

Is “Chemobrain” a Transient State? A Prospective Pilot Study Among Persons with Non-Small Cell Lung Cancer

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Lung cancer is the leading cause of cancer death in the United States, accounting for 29% of all cancer-related deaths.¹ In 2008, an estimated 215,020 people in the United States will be diagnosed with lung and bronchial cancer, and approximately 161,840 will die of the disease.¹ Approximately 87% of these patients will have non-small cell lung cancer (NSCLC), with the majority presenting with locally advanced (stage III) or distant metastatic (stage IV) disease.

Until the early-1990s, the standard of care for patients with stage III NSCLC was radiation therapy alone. However, several trials have established chemoradiotherapy as the new standard.²⁻⁴ Trials comparing radical radiotherapy alone with radical radiotherapy plus chemotherapy in treating NSCLC have shown a 13% reduction in the risk of death (absolute benefit at 2 years, 4%) with the addition of chemotherapy.⁴

However, as noted by Klastersky and Paesmans,⁵ in light of the modest survival improvement of chemotherapy in NSCLC patients, some clinicians are concerned that the negative cognitive side effects of such treatments, commonly referred to as “chemobrain,” might outweigh the survival

Abstract In patients with stage III non-small cell lung cancer (NSCLC), chemotherapy combined with radiation therapy modestly improves survival when compared with radiotherapy alone. In light of the small survival benefit, there is a need to quantify any potential loss of neurocognitive function that may result from chemotherapy in this patient population. The current study examines cognitive functioning in 14 stage III NSCLC patients who received treatment with cisplatin/etoposide/radiotherapy. Patients were assessed before receiving chemotherapy and at 1 and 7 months after treatment. At each time point, participants were administered a comprehensive battery of psychological and neuropsychological tests. In all, 71% of patients demonstrated cognitive impairment prior to any treatment. One month post chemotherapy, the majority of patients (62%) experienced cognitive decline; however, these negative effects apparently dissipated by 7 months post treatment, suggesting that the untoward effects of chemotherapy in these specific patients given this chemotherapy regimen may have been transitory. Cognitive decline did not appear to be associated with age, mood, fatigue, or quality-of-life measures. These findings demonstrated the importance of employing both a pre- and extended post-treatment assessment in chemotherapy research.

benefit. Relatively little research has examined the impact of chemotherapy on cognitive functioning and quality of life (QOL) among lung cancer patients. Furthermore, much of the existing research has been plagued by methodologic difficulties, including patient dropout and death. Klastersky and Paesmans⁵ reviewed randomized trials that successfully included QOL as an endpoint among individuals with advanced NSCLC who received chemotherapy; they found that the reliability and validity of these evaluations were compromised by methodologic problems, yet QOL scores in several trials were better with chemotherapy than with best supportive care. Physical side effects (ie, nausea and vomiting, constipation, hair loss, and peripheral neuropathy) were common in the che-

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motherapy groups but not considered detrimental enough to outweigh the benefits of treatment.

Only one published study has specifically examined cognitive functioning in patients with NSCLC before and after chemotherapy.^{6,7} This Norwegian study employed a brief battery of neuropsychological tests; its results suggested that mild cognitive decline was more closely associated with chemotherapy ($n = 44$) than with radiotherapy ($n = 51$). However, the interval between chemotherapy and neuropsychological testing was only 5 weeks, which may have left participants vulnerable to the acute side effects of chemotherapy. These effects may have dissipated with time and, therefore, may not have been noted over a longer testing interval. Moreover, the results of more recent studies suggested that particular attention should be paid to possible cognitive impairment experienced by cancer patients before treatment. For example, cognitive deficits may exist in patients with small cell lung cancer before any systemic treatment is given.⁸ This phenomenon may result from the advanced age of most lung cancer patients, the presence of microvascular disease in long-time smokers, or the use of multiple medications to treat comorbidities.

