The Cognitive Sequelae of Standard-Dose Adjuvant Chemotherapy in Women with Breast Carcinoma

Results of a Prospective, Randomized, Longitudinal Trial

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BACKGROUND. Retrospective trials have reported that chemotherapy-induced cognitive dysfunction was experienced by a subset of patients with breast carcinoma. However, recent evidence indicated that a subset also exhibited impaired cognitive function at baseline, before the start of chemotherapy. A prospective, longitudinal trial that incorporates baseline neuropsychologic evaluations is necessary to determine to what extent cognitive dysfunction is attributable to chemotherapy in this population.

METHODS. Eighteen women with breast carcinoma underwent a comprehensive neuropsychologic evaluation before treatment and at short-term and long-term intervals after chemotherapy. The incidence, nature, severity, and chronicity of cognitive dysfunction developing in patients with breast carcinoma treated with a standard dose of adjuvant chemotherapy were assessed.

RESULTS. Before the start of systemic therapy, 33% of women in the current cohort exhibited cognitive impairment. At the short-term postchemotherapy time point, 61% of the cohort exhibited a decline relative to baseline in 1 or more domains of cognitive functioning and reported greater difficulty in maintaining their ability to work. The most common domains of cognitive dysfunction were related to attention, learning, and processing speed. At the long-term postchemotherapy time point, approximately 50% of patients who experienced declines in cognitive function demonstrated improvement, whereas 50% remained stable. Self-reported ability to perform work-related activities also improved over this interval. Neither impairment at baseline nor subsequent treatment-related cognitive decline exhibited any statistically significant correlation with affective well-being or with demographic or clinical characteristics.

CONCLUSIONS. The current study is the first longitudinal trial to report evidence of an association between cognitive dysfunction and chemotherapy in a subgroup of women with nonmetastatic breast carcinoma. The importance of using prospective research designs, appropriate cognitive measures, and statistical methods to evaluate subgroup effects was discussed. Identification of mechanisms associated with cognitive dysfunction and of risk factors contributing to subgroup vulnerability is necessary. ***Cancer* 2004;100:2292–9.** *© 2004 American Cancer Society.*

KEYWORDS: cognition disorders, breast neoplasms, drug therapy, systemic chemotherapy.

Women with breast carcinoma represent the second largest group within the community of cancer survivors.[1] Survivors of breast carcinoma are increasingly concerned about the possible cognitive sequelae (called *chemobrain*) associated with adjuvant chemotherapy regimens. To successfully resume their previous professional, scho-

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lastic, and/or social activities, they depend on the integrity of higher-order cognitive functions. Chemotherapy-related cognitive impairment has been reported to occur in 17–75% of patients.[2–7] Rather than frank dementia, subtle alterations across a variety of cognitive domains, including verbal memory, nonverbal memory, information processing speed, and visuospatial function, have been reported. However, these findings have been inconsistent. In studies that used tests with adequate sensitivity and reported patients' performance characteristics relative to published normative data, the performance of patients treated with chemotherapy often fell within the average range.[2]

Due to the lack of prospective, longitudinal trials evaluating the cognitive sequelae associated with systemic chemotherapy in a population of individuals with breast carcinoma, the occurrence of cognitive decline secondary to chemotherapy remains to be established conclusively in this population. Without using a prospective design that includes a pretreatment neuropsychologic assessment, a study cannot necessarily attribute the observed decreases in cognitive performance to chemotherapy.

Anderson-Hanley et al.[8] reported the results of a recent metaanalysis that assessed the cognitive sequelae of chemotherapy regimens in a diverse population. Noteworthy was their finding that there was no evidence of significant changes in cognitive function after treatment with chemotherapy when patients' cognitive function was compared with their performance measured before the start of chemotherapy (i.e., when within-subject comparison was performed). We recently found that approximately 35% of women with breast carcinoma demonstrate impaired cognitive function before the start of adjuvant chemotherapy.[9] Therefore, it remains unclear as to whether cognitive dysfunction develops as a result of chemotherapy or whether the previously reported incidence of cognitive dysfunction represents prechemotherapy deficits. The use of a within-subject design with pretreatment baseline measurements and appropriately timed follow-up evaluation(s) is critical in investigations that seek to determine the effect of a treatment regimen on cognitive function.

