week after the first meeting. She received four cycles of doxorubicin and cyclophosphamide, followed by four cycles of paclitaxel. At time 2, she reported having been amenorrheic since the time 1 meeting. In addition, she continued to report memory problems and complained of problems with the use of her hands and sensory-perceptual alterations in her hands and feet. The symptoms related to the use of her hands and the sensory-perceptual alterations she reported may have been peripheral neuropathies that have been well-documented to be associated with paclitaxel (Michaud, Valero, & Hortobagyi, 2000). She continued to show no depression on the BDI-II. Her performance on the Digit Vigilance and Grooved Pegboard tests declined from time 1 to time 2, indicating a deterioration in concentration and psychomotor efficiency (see Table 2). Scores on the remaining tests either stayed the same or improved from time 1.

One year after participant one completed chemotherapy (time 3), she was taking tamoxifen and continued to be amenorrheic. The use of her hands returned to normal, and her sensory-perceptual alterations abated. Although not depressed, she reported continued difficulty with memory and an inability to return to her work as a bookkeeper. Her performance on the Rey Auditory Verbal Learning Test, Digit Vigilance Test, Grooved Pegboard Test, and Trail Making Test-A and Test-B all deteriorated from time 2 to time 3. The declines observed on the Digit Vigilance, Grooved Pegboard Test, and Rey Auditory Verbal Learning test scores indicated further deterioration from the time 1 assessment.

Although participant 1's scores did not deteriorate on most of the learning and memory measures through the course of the study, her score on the Rey Auditory Verbal Learning Test declined. Each learning and memory test identified in Table 1 evaluates a different aspect of learning and memory. For example, the Rey Complex Figure Test measures the ability to learn and remember a complex figure (visual learning and memory). The Paragraph Recall Subtest of the Rivermead Behavioral Memory Test evaluates the ability to learn and remember new information that is presented verbally in the context of other information, similar to listening to a story. The Rey Auditory Verbal Learning Test measures the ability to learn and remember new information that is not presented in the context of other information, such as lists of unrelated words. Thus, participant 1's performance on the Rey Auditory Verbal Learning Test indicated she was experiencing difficulty learning and remembering this type of information.

The declines observed in participant 1's scores on the other measures indicated deterioration in attention and psychomotor efficiency. Her perceived difficulty with memory may have been a further indication of this problem. Similar to learning and memory, each attention measure listed in Table 1 evaluates a different aspect of attention. The Trail Making Test-B (Reitan, 1958) measures attention, visual search and motor function, and the ability to shift attention. The Digit Vigilance Test measures the ability to sustain attention. The Grooved Pegboard Test and Trail Making Test-A measure psychomotor efficiency, and the Trail Making Test-A also provides information about attention. Attention is a fundamental dimension of cognitive function. If an individual is experiencing difficulty paying attention to information, he or she may be unable to learn and remember that information. Furthermore, each of the tests is timed. The more time it takes to