Similarly, the results of recent research suggests that 35% of women with breast carcinoma demonstrated impaired cognitive function before they started adjuvant chemotherapy.⁹ In the absence of baseline testing, these impairments likely would be interpreted as treatment effects. It is precisely the latter methodologic problem that plagues most studies of the cognitive effects of chemotherapy. Nearly all studies—even the abundant breast cancer trials that suggest chemotherapy-related cognitive decline—include only a retrospective design.¹⁰

Only one prospective study has been published in the breast cancer literature.¹¹ In that research, 18 women treated with standard-dose adjuvant chemotherapy underwent a comprehensive neuropsychological evaluation before treatment and at 3 weeks (short-term follow-up) and 1 year (long-term follow-up) post chemotherapy. Overall, 33% of patients were considered to be impaired at baseline (four patients exhibited impairment on two tests, and two patients exhibited impairment on more than two tests). A comparison of findings at baseline with those at short- and long-term follow-ups showed no statistically significant group difference in patient performance. However, during the period between baseline and short-term assessment, 61% of patients demonstrated a decline in cognitive function that exceeded the reliable change index (RCI),¹² which is the 90% confidence interval for the difference in performance between two evaluations that is expected if no real change has occurred. Declines were most frequently seen in brief attention, learning, and processing speed. However, the results of the 1-year post-chemotherapy neuropsychological evaluation were encouraging—of patients exhibiting a decline 3 weeks post chemotherapy, 45% had stable cognitive function, 45% showed improvement, and 10% had a mixed pattern of results.

The scant prospective literature suggests that a subgroup of individuals who undergo chemotherapy may be at risk for

cognitive decline, but this finding has yet to be conclusively established. The current study reports the results of a prospective longitudinal trial that evaluated the incidence and nature of cognitive dysfunction associated with chemotherapy; this investigation included individuals with stage III NSCLC and used a longitudinal design that incorporated assessments before treatment and 1 and 7 months after therapy. The present research explored how potentially confounding variables (eg, age; anxiety; depression; fatigue; and baseline blood levels of hemoglobin, thyroid stimulating hormone [TSH], and homocysteine [a surrogate marker for B₁₂ or folate deficiency]) might affect the relationship between cognitive function and chemotherapy. In addition, the current study included an exploratory analysis of the relationship between QOL and cognitive functioning.

It was hypothesized that a subgroup of individuals with NSCLC would demonstrate cognitive deficits, as compared with normative data, before they were given chemotherapy. It also was hypothesized that approximately 50% of patients would demonstrate cognitive decline in at least one domain of neuropsychological functioning at 1 month post chemotherapy. It was predicted that preexisting neurocognitive deficits would put individuals at a greater risk for experiencing cognitive declines immediately following chemotherapy. However, at least 50% of individuals who demonstrated cognitive decline at 1 month post chemotherapy were expected to demonstrate recovery in the previously demonstrated areas of cognitive decline at 7 months. Further, it was hypothesized that cognitive decline would be related to lower QOL and greater emotional dysfunction.

Method

PARTICIPANTS

Patients diagnosed with stage IIIA or IIIB NSCLC and scheduled to undergo cisplatin/etoposide/radiotherapy treatment were recruited into the study. Participants were consecutively referred to the Department of Veterans Affairs Medical Center or to the Indiana University Melvin and Bren Simon Cancer Center in Indianapolis, Indiana, for treatment.

Potential participants were excluded from the study if they were younger than 18 years of age. Due to the confounding effects that pre-existing neurologic impairment could have on neuropsychological testing, patients having a history of mental retardation, head injury with loss of consciousness exceeding 5 minutes, stroke, Parkinson's disease, dementia, schizophrenia, bipolar disorder, or hypothyroidism also were excluded.

DESIGN AND PROCEDURE

Written informed consent was obtained for participants agreeing to participate in the study. Participants underwent blood analyses to examine hemoglobin, homocysteine, and TSH levels before receiving any treatment.