Previous research and clinical experience suggested that only a subgroup of women with breast carcinoma is at risk for developing cognitive dysfunction secondary to chemotherapy. Therefore, data-analytic strategies that facilitate subgroup detection are appropriate. Simply examining group means may obscure the detection of subtle cognitive declines in a vulnerable subgroup, as these patients would be averaged together with patients who are not vulnerable and do not show evidence of cognitive decline. In addition, identifying the subgroup of women within a trial who exhibit signs of cognitive decline allows the exploration of potential risk factors, including demographic and clinical characteristics, that may account for their vulnerability.

Given the lack of consistent findings regarding the association between cognitive dysfunction and chemotherapy in a population of individuals with breast carcinoma among the previously published retrospective trials, it is necessary for neuropsychologic assessments performed in subsequent studies addressing this issue to be relatively broad. In addition, the use of measures that are sensitive to subtle cognitive decline, rather than screening measures that are designed to capture more noticeable forms of cognitive dysfunction (e.g., dementia), is important.

The current study reports the results of a prospective, randomized, longitudinal trial that evaluated the incidence, nature, severity, and chronicity of cognitive dysfunction among patients with breast carcinoma who were treated with a standard dose of adjuvant chemotherapy. We employed a longitudinal design that incorporated assessments before treatment and at short-term and long-term intervals after treatment.

MATERIALS AND METHODS

Patients were recruited in conjunction with a randomized Phase III trial approved by the institutional review board of the University of Texas M. D. Anderson Cancer Center (Houston, TX). The trial was a collaborative effort among the Departments of Neuro-Oncology (Section of Neuropsychology), Breast Medical Oncology, and General Oncology. All patients who met initial screening criteria and consented to participate in the trials were entered consecutively into the protocol for evaluation. All patients had a diagnosis of primary breast carcinoma and no evidence of metastatic disease, were $\geq$ 18 years old, had completed $\geq$ 8 years of formal education, and were fluent English speakers. No patient had a previous history of other primary malignancy, previous exposure to chemotherapy, or previous or current neurologic or psychiatric disorders, and no patient had used substances that were active in the central nervous system (CNS) and were believed to affect cognition (e.g., narcotics, antiemetics, or steroids) within 3 weeks before testing.

Twenty-six patients met the initial screening criteria for participation. One patient was excluded from the study due to a previous psychiatric illness. The 25 patients who were contacted consented to participate in the study and underwent neuropsychologic evaluation before beginning to receive systemic therapy. At

TABLE 1
Patient Demographic and Clinical Characteristics

Characteristic	No. receiving FAC (%)[a]
TNM classification	
T1N0M0	5 (28)
T1N1M0	4 (22)
T2N0M0	3 (17)
T2N1M0	4 (22)
T3N1M0	2 (11)
Extent of surgery	
Biopsy	1 (6)
Lumpectomy/mastectomy	17 (94)
Radiotherapy[b]	
Yes	6 (33)
No	12 (67)
Menopausal status	
Premenopausal	9 (50)
Perimenopausal	1 (6)
Postmenopausal	6 (33)
Surgically induced menopause	2 (11)
HRT history	
Yes	6 (33)
No	8 (45)
Unknown	4 (22)
Race	
White	17 (94)
Black	1 (6)
Age (yrs)	
Mean (SD)	45.4 (6.7)
Range	34–63
Education (yrs)	
Mean (SD)	14 (2.6)
Range	12–18

FAC: 5-fluorouracil, doxorubicin, and cyclophosphamide; HRT: hormone-replacement therapy; SD: standard deviation.
[a] Sum of percentages does not always equal 100, due to rounding error. $n = 18$.
[b] To the chest wall, with or without inclusion of regional lymphatic chains.

follow-up, six patients chose not to undergo reevaluation, and one patient switched to a regimen of 5-fluorouracil (5-FU), doxorubicin, and cyclophosphamide (FAC) plus paclitaxel. The final study cohort consisted of 18 patients. Patient demographic and clinical characteristics are summarized in Table 1.