Table 1. Measures of Cognitive Function and Depression

Measure and Administration	Scoring
Attention	
Digit Span Forward (Wechsler, 1981): Participants listen to a series of digits (from four to eight digits in length) and are asked to repeat them aloud in the order given.	Highest number of digits repeated in the forward condition, with higher scores indicating better performance
Digit Span Backward (Wechsler): Participants listen to a series of digits (four to eight digits in length) and are asked to repeat them aloud in the opposite order given.	Highest number of digits repeated in the backward condition, with higher scores indicating better performance
Trail Making Test-B (TMT-B) (Reitan, 1958): The TMT-B consists of 25 circles on a white sheet of paper. The circles contain numbers from 1–13 and letters from A–L. Participants are asked to draw a line consecutively connecting all the circles, alternating between numbers and letters as quickly and accurately as possible.	Number of seconds to complete the task, with higher scores indicating poorer performance
Concentration	
Digit Vigilance Test (*Lafayette Clinical Repeatable Neuropsychological Test Battery,* 1989): Participants are presented with two pages of 59 rows of 35 numbers and are instructed to search for and cross out every target number (six or nine) they detect as quickly and accurately as possible.	Number of seconds to complete both pages of numbers, with higher scores indicating poorer performance
Verbal Learning and Memory	
Rey Auditory Verbal Learning Test (Rey, 1964): Participants listen to a list of 15 nouns read aloud for five consecutive trials, each trial followed by a free recall list. On completion of trial 5, an interference list of 15 words is presented, followed by free recall of that list, and finally followed by free recall of the original list. A delayed recall of the original list is tested 20 minutes later.	Total number of words recalled, with higher numbers of words recalled indicating better performance
Paragraph Recall Subtest of the Rivermead Behavioral Memory Test (Wilson et al., 1989): Participants listen to a brief paragraph, five sentences in length, and are asked to recall as much information (i.e., ideas) as they can from the paragraph.	Number of ideas recalled from the paragraph, with higher numbers of ideas recalled indicating better performance
Visual Learning and Memory	
Rey Complex Figure Test (Osterrieth, 1944): Participants are asked to draw a complex figure from memory immediately and 20 minutes after they copy the design (see Visuospatial Ability below).	The score ranges from 0–36 and is based on the completeness and accuracy of the drawing, with higher scores indicating better performance.
Psychomotor Efficiency	
Grooved Pegboard (GP) Test (Klove, 1963): The GP consists of a 5-inch by 5-inch board containing a set of 25 slotted holes that are randomly positioned. A set of pegs must be rotated by the participant to be inserted correctly into similarly shaped slots, one at a time, as quickly and accurately as possible, first with the dominant hand and then the nondominant hand.	The score is the amount of time (in seconds) to insert the pegs. The higher the score is, the poorer the performance.
Trail Making Test-A (TMT-A) (Reitan)**:** The TMT-A consists of a white sheet of paper on which 25 circles are distributed. Each circle contains a number from 1–25. Participants are asked to draw a line connecting all circles in numerical sequence as quickly and accurately as possible.	Number of seconds to complete the test, with higher scores indicating poorer performance
Visuospatial Ability	
Rey Complex Figure Test (Osterrieth): Participants are asked to copy a complex visual design. (See Visual Learning and Memory above).	The score ranges from 0–36 and is based on the completeness and accuracy of the drawing, with higher scores indicating better performance.
Patient's Assessment of Own Functioning (PAOF) (Chelune et al., 1986): The PAOF is a 33-item, self-report measure in which participants rate the adequacy of their functioning on five subscales: general memory and orientation, language/communication, memory for specific information, cognitive/intellectual, and sensorimotor. Participants rate each item on a six-point scale ranging from never to almost always.	Sum of the ratings to items in each subscale
Depression	
Beck Depression Inventory-Second Edition (BDI-II) (Beck at al., 1996): The BDI-II is a 21-item, self-report measure of the severity of depression. Participants rate symptoms of depression in the past two weeks on a four-point scale.	Sum of the ratings for the 21 items. Cut score guidelines for depression are as follows: minimal (0–13), mild (14–19), moderate (20–28), and severe (29–63).

complete a test, the poorer the performance, indicating an overall "slowing" of thought, actions, and responses.

Case Study 2

Participant two was a 44-year-old, married, Caucasian woman with 12 years of education. She was a mother of three children, who were delivered via cesarean section. She was a licensed practical nurse and, although she had not been employed outside the home in many years, she expressed a desire to return to work. She had undergone a lumpectomy with axillary node dissection for stage I infiltrating ductal carcinoma. At the time 1 meeting, her menstrual history revealed that menarche had occurred at age 12; except for some increase in the amount of blood flow, her menses had been regular and without change in the year preceding her breast cancer diagnosis.

Table 2. Participant Results Over Time

Measure	Participant One			Participant Two		
	Time 1	Time 2	Time 3	Time 1	Time 2	Time 3
Attention and Concentration						
Digit Span Forward (higher scores indicate better performance)	11	10	11	7	10	8
Digit Span Backward (higher scores indicate better performance)	11	10	10	4	5	3
Trail Making Test-B (lower scores indicate better performance)	47	41	52	49	58	56
Digit Vigilance Test (lower scores indicate better performance)	224	361	405	394	306	342
Learning and Memory						
Rey Auditory Verbal Learning Test, delay (higher scores indicate better performance)	12	11	9	12	15	15
Paragraph Recall Subtest of the Rivermead Behavioral Memory Test (higher scores indicate better performance)	3.5	6	6.5	7.5	11	7.5
Rey Complex Figure Test, immediate delay (higher scores indicate better performance)	18	21	27	23	26.5	30
Rey Complex Figure Test, 20-minute delay (higher scores indicate better performance)	18	19.5	27	23	24	30
Psychomotor Efficiency						
Grooved Pegboard Test (lower scores indicate better performance)						
Dominant hand	59	65	64	128	52	63
Nondominant hand	57	69	72	66	58	69
Trail Making Test-A (lower scores indicate better performance)	21	16	20	22	18	23
Visuospatial Ability						
Rey Complex Figure Test, copy (higher scores indicate better performance)	36	36	34	34	33	34
Depression						
Beck Depression Inventory-Second Edition (higher scores indicate more depression)	7	9	9	54	11	35