Patients were evaluated at three time points. First, for the baseline assessment, they were examined immediately before

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

DOMAIN	MEASURE	TEST ABBREVIATION
Premorbid Verbal Intelligence Quotient (VIQ)	American Version of the Nelson Adult Reading Test ¹³ <i>Score used: Estimated VIQ</i>	AMNART
Executive function	Wisconsin Card Sorting Test—64 Card Version ¹⁴ <i>Score used: Conceptual Level Responses Raw Score</i>	WCST-CR
Executive function	Multilingual Aphasia Examination Controlled Oral Word Association ¹⁵ <i>Score used: Phonemic Fluency (FAS) Raw Score</i>	COWA
Visuospatial function	Wechsler Adult Intelligence Scale (Third Edition) Block Design ¹⁶ <i>Score used: Age Scaled Score</i>	Block Design
Memory	Hopkins Verbal Learning Test—Revised ¹⁷ <i>Score used: Immediate Recall Raw Score</i>	Hopkins Immed
Memory	Hopkins Verbal Learning Test—Revised ¹⁷ <i>Score used: Delayed Recall Raw Score</i>	Hopkins Delay
Memory	Rey Complex Figure Test ^{18,19} <i>Score used: Three-Minute Recall Raw Score</i>	RCFT Immed
Attention	Gordon Continuous Performance Test ²⁰ <i>Score used: Total Correct Raw Score</i>	Gordon CPT
Mood symptoms	Patient Health Questionnaire ²¹ <i>Score used: Total Depressive Symptoms Average Total Anxiety Symptoms Average</i>	PHQ PHQ-Depression PHQ-Anxiety
Fatigue	Brief Fatigue Inventory ²² <i>Score used: Average of Raw Score Responses</i>	BFI
Quality of life	Functional Assessment of Cancer Therapy—Lung ²³ <i>Score used: Physical Well-Being Average Score Social/Family Well-Being Average Score Emotional Well-Being Average Score Functional Well-Being Average Score</i>	FACT-L

receiving cisplatin/etoposide/radiotherapy. Second, for the 1-month postchemotherapy assessment, they were evaluated at least 4 weeks, but less than 7 weeks, after receiving two cycles of cisplatin/etoposide/radiotherapy and discontinuing use of drugs that were given to control nausea and emesis or that were known to have central nervous system (CNS) activity. Third, for the 7-month postchemotherapy assessment, patients were evaluated at least 24 weeks, but less than 28 weeks, after the second assessment to allow ample time for cognitive recovery. Each baseline and postchemoradiation interview lasted approximately 2.5 hours; with the exception of a list-learning and memory task for which alternate forms were used, these interviews consisted of the same measures during each session.

To rule out brain metastases, all patients underwent computed tomography (CT) imaging (with contrast) of the head before and, in all but one case, after treatment. When applicable, suspicious findings on CT imaging were evaluated further using magnetic resonance imaging. No patients enrolled in the current study showed evidence of brain metastases on neuroimaging before therapy. All patients who fully completed the study (ie, the nine patients who completed all three evaluations) also had normal head CT scans after the third evaluation. With the exception of one patient, all individuals who either voluntarily dropped out of the study ($n = 1$) or who passed away prior to the completion of the study ($n = 4$) had

normal head CT scans following the last evaluation completed. One of the four patients who passed away prior to study completion did not undergo a head CT scan after his second, and last, evaluation; however, his CT findings were normal 2 months before his second evaluation, and he did not exhibit clinical symptoms suggesting a need to repeat this test.

Materials and Scoring

Patients were evaluated with a comprehensive battery of examiner-administered cognitive tests and self-report questionnaires regarding their mood states and fatigue levels. They also completed a lung cancer-specific QOL questionnaire. Neuropsychological measures were selected based on their sensitivity and 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 1¹³⁻²³ lists study measures employed, their commonly used abbreviations, the principal domain of cognitive functioning with which they correspond, and scores elected for use in the present study.

To reduce type I error, an attempt was made to choose a minimum number of scores for use. Scores from each neuropsychological measure were chosen based primarily upon their usefulness and the availability of information regarding their test-retest reliability when calculating their RCIs. The Gordon

Continuous Performance TEST (CPT) had no published test-retest reliability; thus, it was not used in analyses related to the RCI. The Patient Health Questionnaire (PHQ) was used to assess the presence of five different mental disorders; they were divided into threshold disorders corresponding to specific *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*²⁴ diagnoses (eg, major depressive disorder, panic disorder, other anxiety disorder) and subthreshold disorders involving fewer symptoms than required for any specific DSM-IV diagnoses (eg, other depressive disorders, probable alcohol abuse or dependence). For the Functional Assessment of Cancer Therapy–Lung (FACT–L), the average scores for each subscale were computed without the subjective item inquiring about how functioning in each domain impacted QOL.