Patients were evaluated with a comprehensive battery of cognitive tests, self-report questionnaires regarding their personality traits and affective status, and a breast carcinoma–specific self-report survey of quality of life (QOL). Neuropsychologic evaluations were conducted before the start of systemic chemotherapy (baseline); postchemotherapy, ≥ 3 weeks after cessation of the administration of drugs that were used to control nausea and emesis or that were known to have CNS activity (short-term postchemotherapy time point, approximately 6 months after baseline); and 1 year postchemotherapy (long-term postchemotherapy time point, approximately 18 months after baseline; Fig. 1). Neuropsychologic tests were selected based on their sensitivity and their suitability for use as a brief assessment that could be repeated up to three times with minimal practice effects and patient fatigue. Alternate forms of assessment were used to minimize practice effects when possible. Table 2 summarizes the tests that were used and indicates those with alternate forms.

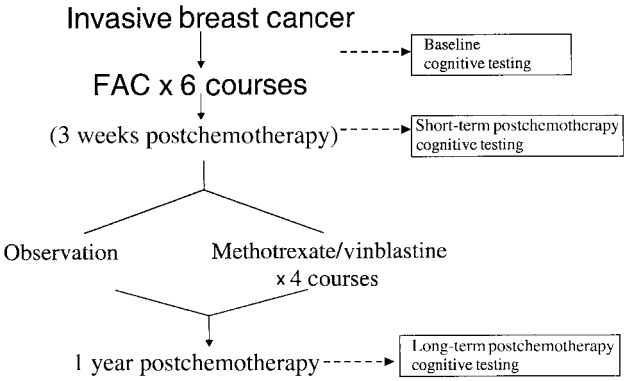

FIGURE 1. Treatment schema. FAC: 5-fluorouracil, doxorubicin, and cyclophosphamide.

TABLE 2
Neuropsychological Tests and Mood Measures Grouped by Principal Domain

Domain	Measure	Test Abbreviation
Attention	WAIS-R[10] Digit Span	Digit Span
Attention	WAIS-R Arithmetic	Arithmetic
Processing speed	WAIS-R Digit Symbol	Digit Symbol
Processing speed	Trail Making Test[11] Part A	TMTA
Learning	VSRT[11] Long-Term Storage[a]	VSRT LTS
Learning	NVSRT[12] Long-Term Storage[a]	NVSRT LTS
Memory	VSRT Delayed Recall[a]	VSRT DR
Memory	NVSRT Delayed Recall[a]	NVSRT DR
Executive function	MAE[13] Controlled Oral Word Association[a]	COWA
Executive function	Trail Making Test Part B	TMTB
Executive function	Booklet Category Test[15]	CT
Executive function	WAIS-R Similarities	Similarities
Visuospatial function	WAIS-R Block Design	Block Design
Motor skill	Grooved Pegboard[16]	GP
Mood	MMPI[16] (Depression scale)	MMPI (Scale 2)
Mood	MMPI (Psychasthenia/Anxiety scale)	MMPI (Scale 7)
QOL	Functional Assessment of Cancer Therapy—Breast Module[18]	FACT

WAIS-R: Wechsler Adult Intelligence Scale—Revised; VSRT: Verbal Selective Reminding Test; NVSRT: Nonverbal Selective Reminding Test; MAE: Multilingual Aphasia Examination; MMPI: Minnesota Multiphasic Personality Inventory; QOL: quality of life.
[a] Alternate forms used.

Statistical Analysis

Published normative data that adjusted for age, education, and gender where appropriate were used to convert patients' raw cognitive test scores into standardized scores (z scores; mean = 0, standard deviation [SD] = 1) to facilitate comparisons among measures. Paired t tests were performed to assess mean group differences between patient performance at baseline and at the short-term postchemotherapy assessment for each cognitive test. In addition, paired t tests were conducted to evaluate mean group differences in cognitive test performance between the short-term and long-term postchemotherapy assessments. In an effort to control for multiple comparisons, only differences for which $P \leq 0.01$ were considered to be statistically significant in all analyses conducted.

