Original Article

Acute and Late Onset Cognitive Dysfunction Associated With Chemotherapy in Women With Breast Cancer

Jeffrey S. Wefel, PhD[1]; Angele K. Saleeba, PhD[1]; Aman U. Buzdar, MD[2]; and Christina A. Meyers, PhD[1]

BACKGROUND: Growing evidence supports cognitive dysfunction associated with standard dose chemotherapy in breast cancer survivors. We determined the incidence, nature, and chronicity of cognitive dysfunction in a prospective longitudinal randomized phase 3 treatment trial for patients with T1-3, N0-1, M0 breast cancer receiving 5-fluorouracil, doxorubicin, and cyclophosphamide with or without paclitaxel. **METHODS:** Forty-two patients underwent a neuropsychological evaluation including measures of cognition, mood, and quality of life. Patients were scheduled to be assessed before chemotherapy, during and shortly after chemotherapy, and 1 year after completion of chemotherapy. **RESULTS:** Before chemotherapy, 21% (9 of 42) evidenced cognitive dysfunction. In the acute interval, 65% (24 of 37) demonstrated cognitive decline. At the long-term evaluation, 61% (17 of 28) evidenced cognitive decline after cessation of treatment. Within this group of patients, 71% (12 of 17) evidenced continuous decline from the acute interval, and, notably, 29% (5 of 17) evidenced new delayed cognitive decline. Cognitive decline was most common in the domains of learning and memory, executive function, and processing speed. Cognitive decline was not associated with mood or other measured clinical or demographic characteristics, but late decline may be associated with baseline level of performance. **CONCLUSIONS:** Standard dose systemic chemotherapy is associated with decline in cognitive function during and shortly after completion of chemotherapy. In addition, delayed cognitive dysfunction occurred in a large proportion of patients. These findings are consistent with a developing body of translational animal research demonstrating both acute and delayed structural brain changes as well as functional changes associated with common chemotherapeutic agents such as 5-flouorouracil. ***Cancer*** **2010;116:3348–56.** © *2010 American Cancer Society.*

KEYWORDS: cognition disorders, memory, neuropsychological tests, systemic chemotherapy, breast neoplasms.

Reduced recurrence and improved survival has been reported for women with primary breast cancer who receive systemic chemotherapy.[1] However, breast cancer patients receiving chemotherapy are known to be at risk for adverse side effects such as bone marrow suppression, nausea, and cardiotoxicity.[2] The incidence of neurotoxicity is less well known and the traditional definition of neurotoxicity does not address the full range of central nervous system sequelae associated with chemotherapy.

"Neurotoxicity" is often defined as peripheral neuropathy or encephalopathy.[3] Unfortunately, the neuropsychological manifestations of neurotoxicity such as memory loss are not as well described in the literature. 5-fluorouracil, Adriamycin, and cyclophosphamide (FAC), with or without paclitaxel, is a commonly used regimen for the treatment of breast cancer. FAC has been associated with neutropenia, secondary leukemia, and transient encephalopathy.[4-7] Although little is known regarding the neuropsychological effects of this regimen, more is known about the individual agents. Acute and delayed neurotoxic reactions including encephalopathy characterized by confusion, disorientation, and higher order cognitive deficits have been associated with 5-fluorouracil.[8,9] Paclitaxel stabilizes the polymerized form of microtubules, which leads to large numbers of microtubules aggregated in unusual arrays and degeneration of the nerve axon.[10,11] Although this axonopathy is well described for peripheral nerve injury, central nervous system axons are also at risk and acute encephalopathy after paclitaxel has been described.[12-14]

Corresponding author: Jeffrey S. Wefel, PhD, Department of Neuro-Oncology, The University of Texas M. D. Anderson Cancer Center, P.O. Box 301402-Unit 431, Houston, TX 77230-1402; Fax: (713) 794-4999; jwefel@mdanderson.org

[1]The University of Texas M. D. Anderson Cancer Center, Section of Neuropsychology, Department of Neuro-Oncology, Houston, Texas; [2]The University of Texas M. D. Anderson Cancer Center, Department of Breast Medical Oncology, Houston, Texas

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Table 1. Neuropsychological Tests and Mood Measures Grouped by Principal Domain