Statistical Considerations

Published normative data 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). Each patient's baseline test performance was judged to indicate impairment if one of two criteria was met.

Patients having z scores of -1.5 or less for more than one test were considered to have cognitive impairment; a designation of cognitive impairment was also given to all patients having z scores of -2.0 or less for just one test. This approach was used 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 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 upon normative assumptions.

To control for multiple comparisons, only differences of $P \leq 0.01$ were considered to be statistically significant in all analyses conducted. Paired t -tests were performed to assess mean group differences between patient performance at baseline and at the 1- and 7-month postchemotherapy assessments, respectively, for each cognitive test. In addition, paired t -tests were conducted to evaluate mean group differences in cognitive test performance between the two postchemotherapy assessments.

Comparing group differences in test scores between time points is useful; however, the utility of statistical significance tests (eg, t -tests) to evaluate treatment effects is limited in at least two respects.¹² First, such tests provide no information on the variability of response to treatment within the sample; that is, they are unable to identify a particular subgroup of individuals at possible risk of cognitive decline. Second, whether or not a treatment effect is statistically meaningful may have little to do with its clinical significance.

To address the latter issues, Jacobson and colleagues²⁵ proposed an RCI that later was amended by Christensen and Mendoza.²⁶ As explained in detail by Jacobson and Truax,¹² the resulting RCI is:

$$RC = \frac{X_2 - X_1}{S_{diff}}$$

where X_1 represents a subject's pretest score, X_2 represents that same subject's posttest score, and S_{diff} is the standard error of the difference between the two test scores. S_{diff} may be computed directly from the standard error of measurement (S_E), according to this equation:

$$S_{diff} = \sqrt{2(S_E)^2}$$

where $S_E = S_1\sqrt{1-r_{xx}}$, S_1 represents the SD of test scores, and $1-r_{xx}$ represents the test-retest reliability of the measure. S_{diff} then represents the spread of the distribution of change scores that would be expected if no actual change occurred.

An RCI larger than 1.65 would be unlikely to occur ($P < 0.10$) without actual change. Thus, in the present study, the RCI was used to determine the frequency of change in cognitive function from one assessment to the next.

In the present study, test-retest reliability and SDs for each test score were derived from published data—typically, from information in the test manual. Tests with published test-retest reliability possess inherent error; therefore, the RCI allows identification of changes in test scores that are clinically and statistically meaningful for each patient. In the current study, the index represented the 90% confidence interval for the difference in performance between two evaluations that would be expected if no real change occurred. Importantly, the level of analysis for the RCI entailed each individual patient, not the group as a whole.

One-tailed Pearson correlation coefficients were computed to examine the relationship between baseline cognitive function/mood variables/QOL and baseline homocysteine, TSH, and hemoglobin levels, respectively. Correlation coefficients also were computed to examine the associations between mood measures/fatigue/QOL/age and cognitive test results at each assessment time point. Independent t -tests were used to compare patients who experienced cognitive decline with those who did not in terms of QOL, fatigue, mood, and age. A frequency table was used to examine whether or not individuals who were cognitively impaired at baseline were at greater risk for cognitive decline postchemotherapy.

Results

Participants were recruited over a period of 1 year, 7 months. Twenty patients met the initial screening criteria for participation. Four female and one male patient declined to participate; most of these individuals indicated that they were too emotionally overwhelmed to take part. At the first testing session, one patient displayed disinterest in the testing and did not appear to be putting forth optimal effort; thus, his results were excluded from the study, and he declined to participate in subsequent testing sessions. Thus, data from