She reported that, in the past year or more, she was forgetful of things and the names of people and she often failed to finish something she started because she forgot what she was doing. She was severely depressed at time 1 and had been prescribed fluoxetine and alprazolam. A psychiatric referral, although offered, was declined.

Participant two started chemotherapy one week after the time 1 meeting. She received four cycles of doxorubicin and cyclophosphamide, followed by four cycles of paclitaxel. That treatment was followed by six weeks of radiation therapy. At time 2, she continued to take fluoxetine and alprazolam and was not depressed, as evidenced by her score on the BDI-II (see Table 2). She also was taking tamoxifen. She had one menses the first month after her time 1 visit, then experienced amenorrhea. She continued to complain of the same problems with memory. Scores on the tests of the neuropsychological battery improved except for the Trail Making Test-B, which increased at time 2, indicating a potential deterioration in attention, learning, and memory (see Table 2). The improvement in her scores also may have been partially attributable to practice effects, the phenomenon of improved scores with repeated neuropsychological assessment (McCaffrey & Westervelt, 1995).

At time 3, participant two continued to take tamoxifen and fluoxetine. However, her score on the BDI-II indicated that she was severely depressed again. She also reported that she had been separated from her husband between times 2 and 3. She had one random menses in the preceding year and complained of increased problems with the use of her hands that may have been related to her paclitaxel therapy (Michaud et al., 2000). She reported difficulty performing higher cognitive tasks such as planning and organizing, working with numbers, and problem solving.

Participant two deteriorated on many of the tests of the neuropsychological battery from time 2 to time 3. With the exception of her performance on the Grooved Pegboard Test, the scores at time 3 were almost at the same level as her scores at time 1. Most notable was the correlation between participant 2's performance on the neuropsychological battery and the measure of depression. When her depression scores were high, indicating severe depression, her performance on the neuropsychological measures was poorer. Conversely, when she was not depressed, as indicated by her score on the BDI-II, her performance on the neuropsychological measures improved.

Discussion

Clearly, the two women with early-stage breast cancer described in these case studies experienced cognitive dysfunction, including deficits in attention and concentration, learning and memory, psychomotor efficiency, and visuospatial ability, as long as one year after completing chemotherapy. The deficits in cognitive function experienced by these participants are similar to those reported previously in women receiving adjuvant chemotherapy for breast cancer (Berglund et al., 1991; Brezden et al., 2000; Cimprich, 1992; Paganini-Hill & Clark, 2000; Schagen et al., 1999; van Dam et al., 1998; Wieneke & Dienst, 1995). Cognitive dysfunction was documented in this study by tests in the neuropsychological battery as well as the measure of perceived cognitive function. Re-

ports of problems with memory were consistent throughout all three time points, with participant one experiencing more severe and progressive deterioration in cognitive function. Although participant two had more complaints of problems with memory and attention throughout the study, the complaints may have been partially attributable to the presence of severe depression at times 1 and 3. With the diagnosis of breast cancer complicated by cognitive dysfunction, neither woman felt able to work outside the home.

Both women perceived problems with cognitive function before deterioration was detected in their scores on the neuropsychological tests. The perceived problems with cognitive function that were reported at time 1 may have been associated with the fact that both women were adjusting to the news of a breast cancer diagnosis and treatment. Subjective complaints of cognitive dysfunction have been reported to precede or occur in the absence of objectively measured cognitive dysfunction. This has been observed particularly in patients with intact higher level cognitive function, which includes planning and organizing, working with numbers, and problem solving (Schagen et al., 1999). Thus, these case studies illustrate the need for future research to evaluate cognitive function over time, using both objective and subjective measures. These case studies also suggest the need to study the relationship between cognitive function and reproductive hormone levels in premenopausal women with early-stage breast cancer. Both women experienced a change in reproductive status from premenopause to menopause after chemotherapy, as evidenced by amenorrhea and reproductive hormone levels.