Domain	Test/Measure	Abbreviation	RCI Study
Attention	WAIS-R[44] Digit Span	Digit span	Wechsler, 1981[44]
Processing speed	WAIS-R Digit Symbol	Digit symbol	Wechsler, 1981[44]
	Trail Making Test[45] Part A	TMTA	Levine, 2004[46]
Learning and memory	[a]Hopkins Verbal Learning Test[47]Total Trials 1-3	HVLT total	Benedict, 1998[48]
Executive function	[a]MAE Controlled Oral Word Association[49]	COWA	Ruff, 1996[50]
	Trail Making Test Part B	TMTB	Levine, 2004[46]
Mood	Beck Depression Inventory[51]	BDI	n/a
	State-Trait Anxiety Inventory[52]	STAI	n/a
QOL	Functional Assessment of Cancer Therapy-Breast Module[53]	FACT	n/a

RCI indicates practice effect-adjusted Reliable Change Index; WAIS-R, Wechsler Adult Intelligence Scale-Revised; MAE, Multilingual Aphasia Examination; QOL, Quality of Life.
[a] Alternate forms used.

Breast cancer survivors are concerned about the possible cognitive sequelae (coined "chemobrain") associated with chemotherapies. Women with breast cancer represent a growing group of cancer survivors who frequently want to return to their occupational, scholastic, or familial activities, which rely heavily on the integrity of their cognitive functioning, highlighting the need to clearly understand the impact of chemotherapy on the brain.

Longitudinal prospective trials incorporating assessment of cognitive function have generally reported between 20% and 61% of women with breast cancer demonstrate alterations in cognitive function after receiving standard dose chemotherapy.[15-22] Methodologically, the inclusion of a pretreatment baseline is critical as several studies have demonstrated that up to a third of women evidence cognitive dysfunction before administration of systemic chemotherapeutic agents.[17,18,20,23,24]

The following study reports the results of a prospective randomized longitudinal trial that included examination of the incidence, nature, and chronicity of cognitive dysfunction in breast cancer patients treated with standard dose adjuvant chemotherapy. Patients received an evaluation of their cognitive function, affective status, and quality of life (QOL) before treatment, during, and shortly after treatment, and again at a late follow-up point after treatment to monitor for any persistent or delayed cognitive sequelae.

MATERIALS AND METHODS

Patients were recruited in conjunction with a randomized phase 3 trial approved by the Institutional Review Board of The University of Texas M. D. Anderson Cancer Center.[25] Patients with histologically confirmed invasive but noninflammatory carcinoma of the breast were eligible. All patients who met initial screening criteria and consented to participate in the trial were consecutively registered into the protocol for evaluation. All patients had no evidence of metastatic disease, were at least 18 years old, completed 8 or more years of formal education, and were fluent English speakers. No patient had a prior history of other primary cancer, previous exposure to chemotherapy, prior or current neurologic or psychiatric disorders, or used substances active in the central nervous system that were thought to affect cognition (eg, narcotics, steroids) within 3 weeks before testing.

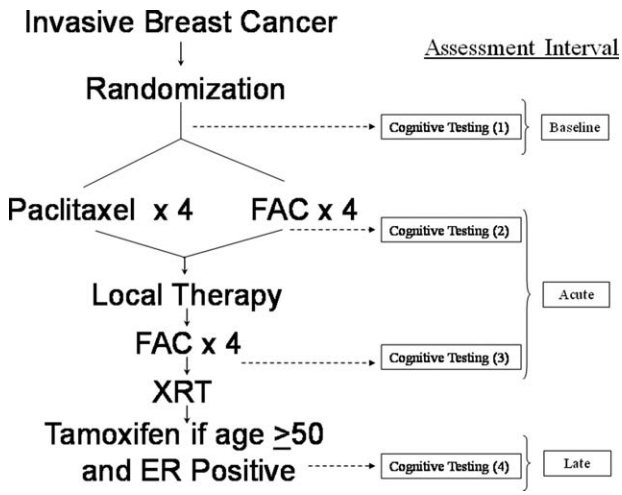

Figure 1. The treatment schema is depicted.