Table 2
Patient Baseline Demographics
and Clinical Characteristics

DEMOGRAPHIC	VALUE
TNM classification, n	
T1N2M0	1
T2N2M0	4
T3N1M0	3
T3N2M0	1
T3N3M0	1
T4N2M0	2
T4N3M0	1
TxN2M0	1
Gender, n (%)	
Male	13 (93%)
Female	1 (7%)
Race, n (%)	
White	13 (93%)
Black	1 (7%)
Age, y	
Mean (SD)	60.2 (11.3)
Patient range	34–80
Education, y	
Mean (SD)	11.8 (1.6)
Patient range	8–14
Premorbid Verbal Intelligence score	
AMNART Estimated VIQ	105.9 (8.4)
Patient range	88.0–120.0
Hemoglobin level	
Mean (SD)	13.4 (1.6)
Patient range	10.7–16.5
Normal range	14–18 g/dL
Homocysteine level	
Mean (SD)	10.2 (3.9)
Patient range	5.5–20.8
Normal range	5.9–15.3 mCmol/L
Thyrotropin level	
Mean (SD)	1.8 (1.0)
Patient range	0.6–3.3
Normal range	0.4–4.2 mCU/mL

Abbreviations: TNM = tumor-node-metastasis; AMNART = American Version of the Nelson Adult Reading Test; VIQ = Verbal Intelligence Quotient

14 patients were available for the baseline evaluation. Demographics and clinical characteristics of these patients are presented in Table 2.

NEUROPSYCHOLOGICAL TESTING

Baseline. Overall, 71% of patients (n = 10) were judged to be cognitively impaired on the basis of neuropsychological testing at baseline. Impairments at baseline were most commonly seen on a test of list-learning and memory (Hopkins Verbal Learning Test–Revised Immediate Recall [Hopkins Immed] and –Revised Delayed Recall [Hopkins Delay]) and on a test of conceptual flexibility (Wisconsin Card Sort-

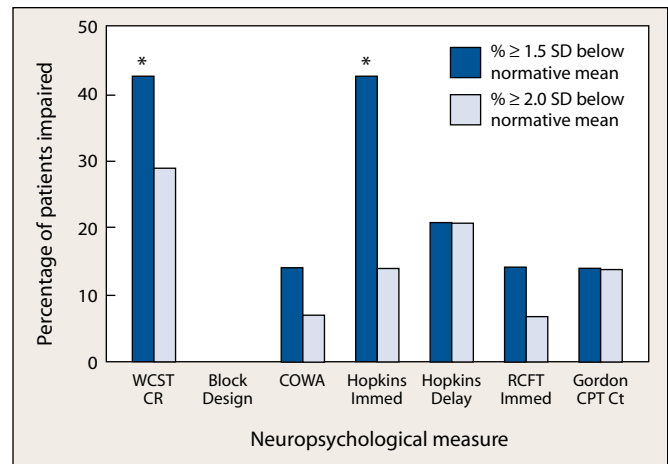


Figure 1 Frequency of Cognitive Impairment at Baseline

* $P = 0.001$ (binomial test)

Abbreviations: WCST CR = Wisconsin Card Sorting Test Conceptual Level Responses; COWA = Controlled Oral Word Association Test; Hopkins Immed = Hopkins Verbal Learning Test–Revised Immediate Recall; Hopkins Delay = Hopkins Verbal Learning Test–Revised Delayed Recall; RCFT Immed = Rey Complex Figure Test Three-Minute Recall; Gordon CPT Ct = Gordon Continuous Performance Test Total Correct

ing Test Conceptual Level Responses [WCST-CR]; Figure 1). Impairments were demonstrated, but less commonly so, on tests of sustained attention (Gordon Continuous Performance Test [CPT]), verbal phonemic fluency (Controlled Oral Word Association [COWA]), and visuospatial learning and memory (Rey Complex Figure Test Three-Minute Recall [RCFT Immed]). No patient demonstrated impairment on a test of visuospatial construction (Block Design). In terms of both conceptual flexibility (WCST-CR) and immediate verbal learning and memory (Hopkins Immed), 43% (n = 6) of the study cohort exhibited impairment; this frequency was significantly elevated when compared with normative expectations ($P = 0.0001$; Figure 1).

No statistically significant correlations were shown between laboratory values of TSH, homocysteine, or hemoglobin and any of the mood variables, QOL variables, or cognitive test scores. It should be noted that TSH and homocysteine levels were not available for one patient. Thirteen of 14 patients had normal homocysteine levels (ie, 5.9–15.3 mCmol/L). One patient had an elevated homocysteine level (20.8 mCmol/L).