Given the previous retrospective research and our clinical experience, we sought to determine whether there was a subset of patients who exhibited cognitive impairment at baseline and/or cognitive deterioration after treatment. Each patient's baseline test performance was judged to indicate impairment if one of two criteria was met. First, patients with z scores ≤ -1.5 for the results of more than 1 test were considered to have cognitive impairment. Second, all patients with z scores ≤ -2.0 for the results of a single test were classified as having cognitive impairment. This approach was designed to minimize the number of potential false-positive errors resulting from multiple tests and to determine the frequency of actual impairment, rather than the frequency of low performance scores. In a normal, healthy population, performance scores that are 1.5 and 2.0 SDs less than the mean score correspond to the 6.5th and 2nd percentiles of the population, respectively. Binomial testing was performed to determine whether the observed frequency of impairment with respect to each test at baseline differed from the frequency of 6.5% that was expected based on normative assumptions.

Because the error inherent in test scores is known for tests with published test-retest reliability, changes in test scores that are clinically *and* statistically meaningful can be identified. The reliable change index (RCI)[19] was used to determine the frequency of change in cognitive function from one assessment to the next. The index is derived from the standard error of measurement of each test, and it represents the 90% confidence interval for the difference in performance between two evaluations that is expected if no real change has occurred. Because the test-retest reliability is unknown for the Verbal Selective Reminding Test Long-Term Storage (VSRT LTS) and the Nonverbal Selective Reminding Test Long-Term Storage (NVSRT LTS), we used a change in performance of $\pm$ 1.5 SDs as the RCI for these two tests.

Minnesota Multiphasic Personality Inventory profiles for all patients yielded adequate validity scale indices to be considered for further clinical scale interpretation.[20] Scale 2 measures depression via items that address affective (e.g., poor morale), cognitive (e.g., hopelessness), and physical symptoms (e.g., sleep disturbances). Scale 7 measures anxiety across the domains of neuroticism, anxiety, withdrawal, poor concentration, agitation, psychotic tendencies, and poor physical health. Each scale is converted into a standardized T-score (mean = 50, SD = 10) for the purpose of comparison. Spearman rho correlations between standardized mood variables and cognitive measures were assessed at each time point using a corrected alpha level of 0.01 to establish statistical significance.

The Functional Assessment of Cancer Therapy—Breast Module (FACT) is a self-report measure that addresses issues related to the QOL of patients with breast carcinoma. Subscales assessing physical, emotional, social, and functional well-being are generated, as is a subscale comprising items specific to a population of individuals with breast carcinoma (e.g., "I am able to feel like a woman"). Subscale ratings were compared between patients classified as having impairment and patients classified as not having impairment at baseline using independent sample t tests. At follow up, independent sample t tests were used to compare subscale ratings between patients classified as exhibiting cognitive decline and those classified as exhibiting stabilization or improvement in cognitive status.

RESULTS

Based on the aforementioned criteria, 33% of patients were classified as having impairment at baseline (4 patients exhibiting impairment on 2 tests and 2 patients exhibiting impairment on more than 2 tests). In terms of both verbal learning and memory (binomial $P = 0.02$ for both), 24% of the study cohort exhibited impairment, a significantly higher frequency compared with normative expectations (Fig. 2). There were no significant differences between patients classified as having impairment and those classified as not having impairment at baseline in terms of QOL (i.e., FACT total and subscales: all P values > 0.4). Patients classified as having impairment at baseline were not statistically significantly different from patients classified as not having impairment in terms of age ($t[16] = -0.08$; $P = 0.46$; mean [years] $\pm$ SD, 43.7 $\pm$ 7.0 vs. 46.3 $\pm$ 6.7), education ($t[15.2] = -2.10$; $P = 0.053$; mean