Patients were evaluated with a battery of standardized cognitive tests, mood measures, and a QOL questionnaire (Table 1) according to the study schema depicted in Figure 1. Cognitive testing was conducted at baseline and then on average 2.9 months (standard deviation "SD" = 0.59), 7.0 months (SD, 1.4), and 13.1 months (SD = 2.8) after baseline. Neuropsychological tests were selected based on their sensitivity and suitability

Table 2. Patient Demographic and Clinical Characteristics

Characteristic	FAC-TAX (N=42)	
	No.	%
TNM classification		
T1, N0, M0	2	5
T1, N1, M0	6	14
T2, N0, M0	9	21
T2, N1, M0	14	33
T3, N0, M0	3	7
T3, N1, M0	8	19
Type of surgery		
Segmental+axillary dissection	9	21
Modified radical	33	79
Radiotherapy[a]		
Yes	22	52
No	21	48
Menopausal status		
Premenopausal	20	48
Perimenopausal	1	2
Postmenopausal	16	38
Surgical menopausal	5	12
HRT history		
Yes	12	29
No	17	40
Unknown	13	31
Race		
White	31	74
Hispanic	7	17
Black	4	10
Age		
Mean (SD)	48.8 (8.1)	—
Range	33-65	—
Education		
Mean (SD)	13.0 (2.5)	—
Range	8-18	—

FAC-TAX indicates 5-fluorouracil, adriamycin, cyclophosphamide ± paclitaxel; HRT, hormone replacement therapy; SD, standard deviation.
Percentage does not always equal 100 because of rounding.
[a] To the chest wall with or without inclusion of regional lymphatic chains.

for a brief assessment that could be repeated with minimal practice effects and patient fatigue. Alternate forms were used to minimize practice effects when possible.

Eighty-five patients met screening criteria for participation. Forty-three patients were not enrolled in the trial for the following reasons: unable to contact (n = 21), time constraints (n = 10), travel limitations (n = 4), previous psychiatric illness (n = 4), non-English speaker (n = 3), and <8 years education (n = 2). Forty-two patients were contacted, consented, and underwent neuropsychological evaluation before beginning systemic therapy. Patient demographic and clinical characteristics are in Table 2.

Statistical Analysis

Published normative data that adjusts for age, education, and gender where appropriate were used to convert patients' raw cognitive test scores to standardized scores (z scores; mean, 0; SD, 1) to facilitate comparisons among measures. Each patient's baseline cognitive function was operationally defined as impaired (OCFI-I) or not impaired (OCFI-NI) using a 2-part criterion that has been previously described.[23] By using curves based on the binomial probability distribution,[26] it was determined that in a battery of 6 independent tests, approximately 12% of the population would perform 2 SDs below the mean on a single measure and 5% of the population would perform 1.5 SDs below the mean on 2 measures. Thus, if the incidence of OCFI-I was equal to or greater than the more conservative estimate of 12%, then it was considered significant.

Longitudinal data analysis was performed using a practice effect adjusted[27] Reliable Change Index (RCI).[28] Because the inherent error in test scores is known for tests with published test-retest reliability, a change in score that is clinically, as well as statistically meaningful, can be determined. The RCI was used to determine the frequency of change in cognitive function between each assessment (i.e., Baseline to Acute and Acute to Late). The published study from which the RCI was determined is listed for each test in Table 1.

Spearman's rho correlations were performed between mood and standardized cognitive measures at each time point. Independent sample t tests and chi-square analyses were conducted to determine whether there were differences between impaired and nonimpaired patients at baseline on measures of QOL, mood, demographic, or clinical characteristics. Similar analyses, including baseline cognitive impairment status, were conducted to examine differences between patients classified as evidencing acute and late cognitive decline and those classified as nondecliners. All analyses used an alpha level of $P \leq .01$ to establish statistical significance.

RESULTS

Baseline Interval

At baseline, 21% (n = 9/42) were classified as OCFI-I (3 patients were impaired on a single test and 6 patients were impaired on 2 or more tests). On average, OCFI-I patients exhibited impairment on 2.1 tests, while OCFI-NI patients were impaired on 0.1 measures, which was significantly different (t [40] = 9.97; $P < .0001$). Measures

of psychomotor processing speed and executive function showed impairment that exceeded the a priori defined expected rates; whereas a measure of learning and memory approached significance (Fig. 2). The Trail Making Test (TMT) and Hopkins Verbal Learning Test (HVLT) Total Recall identified 100% (9 of 9) of patients classified as OCFI-I at baseline.