Participant two experienced depression in conjunction with cognitive dysfunction, with severe depression at times 1 and 3 despite her use of antidepressant medication. Interestingly, at time 2, when participant two was not depressed (as measured by the BDI-II), almost all of her scores on the measures of cognitive function improved from time 1. Cognitive dysfunction and depression frequently accompany one another (Cohen et al., 1982; Tarbuck & Paykel, 1995; Weingartner & Silberman, 1982). The dimensions of cognitive function that most commonly deteriorate in depressed individuals include attention and concentration, learning and memory, and psychomotor efficiency (Sweet, Newman, & Bell, 1992; Tarbuck & Paykel). Additional investigation is needed to discern the role of depression in cognitive dysfunction experienced by women with breast cancer who receive chemotherapy and to delineate the role of depression in relationship to premature menopause in women who are premenopausal at the time of a breast cancer diagnosis.

The results of these two case studies must be interpreted with caution. Clearly, no generalizations can be made from the experiences of these participants. Furthermore, although each subject in this investigation served as her own control over time, the study used no control or comparison subjects. Additionally, as a result of the standardization of breast cancer treatment, randomization of subjects to treatment groups was not possible. The improvement observed in scores on some of the cognitive function measures may have been influenced by practice effects, the phenomenon of improved performance on neuropsychological tests that occurs with repeated measurement (McCaffrey & Westervelt, 1995). Strategies to minimize practice effects (i.e., use of alternate, equivalent versions of instruments when available and attempts to provide sufficient time intervals between testing) were instituted (Bender et al., 2001). However, the potential influence of practice effects in any study that uses repeated neuropsychological testing cannot be completely eliminated because they can emerge as early as the second testing (McCaffrey & Westervelt).

Nursing Implications

Early identification of cognitive dysfunction is critical because of the potential impact of this problem on the ability of women to maintain usual family, career, and community responsibilities (Bender et al., 2001). Patients and their families must be educated about the potential for cognitive dysfunction. Family members play a key role in the early identification of cognitive dysfunction because anecdotal reports suggest that they frequently recognize the subtle, early signs of cognitive dysfunction before healthcare providers or patients themselves. Reports of changes in attention or memory should prompt nurses to initiate a thorough assessment of cognitive function (Bender, 1994).

Patients experiencing cognitive dysfunction should try to incorporate sufficient periods of uninterrupted sleep into their lives because sleep deprivation can aggravate the problem. They also should be taught to avoid the use of alcohol, medications, or other agents that could intensify the problem. Cognitive dysfunction usually is not a severe consequence of adjuvant chemotherapy for breast cancer. However, in more severe cases, patients may be required to avoid self-administration of medications and operation of machinery; family members may need to have more constant contact with patients to ensure their well-being.

Finally, depression and cognitive dysfunction can accompany one another in patients with cancer (Curran, 1992). Thus, nurses must report immediately any manifestations of depression that persist for two weeks at any time during and after treatment, including depressed mood, marked diminished interest or pleasure in activities, unexplained weight loss, sleep changes, diminished ability to think or concentrate, preoccupation with worthlessness, and suicidal ideation.

Conclusions

A comprehensive description of cognitive dysfunction and improved understanding of the interrelationships among cognitive dysfunction, reproductive hormone levels, and depression in women with breast cancer receiving adjuvant chemotherapy may hasten the development of interventions for the management of cognitive dysfunction. Behavioral strategies that women can integrate into their lives to compensate for cognitive dysfunction may improve their ability to organize information, maintain attention, and enhance encoding of information for future recall. In addition to behavioral strategies to address these problems, pharmacologic therapies, including antidepressants and psychostimulants, may be added to the management of cognitive dysfunction and depression (Bender et al., 2001).

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For more information . . .

- National Alliance of Breast Cancer Organizations
  www.nabco.org
- The Breast Cancer Site
  www.thebreastcancersite.com
- Y-ME National Breast Cancer Organization
  www.y-me.org

Links can be found using ONS Online at www.ons.org.