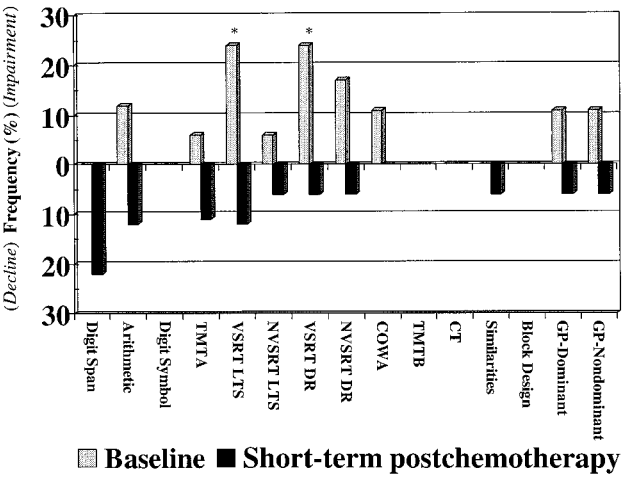

FIGURE 2. Frequency of impairment at baseline and treatment-related cognitive decline. Cognitive decline was assessed using the reliable change index. *: $P = 0.02$ (binomial test); GP: Grooved Pegboard Test; CT: Booklet Category Test; TMTA: Trail Making Test Part A; TMTB: Trail Making Test Part B; COWA: Controlled Oral Word Association Test; VSRT: Verbal Selective Reminding Test; NVSRT: Nonverbal Selective Reminding Test; LTS: Long-Term Storage Test; DR: Delayed Recall Test.

[years] ± SD, 12.7 ± 1.6 vs. 14.8 ± 2.7), menopausal status (χ^2[1, $N = 18$] = 0.11; $P = 0.74$), hormone replacement therapy (HRT) history (χ^2[1, $N = 7$] = 2.92; $P = 0.09$), radiotherapy (χ^2[1, $N = 18$] = 1.13; $P = 0.29$), or tumor stage (χ^2[1, $N = 18$] = 0.52; $P = 0.47$).

Paired-sample t tests were conducted to evaluate whether the patient cohort as a whole experienced a statistically significant short-term decline in cognitive function (Table 3). The results indicated that the mean group performance on the Wechsler Adult Intelligence Scale—Revised (WAIS-R) Digit Symbol and the Booklet Category Test improved significantly relative to the mean baseline performance. WAIS-R Block Design, VSRT LTS, and NVSRT LTS test results suggested trends toward improved performance relative to baseline, but these trends did not meet the corrected alpha criterion for statistical significance.

Paired-sample t tests were conducted to evaluate whether patients, as a group, demonstrated a statistically significant decline in cognitive function between the short-term and long-term postchemotherapy time points. Three patients did not return for a follow-up evaluation at the long-term postchemotherapy time point: two were unable to schedule an evaluation, and one developed leukemia in the interval following the short-term postchemotherapy time point and was withdrawn from the trial. Patients who were randomized to receive FAC before receiving methotrexate and vinblastine (MV; $n = 6$) and those who were randomized to receive FAC alone ($n = 9$) were analyzed separately. However, the results did not differ between these two groups, and thus, the entire cohort was analyzed together to increase statistical power. The results indicated that there were no significant mean group differences in patient performance between the short-term and long-term time points.

Correlation coefficients for the associations between mood measures and cognitive test results at each assessment time point were computed. There were no statistically significant relations between either depression or anxiety and any test of cognitive function at any time point (all P values ≥ 0.02). Furthermore, for associations that approached significance, the correlation coefficient suggested a positive relation, indicating that as affective distress increased, cognitive performance also improved (e.g., correlation between anxiety and Controlled Oral Word Association results at the short-term postchemotherapy assessment: Spearman rho = 0.56; $P = 0.02$).