Self-report of depressive (Beck Depression Inventory "BDI") or anxious (State Trait Anxiety Inventory "STAIS") symptomatology were not significantly correlated with any cognitive test at baseline. There were no significant differences between OCFI-I and OCFI-NI patients in self-reported QOL at baseline. OCFI-I patients were older than OCFI-NI patients (t [40] = 3.31; P<.005; mean in years ±SD, 55.9 ± 7.5 and 46.8 ± 7.2, respectively). OCFI-I patients did not differ from OCFI-NI patients in education, menopausal status, hormone replacement therapy history, or tumor stage (stage I and IIA tumors were grouped and compared with stage IIB and IIIA or IIIB tumors). Patients (29) who underwent surgery before the baseline evaluation were no more likely to be classified as OCFI-I than those who had not undergone surgery. The number of days between surgery and the first testing was not significantly different between OCFI-I and OCFI-NI patients. The proportion of patients that completed each therapy at each time point is listed in Table 3.

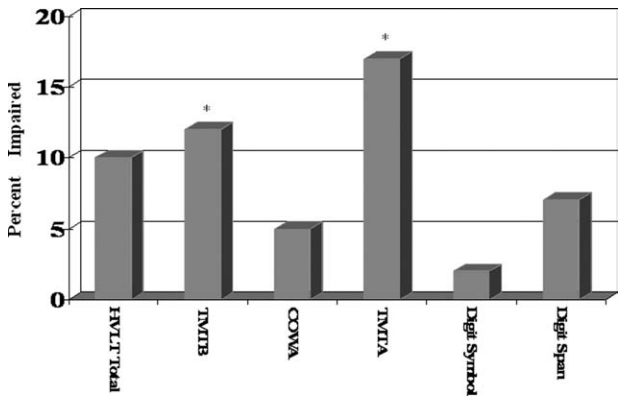

Figure 2. The frequency of baseline impairment is depicted. *Exceeds expectations based on Ingraham and Aiken (1996) binomial distribution curves.

Acute Interval

Differences in cognitive function between patients randomized to the FAC-only study arm versus paclitaxel + FAC study arm could not be evaluated as only 8 subjects were randomized to the FAC-only study arm and underwent neuropsychological evaluation. Because of the small sample size, patients in both arms of the study were combined for longitudinal analysis of cognitive functioning. Three patients never returned for follow-up evaluation for the following reasons: unable to reschedule (2) and treated in another state (1). Two patients were evaluated at baseline and at the long-term postchemotherapy time point (both received therapy out of the state or country). Thus, 37 patients were seen at least once during or shortly after chemotherapy and were available for longitudinal analysis. For patients evaluated at both time points in the acute interval, if either of the evaluations met criteria for decline, then they were considered to have declined. In these cases, the evaluation with evidence of decline was used to examine changes from the acute to late time point.

Approximately 65% (24 of 37) demonstrated an acute decline in cognitive function during or shortly after completion of chemotherapy (mean months since completion of chemotherapy, 1.6; SD, 1.2). For patients who declined on treatment, none subsequently improved at the evaluation shortly after chemotherapy. Thirty-eight percent (9 of 14) declined on 1 measure, 58% (14 of 24) declined on 2 measures, and 4% (1 of 24) declined on 3 measures. Figure 3 shows the frequency of acute changes for each cognitive test. The HVLT and TMT identified

Table 3. Proportion of Patients That Completed or Were Receiving Therapy at Each Assessment Interval

Therapy	Baseline n=42	Acute n=37	Late n=28
Surgery completed (% yes)	69	100	100
Radiation completed (% yes)	2	3	57
Neoadjuvant chemotherapy completed (% yes)[a]	0	49	64
Adjuvant chemotherapy completed (% yes)	0	100	100
Current hormonal therapy (% yes)	0	3	10

[a] Neoadjuvant therapy was not administered to all patients; thus, this value does not total 100%. However, all patients did receive adjuvant chemotherapy.