1-Month Postchemotherapy. Thirteen of the 14 patients who completed the baseline evaluation were able to complete the 1-month post-treatment evaluation. One patient passed away before this evaluation could be accomplished.

At 1 month after chemotherapy, 62% (n = 8) of patients demonstrated a decline in cognitive function on at least one of the six neuropsychological measures that exceeded the RCI (Figure 2). Twenty-three percent (n = 3) experienced declines on at least two of the seven measures, and 8% (n = 1) experienced declines on three of the seven measures. Declines were most commonly seen on the measure of conceptual flexibility, but they also were noted on all five other neuropsychological measures.

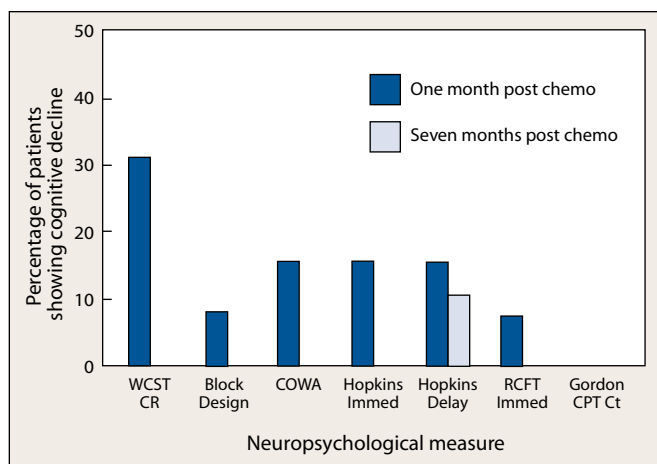


Figure 2 Frequency of Cognitive Decline Exceeding the Reliable Change Index at Baseline and 1 and 7 Months Post-Chemotherapy as Compared With Baseline

Abbreviations: WCST CR = Wisconsin Card Sorting Test Conceptual Level Responses; COWA = Controlled Oral Word Association Test; Hopkins Immed = Hopkins Verbal Learning Test–Revised Immediate Recall; Hopkins Delay = Hopkins Verbal Learning Test–Revised Delayed Recall; RCFT Immed = Rey Complex Figure Test Three-Minute Recall; Gordon CPT Ct = Gordon Continuous Performance Test Total Correct

Paired-sample *t*-tests were conducted to evaluate whether the entire patient cohort experienced a statistically significant short-term decline in cognitive function at 1 month postchemotherapy. There were no statistically significant mean group differences on any test scores. However, there was a trend for worse performance on the COWA at the 1-month postchemotherapy evaluation (mean = 31.0; SD = 10.2) as compared with the baseline evaluation (mean = 36.8; SD = 13.4; $t[12] = 2.7$; $P = 0.019$). Table 3 includes standardized mean scores for the sample on neuropsychological measures. Results of independent sample *t*-tests showed no significant differences in terms of QOL, fatigue, mood, or age at baseline or at 1 month postchemotherapy between patients who experienced cognitive decline at 1 month post-chemotherapy and those who did not.

We also were interested in whether or not preexisting cognitive impairments increased the risk for cognitive decline at 1 month postchemotherapy. Our sample size was small; however, the data suggest that demonstration of cognitive impairments at baseline more than doubles a patient's risk for cognitive decline at 1 month after chemotherapy (Table 4). In fact, the results suggest that 70% of patients with such impairment before chemotherapy and just 33% of patients without such impairments will experience cognitive decline 1 month after chemotherapy.

Comparing Results 1 and 7 Months Post Chemotherapy. Five of the eight patients who demonstrated cognitive declines exceeding the RCI at 1 month post chemotherapy also com-