Within-subject analyses revealed that during the period between baseline and short-term assessment, 61% of patients demonstrated a decline in cognitive function that exceeded the RCI. Thirty-nine percent experienced declines in 1 measure, 11% experienced declines in 2 measures, and 11% experienced declines in 3 measures. Significant declines in performance were most common for the WAIS-R Digit Span (22%), the WAIS-R Arithmetic (12%), the VSRT LTS (12%), and the Trail Making Test Part A (11%). In addition, 6% of patients exhibited declines on the WAIS-R Similarities, the VSRT Delayed Recall (DR), the NVSRT LTS, the NVSRT DR, and the Grooved Pegboard Test (dominant and nondominant hand; Fig. 2). There were no significant differences in overall QOL (i.e., FACT total and subscales: all P values > 0.2) between patients who had cognitive declines and those who did not. However, patients who experienced cognitive declines reported greater difficulty working compared with patients who did not experience a decline in cognitive function (Table 4). Patients who exhibited cognitive decline after chemotherapy were not statistically significantly different from those who did not in terms of age (t[16] = 0.19; $P = 0.85$; mean [years] ± SD, 45.6 ± 5.3 vs. 45.0 ± 9.0), education (t[16] = −0.41; $P = 0.69$; mean [years] ± SD, 13.9 ± 2.5 vs. 14.4 ± 2.8), menopausal status (χ^2[1, $N = 18$] = 1.17; $P = 0.28$), HRT history (χ^2[1, $N = 7$] = 0.47; $P = 0.50$), radiotherapy (χ^2[1, $N = 18$] = 2.92; $P = 0.09$), tumor stage (χ^2[1, $N = 18$] = 0.004; $P = 0.95$), or baseline impairment status (χ^2[1, $N = 18$] = 0.12; $P = 0.73$).

Patients underwent neuropsychologic evaluation 1 year after the completion of chemotherapy to evaluate the persistence of cognitive decline. Of the patients who did not undergo this long-term postche-

TABLE 3
Mean Values, Standard Deviations, and Paired *t* Test Results for Measures of Cognitive Function

Measure	Baseline		Short-term postchemotherapy		Long-term postchemotherapy	
	Mean (SD)	No. of patients	Mean (SD)	No. of patients	Mean (SD)	No. of patients
Digit Span[a]	11.06 (2.69)	18	10.72 (3.29)	18	11.29 (3.02)	14
Arithmetic[a]	10.22 (2.56)	18	11.12 (3.02)	17	11.00 (2.80)	14
Digit Symbol[a]	11.61 (2.55)	18	12.67 (2.77)[b]	18	13.27 (3.17)	15
TMTA[c]	0.41 (0.89)	18	0.51 (1.05)	18	0.55 (0.89)	15
VSRT LTS[c]	−0.76 (1.20)	18	−0.26 (1.30)[d]	18	−0.24 (1.01)	15
NVSRT LTS[c]	0.11 (0.83)	18	0.66 (0.84)[d]	18	0.54 (1.06)	15
VSRT DR[c]	−1.03 (2.14)	18	−0.90 (1.50)	18	−0.25 (0.81)	15
NVSRT DR[c]	0.00 (1.04)	18	0.45 (1.40)	18	0.28 (1.43)	15
COWA[c]	0.29 (1.06)	18	0.41 (0.84)	18	0.86 (0.76)	15
TMTB[c]	0.56 (0.88)	18	0.78 (1.02)	18	0.79 (1.12)	15
CT[c]	0.04 (0.94)	17	0.85 (0.75)[b]	17	1.06 (0.87)	14
Similarities[a]	11.11 (2.59)	18	11.72 (2.74)	18	11.07 (2.70)	14
Block Design[a]	11.44 (2.85)	18	12.39 (3.36)[d]	18	12.71 (3.77)	14
GP—dominant hand[c]	0.20 (1.32)	18	0.04 (1.59)	18	0.23 (1.41)	15
GP—nondominant hand[c]	−0.23 (0.97)	18	0.09 (0.98)	18	0.12 (1.07)	15

SD: standard deviation; TMTA: Trail Making Test Part A; TMTB: Trail Making Test Part B; VSRT: Verbal Selective Reminding Test; NVSRT: Nonverbal Selective Reminding Test; LTS: Long-Term Storage; DR: Delayed Recall; COWA: Controlled Oral Word Association Test; CT: Booklet Category Test; GP: Grooved Pegboard Test.