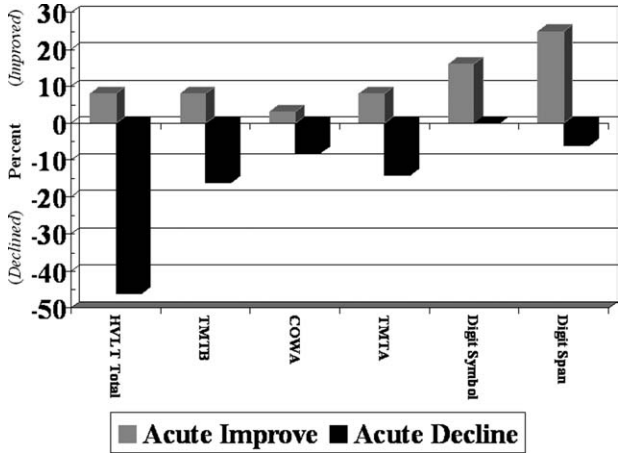

Figure 3. The frequency of acute treatment-related changes in cognitive function based on the practice effect adjusted reliable change index is depicted.

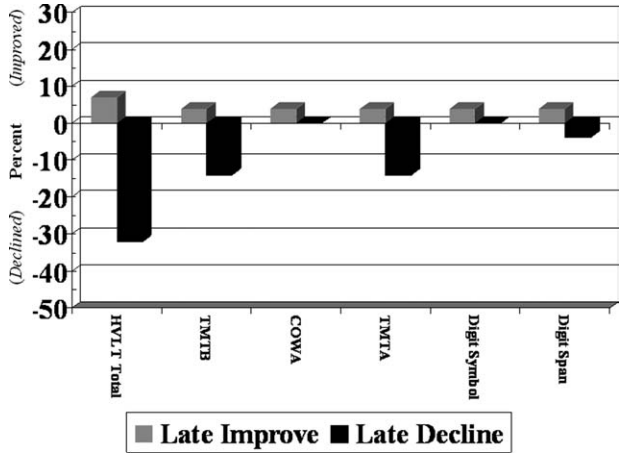

Figure 4. The frequency of late emerging changes in cognitive function based on the practice effect adjusted reliable change index is depicted.

92% (22 of 24) of patients classified as demonstrating acute cognitive decline. Digit Span and Digit Symbol showed the greatest frequency of improvement.

There were no significant differences between patients who acutely declined on chemotherapy compared with those that did not decline in terms of mood, overall QOL, or ability to work. Pretreatment cognitive status and demographic/clinical characteristics were not related to acute decline.

Late Interval

Approximately 13 months after the baseline evaluation and 7.7 months (SD, 3.1) after completion of chemotherapy, 76% (28 of 37) patients who were evaluated during or shortly after completion of chemotherapy underwent a late post-treatment evaluation. Four patients who evidenced acute cognitive decline did not return for a late evaluation for the following reasons: no show (2), treatment discontinued because of side effects including cognitive dysfunction (1), and development of metastatic disease (1). Five patients who did not acutely decline were not evaluated post-treatment for the following reasons: no show (3), treatment discontinued because of side effects including cognitive dysfunction (1) and development of recurrent breast cancer (1). Approximately 61% (17 of 28) of patients who returned for the late evaluation demonstrated cognitive decline relative to their test performance during the acute interval. Of these patients, 71% (12 of 17) demonstrated both acute and late cognitive decline (ie, continued decline), whereas 29% (5 of 17) demonstrated new onset cognitive decline that was not present in the acute interval. Approximately 39% (11 of 28) did not evidence late cognitive decline relative to their acute interval testing. Of these, 73% (8 of 11) declined in the acute interval and were largely stable with no evidence of significant improvement (with the exception of 2 patients who demonstrated improvement on the memory test alone); whereas 27% (3 of 11) did not decline at any time point. The vast majority (94%) of patients (16 of 17) exhibiting late decline did so on 1 test. Improvement was rare in the late interval; the TMT and HVLT again identified 94% of patients with late decline. Figure 4 shows the pattern of late emerging changes on each cognitive test.

There was a trend for those who declined at the late evaluation to have been impaired at baseline. There was no association with late decline and demographic/clinical characteristics. Only 18% (3 of 17) of patients who evidenced late decline were on hormonal therapy (ie, tamoxifen) at the time of the evaluation, and no nondecliners were on hormonal therapy. Similarly, only 18% (3 of 17) patients who evidenced late decline were randomized to the FAC-only study arm compared with 9% (1 of 11) nondecliners. There was no significant difference between late decliners and nondecliners in self-reported ability to work. Table 4 provides a summary of the mean standardized test performance at each time point.