Table 3

Mean Values and Standard Deviations for Measures of Cognitive Function*

	BASELINE MEAN (SD)	1 MO POST CHEMO MEAN (SD)	7 MO POST CHEMO MEAN (SD)
All patients	(n = 14)	(n = 13)	(n = 9)
WCST CR [†]	40.9 (10.9)	39.2 (8.4)	51.0 (13.4)
Block Design [‡]	9.6 (1.6)	10.0 (2.2)	9.8 (3.0)
COWA [†]	47.9 (12.1)	44.7 (7.1)	47.9 (15.4)
Hopkins Immed [†]	39.8 (12.7)	41.2 (11.4)	40.6 (8.5)
Hopkins Delay [†]	42.6 (8.7)	41.7 (10.9)	42.8 (13.7)
RCFT Immed [†]	47.0 (15.1)	54.2 (15.8)	54.6 (14.0)
Gordon CPT Ct [§]	96.9 (16.7)	100.8 (8.5)	101.1 (16.0)
Only patients completing all evaluations	(n = 9)	(n = 9)	(n = 9)
WCST CR [†]	41.7 (9.6)	40.6 (8.9)	51.0 (13.4)
Block Design [‡]	9.2 (1.8)	10.8 (2.1)	9.8 (3.0)
COWA [†]	47.7 (13.7)	46.0 (8.0)	47.9 (15.4)
Hopkins Immed [†]	38.8 (6.2)	45.0 (8.8)	40.6 (8.5)
Hopkins Delay [†]	41.7 (8.2)	44.8 (8.5)	42.8 (13.7)
RCFT Immed [†]	43.2 (14.6)	49.6 (13.3)	54.6 (14.0)
Gordon CPT Ct [§]	101.2 (16.0)	102.9 (8.2)	101.1 (16.0)

*For ease of interpretation, standardized scores are provided; however, the specific scores (raw versus standardized) used in the statistical analyses were chosen based on their usefulness and the availability of information regarding their test-retest reliability for use in calculating their reliable change indices. These scores are identified in Table 1.

[†]*t*-test scores (mean = 50, SD = 10)

[‡]Age-scaled scores (mean = 10; SD = 3)

[§]Standard scores (mean = 100, SD = 15)

Abbreviations: WCST CR = Wisconsin Card Sorting Test Conceptual Level Responses; COWA = Controlled Oral Word Association Test; Hopkins Immed = Hopkins Verbal Learning Test–Revised Immediate Recall; Hopkins Delay = Hopkins Verbal Learning Test–Revised Delayed Recall; RCFT Immed = Rey Complex Figure Test Three-Minute Recall; Gordon CPT Ct = Gordon Continuous Performance Test Total Correct

pleted their 7-month postchemotherapy assessment; two other patients passed away after their 1-month assessment but before their 7-month evaluations could be accomplished, and another patient dropped out due to an unrelated disagreement with a primary care physician. The 7-month evaluation showed all five of these patients achieved clinically and statistically significant cognitive improvement when compared with their 1-month follow-ups. That is, all of these patients showed a decline in some areas at the 1-month follow-up; however, at the 7-month follow-up, all scores for each of these areas improved to the extent that they exceeded the RCI.

Paired sample *t*-tests were conducted to evaluate whether the patient group as a whole demonstrated a statistically significant decline in cognitive function between the 1- and 7-month postchemotherapy assessments. Nine patients remained in the study (three passed away since their 1-month post-chemotherapy evaluation, and one dropped out for reasons cited above). The results showed a trend suggestive of improvement on the WCST-CR score at the 7-month postchemotherapy follow-up (mean = 43.1; SD = 15.1) as compared with that found during the 1-month follow-up (mean = 32.1; SD = 15.1; $t[8] = 3.2, P = 0.013$). Table 3 contains standardized mean scores for the sample on neuropsychological measures.

7-Months Post Chemotherapy Compared With Baseline. When test scores from the 7-month postchemotherapy evaluation were compared with those from baseline, only one patient demonstrated a cognitive decline that exceeded the RCI as compared with his baseline performance; further, that finding entailed just one score from one measure (Figure 2). Paired sample *t*-tests that evaluated whether the group demonstrated a statistically significant decline in cognitive function between the baseline and 7-month postchemotherapy assessments indicated no significant differences between group performances on any measure.

POTENTIALLY CONFOUNDING PSYCHIATRIC VARIABLES

The PHQ assessed patients for the presence of major depressive disorder, other depressive disorder, panic disorder, other anxiety disorder, and probable alcohol abuse or dependence. At the baseline evaluation ($n = 14$), one patient met the criteria for other anxiety disorder. This patient did not meet the criteria for any disorders at either of the subsequent evaluations; however, this individual experienced a decline in at least one area of cognitive function that exceeded the RCI at the 1-month postchemotherapy evaluation.