[a] Scaled scores (mean, 10; standard deviation, 3).

[b] $P \leq 0.01$, indicating a significant change relative to baseline.

[c] *z* scores (mean, 0; standard deviation, 1).

[d] $P \leq 0.05$, indicating a significant change relative to baseline.

TABLE 4
Self-Reported Ability to Work (Including Work at Home) as Documented on the FACT Administered at the Short-Term Postchemotherapy Time Point

Able to work?	Cognitive decline (n = 7)[a]	No cognitive decline (n = 7)
Not at all	14	0
A little bit	0	0
Somewhat	43	0
Quite a bit	0	14
Very much	43	86

FACT: Functional Assessment of Cancer Therapy—Breast Module.

[a] A subset of patients did not complete the quality of life/questionnaire at the short-term follow-up time point due to time constraints.

TABLE 5
Self-Reported Ability to Work (Including Work at Home) as Documented on the FACT Administered at the Long-Term Postchemotherapy Time Point among Patients Classified as Having Experienced Cognitive Decline at the Short-Term Evaluation

Able to work?	No. of patients (n = 6)[a]
Not at all	0
A little bit	0
Somewhat	17
Quite a bit	0
Very much	83

FACT: Functional Assessment of Cancer Therapy—Breast Module.

[a] A subset of patients did not complete the quality of life questionnaire at either short-term or long-term follow-up due to time constraints.

motherapy assessment, two did not exhibit treatment-related declines in cognitive function at the short-term assessment, whereas one was classified as having experienced a decline. (This patient was reevaluated approximately 6 years later and exhibited stabilization or improvement in all domains of cognitive function.) Of the patients who exhibited cognitive decline at the short-term postchemotherapy time point, 45% had stable cognitive function, 45% exhibited improvement, and 10% had a mixed pattern of results (i.e., improvement on some tests and stabilization on others) at the long-term postchemotherapy assessment. Self-reported ability to work also appeared to improve at the long-term assessment time point (Table 5).

DISCUSSION

The current prospective, randomized, longitudinal trial was initiated to determine the cognitive sequelae of adjuvant chemotherapy in a population of patients with breast carcinoma. To our knowledge, ours is the first published trial to evaluate cognitive functioning using a longitudinal design, which included preche-

motherapy and postchemotherapy cognitive assessments. We assessed demographic and clinical characteristics as risk factors for both prechemotherapy cognitive impairment and chemotherapy-associated cognitive decline. We also investigated the associations among mood, QOL, and cognitive functioning.

Consistent with our hypothesis, the results of the current investigation indicated that despite the absence of a statistically significant mean group decline in cognitive function associated with a standard dose of FAC chemotherapy, a subset of women demonstrated a decline in cognitive function after chemotherapy. During the period between baseline and short-term assessment, 61% of patients experienced a decline in 1 or more aspects of cognitive functioning that was not associated with mood, demographic characteristics, clinical features, or baseline cognitive impairment. The most commonly affected domains included attention, learning, and processing speed; these findings are consistent with the disruption of frontal network systems. The observed declines in cognitive function generally were quite subtle and often were associated with performance results that fell within the average range when compared with the results of demographically similar healthy control individuals. Nonetheless, these declines appear to be indicative of a central neurotoxicity that is associated with a higher incidence of functional loss (i.e., decreased ability to work). One year after the completion of adjuvant FAC treatment, approximately one-half of all patients who developed neurotoxicity experienced an improvement in cognitive function, whereas the remaining one-half had cognitive function scores that remained below baseline (i.e., prechemotherapy) levels. In addition, the majority of patients who experienced acute neurotoxicity reported improvements in their ability to perform work-related activities at the long-term postchemotherapy evaluation. It is noteworthy that the use of MV following FAC treatment was not associated with cognitive dysfunction; however, given the small size of the current study cohort, this conclusion is tentative.