DISCUSSION

By using rigorous criteria, 21% of patients demonstrated evidence of cognitive dysfunction before initiation of systemic therapy (ie, OCFI-I). Older patients appeared more at risk for cognitive impairment before chemotherapy, but there were no differences between OCFI-I versus

Table 4. Mean (±SD) Performance on Cognitive Tests at Each Time Point

Test	Time Point 1 Mean (SD) n=42	Time Point 2 Mean (SD) n=30	Time Point 3 Mean (SD) n=33	Time Point 4 Mean (SD) n=28
HVLT total[a]	0.09 (0.86)	−0.62 (1.21)	−0.25 (1.41)	−0.44 (1.23)
TMTB[a]	−0.18 (2.51)	0.25 (1.63)	0.33 (1.55)	0.15 (1.22)
COWA[a]	0.29 (0.96)	0.21 (0.89)	0.27 (0.98)	0.30 (1.15)
TMTA[a]	−0.34 (1.57)	−0.27 (1.62)	0.40 (1.07)	0.56 (1.29)
Digit symbol[b]	11.71 (2.45)	12.86 (2.13)	13.27 (2.18)	13.25 (2.03)
Digit span[b]	9.00 (2.48)	10.00 (2.29)	10.16 (2.91)	10.04 (2.67)

SD indicates standard deviation.
[a] *z* scores.
[b] Scaled scores.

OCFI-NI patients on any other clinical, mood, or demographic variable. The domains most commonly affected included learning and memory, executive function, and processing speed. The incidence of OCFI-I is very similar to that reported in several other studies that assessed pretreatment cognitive function.[17,20,23] This finding underscores the importance of designing studies with a pretreatment baseline evaluation. Cross-sectional studies assessing the prevalence of cognitive dysfunction posttreatment are prone to an unacceptably high error rate.[15]

Acute decline in cognitive function during and/or shortly after chemotherapy occurred in 65% of patients. The most common domains affected included learning and memory, executive function, and processing speed. The incidence and pattern of acute decline is consistent with our previous longitudinal trial.[15] There were no differences between patients with acute decline versus those that did not decline on any clinical, mood, or demographic variable. Baseline impairment status was not a risk factor for acute decline.

Late cognitive decline occurred in 61% of patients, with approximately 30% of these patients demonstrating new onset, delayed cognitive dysfunction that was not present earlier. Learning and memory declined most frequently at the late evaluation, with less frequent declines in executive function and processing speed. There were no differences between patients evidencing late decline versus those that did not decline on any clinical, mood, or demographic variable. However, there was an intriguing trend for baseline impairment status to be related to late decline. All patients (7 of 7) who were classified as impaired at baseline were subsequently classified as demonstrating late decline; whereas only 48% (10 of 21) of patients nonimpaired at baseline were subsequently classified as demonstrating late decline. This suggests that pretreatment cognitive impairment may be related to increased risk for cognitive dysfunction that does not recover or emerges in the late postchemotherapy epoch. It is possible that baseline impairment reflects diminished brain/cognitive reserve.[57] The effect of this diathesis may not become differentially evident during and shortly after chemotherapy when the adverse effects of these therapies may potentially be overshadowed by stronger acute biological alterations (eg, encephalopathy, anemia, neutropenia, proinflammatory cytokine cascades).[4-14] However, in the postchemotherapy period, the impact of diminished brain/cognitive reserve may play a greater role in the vulnerability of the failure to fully recover from acute treatment related changes in cognition and/or development of late cognitive decline. Given the marginal significance of this finding in a small sample, this will clearly need to be replicated in future studies.

The improvements on a measure of auditory attention (Digit Span) and graphomotor speed (Digit Symbol) that were evident at the acute evaluation tended to dissipate at the late evaluation. The significance of these findings is unclear. Notably, despite improvements in attention, learning and memory performance declined suggesting that these cognitive processes may be differentially affected. In addition, other measures requiring graphomotor processing speed (TMTA and TMTB) showed a consistent pattern of decline in both the acute and late period.

Acute decline has been reported by several investigators that have longitudinally studied women with breast cancer that received a fluorouracil-containing treatment regimen.[16-18,22,54,55] The prevalence rates of cognitive decline have generally ranged from 20% to 55% in studies[16,29] reporting results using RCI or standardized regression-based methodologies. Most studies, like the current

study, have not found an association between changes in mood and changes in cognition. Declines in memory, executive function, and processing speed are most frequently identified. However, the pattern and incidence of cognitive dysfunction is not always consistent between studies. Potential reasons for this have been previously described[29] and include inclusion of heterogeneous treatment regimens and patient populations, and application of incongruous criteria and/or statistical methods to determine cognitive outcomes. Differences in the cognitive tests used in different studies have also likely contributed significantly to discrepant findings. For example, different tests of learning and memory have been used, frequently without alternate forms to reduce practice effects.[16-18,20,22,29,54,55] In the current trial, we used a learning and memory test with alternate forms and found declines in learning and memory to be the most common adverse effect. Studies that did not use memory tests with alternate forms may have underestimated the degree of cognitive decline.[56]

Differences in control groups also likely contribute to differences in reported rates of cognitive impairment and cognitive decline. We used published normative data from healthy controls in this study. When modeling change over time (eg, when using RCI methodologies), the RCI value will depend on the sample used to establish this value. By using a common published control sample (ie, normative studies) all investigators can compare their data with a similar RCI value. Using only local control samples will result in a variety of RCI values that will hamper comparisons across studies. Published normative data from healthy controls usually contain larger sample sizes that are likely to provide a better estimate of the population parameter under investigation (eg, memory). However, one must always balance this against potential sample differences (eg, sociodemographic factors such as age) that are related to the parameter under study and may differ significantly between the study population and the control population. Local control samples may afford greater precision in measuring changes over time because of consistency in test-retest intervals. However, although some studies report practice effect differences based on follow-up interval,[30] others have found limited impact in domains of cognition such as memory.[31-34] Nevertheless, studies in this area may benefit by obtaining both a large matched local control sample and using tests with published normative data to benefit from the merits of both approaches. On the basis of the results of this study, investigators may wish to consider using the HVLT-Revised and TMT as a component of their assessment batteries, given their demonstrated relative sensitivity in this population, availability of alternate forms for the memory measure to diminish practice effects, good psychometric properties and available population normative data.

This study replicates the findings from our previous longitudinal trial in women with breast cancer receiving FAC-based chemotherapy in which we observed frequent acute decline in cognitive function that often did not improve in the year after completion of chemotherapy.[15] However, in the current study, we additionally observed progressive and delayed cognitive decline that does not appear to be attributable to other interventions (eg, chest wall radiation or hormonal therapy) or progressive or metastatic disease. This is very concerning as clinical lore has suggested that treatment-related cognitive dysfunction should dissipate over time.

Recent preclinical animal models are helping define potential mechanisms underlying chemotherapy-induced cognitive dysfunction.[35-43] Mice treated with fluorouracil and methotrexate demonstrated acute deficits on cognitive tasks that assess the integrity of hippocampal and frontal lobe function.[37] Recently, it has been reported that mice given clinically relevant doses of 5-fluorouracil demonstrated both acute inflammation and vascular injury, followed by delayed damage to myelinated tracts in the brain.[38] The acute inflammation and vascular injury was transient and found primarily in the subventricular zone, dentate gyrus and corpus collosum, all of which are critical for normal cognitive function. The delayed effects included increased apoptosis, suppression of proliferation in double-cortin+ neuronal progenitors and oligodendrocyte-type-2 astrocyte progenitor cells as well as progressive loss of Olig2+ cells. Delayed damage to myelinated tracts would be predicted to result in diminished learning and memory, executive function, and processing speed. The predicted pattern of cognitive dysfunction and the progressive and late emerging toxicity caused by 5-fluorouracil in the animal model corresponds with our observations in this study.

As the survivorship community continues to grow and more cancer patients are at risk for both acute and delayed cognitive decline, it is critical to understand the pathophysiologic mechanisms. Clinical and translational research using neuropsychological tests, imaging techniques, biomarkers, and animal models are essential to accelerate our understanding of these toxicities, identify at-risk subgroups, and develop intervention and neuroprotective strategies. Future neuropsychological studies

would benefit from examining larger samples of homogeneously treated patients to replicate these findings and to determine whether these adverse effects are specific to certain chemotherapeutic regimens. Extending the postchemotherapy follow-up interval to at least 1 year is clearly warranted and will help inform patients and clinicians about critical survivorship issues.

CONFLICT OF INTERESTS DISCLOSURES

The authors made no disclosures.

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