These findings are consistent with published retrospective, postchemotherapy reports[2–7] that identified a subgroup of patients who experienced cognitive declines that were attributable to chemotherapy. However, a cautionary note is warranted. We evaluated the classification accuracy that was achieved when patients were classified as having experienced cognitive deterioration or not having experienced cognitive deterioration based on short-term postchemotherapy assessment results, as doing so approximated the methods used in previously published retrospective studies. We compared the resulting classification with our prospectively based classification, which was arrived at using patients' own baseline and short-term postchemotherapy results in conjunction with the RCI. We found that approximately 46% of patients would not have been classified as having experienced a decline in cognitive function based on their postchemotherapy evaluations alone had they not undergone baseline cognitive assessment. This unacceptably high rate of false-negative results further underscores the absolute necessity of performing pretreatment assessment in characterizing the impact of treatment on cognitive function.

The occurrence of a central neurotoxicity associated with FAC chemotherapy is consistent with previous reports of adverse events, including transient encephalopathy,[21] in patients receiving FAC. Toxic reactions to 5-FU,[22] a component of FAC, also have been reported; these reactions were quite serious and warrant further inquiry. Although the majority of women may experience little or no cerebral neurotoxicity, encephalopathic responses related to preexisting enzyme deficiencies in rare cases are a very real concern, especially if such responses can be anticipated and prevented. It is noteworthy that before chemotherapy, nearly 33% of patients in the current trial exhibited impaired cognitive function (according to conservative criteria for classification) that was not associated with mood, demographic characteristics, or clinical factors. Investigations into the mechanisms responsible for both impaired cognitive function at baseline and treatment-related neurotoxicity, as well as the host vulnerabilities that permit a subset of this population to experience neurotoxicity, are necessary.

The etiologic mechanisms underlying chemotherapy-induced cognitive dysfunction may differ from one chemotherapeutic agent to another. Several potential mechanisms underlying neurologic injury have been discussed previously, including direct injury to both cerebral gray and white matter; microvascular injury, such as that associated with leukoencephalopathy; and secondary injury as a result of immune-mediated inflammatory responses.[23] Previous reports describing 5-FU–induced neurotoxicity have suggested that interventions involving thiamine and steroids may be effective[22,24]; better identification of subtle neurotoxicities will be helpful in detecting potential neurotoxic processes at an early stage, when they may be more likely to respond well to such interventions. In this regard, neuropsychologic evaluations can contribute significantly to the monitoring of patients who are receiving systemic chemotherapy for breast carcinoma or some other type of malignant disease.

It is clear that chemotherapy trials must carefully evaluate homogeneous regimens in homogeneous

populations, because these treatment regimens may have properties that make them differentially neurotoxic to patients with different characteristics. From the standpoint of documenting the more common responses to FAC and other adjuvant regimens, replication and extension of the results of the current study are needed. The use of normative controls, as in the current study, allows comparisons with healthy, demographically matched individuals (stratified by age, education, gender, and handedness when necessary) to be made so that relative performance deficits can be detected. However, the simultaneous examination of a similar population of patients who do not receive the study intervention will assist in identifying differential practice effects and control for potential disease-related factors that may contribute to cognitive dysfunction in the absence of a potentially neurotoxic therapy regimen. Data-analytic methods that reliably identify subgroups must be employed and validated, because not all women who are exposed to chemotherapy develop cognitive dysfunction. It is necessary for increased efforts to be channeled not only toward the identification of cognitive decline in association with cancer treatment but also toward the elucidation of the mechanisms underlying these effects and of any potential host factors that may contribute to an individual's susceptibility. Such information would aid in the selection of patients for whom treatment was likely to have optimal efficacy relative to toxicity and would allow the exploration of potential preventative or palliative interventions.

Although FAC-based adjuvant therapy is associated with an excellent response rate, it is likely that the use of higher doses, different combinations, and additional agents will continue to be explored. Any benefits yielded by novel treatment regimens will need to be assessed against treatment-related toxicity. Since the inception of this study in the early 1990s, many novel types of therapy have been developed. Consequently, the burden of balancing side effects with the benefits of potentially life-saving treatment continues to grow heavier.

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