At the 1-month postchemotherapy evaluation ($n = 13$), one patient met the criteria for major depressive disorder and other anxiety disorder. Another patient met the criteria for other depressive disorder and probable alcohol abuse or dependence and was diagnosed with the latter after admitting to having driven a car after having several drinks or drinking too much during the previous 6 months.

At the 7-month postchemotherapy evaluation ($n = 9$), the patient who met the criteria for major depressive disorder and other anxiety disorder at the 1-month post-chemotherapy

Table 4

Baseline Cognitive Status and Risk for Cognitive Decline at 1 Month Post Chemotherapy

	COGNITIVELY IMPAIRED AT BASELINE ($n = 10$) n (%)	NOT COGNITIVELY IMPAIRED AT BASELINE ($n = 3^*$) n (%) [*]
Cognitive decline post chemo	7 (70.0%)	1 (33.3%)
No cognitive decline post chemo	3 (30.0%)	2 (66.6%)

^{*}One additional patient was not cognitively impaired at the baseline assessment. However, he passed away before his 1-month postchemotherapy evaluation; thus, his results are not included herein.

evaluation continued to satisfy the criteria for major depressive disorder. Both patients who satisfied the criteria for newly diagnosable psychiatric conditions at the 1-month postchemotherapy evaluation also experienced cognitive declines that exceeded the RCI on at least one measure.

No statistically significant correlations were shown at any of the three assessment time points between neuropsychological test results and mood ratings, fatigue rating, QOL variables, or age.

Discussion

This prospective, longitudinal, pilot study was initiated to explore the cognitive effects of chemotherapy in a group of NSCLC patients. To our knowledge, within the NSCLC population, this is only the second published trial to examine cognitive functioning using a longitudinal design. This study improved upon the original study^{6,7} by providing longer-term follow-up and more comprehensive assessments. This extended longitudinal design rarely has been used to study the effects of chemotherapy. Even within the breast cancer literature, only one published study appears to have been conducted prospectively.¹¹

Results of the current study suggested that the large majority (71%) of NSCLC patients demonstrate cognitive impairments before receiving chemotherapy. In tests of conceptual flexibility and immediate verbal learning and memory, a significantly greater number of patients than would be expected based upon normative data performed in the impaired ranges at baseline. The demonstration of cognitive deficits before treatment doubled the risk for cognitive decline at 1-month post chemotherapy. Baseline cognitive test scores were not significantly correlated with laboratory TSH, homocysteine, or hemoglobin values.

At 1 month post chemotherapy, 62% of patients demonstrated a cognitive decline on at least one of the six neuropsychological tests examined. Declines were most commonly seen on a measure of conceptual flexibility, but they also occurred on all other cognitive tests. Detection of cognitive decline at such a brief retest interval (~3 months) is difficult, even when alternate forms are used (as on the Hopkins Verbal Learning Test-Revised), because patients typically score bet-

ter on the second assessment than on the first; in fact, gains associated with prior testing typically take up to 7 or more years to dissipate.²⁷ Thus, the finding of decreased cognitive function among this very small pilot sample (n = 13 at retest) is of clinical relevance.

On the positive side, the neurocognitive decline experienced by this subgroup apparently ameliorated with time as brains recovered from the neurotoxic insult of chemotherapy. All patients who completed their 7-month follow-ups showed improvements on measures for which they demonstrated cognitive decline at the 1-month follow-up that exceeded the RCI, suggesting that cognitive declines were only temporary. In fact, a comparison of test scores from the 7-month postchemotherapy evaluations with baseline data showed that only one patient suffered a cognitive decline that exceeded the RCI when compared with his baseline performance—and that decline involved only one score from one measure (Figure 2).

In terms of potential psychiatric contributions to cognitive decline, there were no statistically significant correlations between neuropsychological test results and mood ratings, fatigue rating, QOL variables, or age at any of the three assessment time points. Moreover, there were no significant differences between patients who experienced cognitive decline at 1 month post chemotherapy and those who did not in terms of QOL, fatigue, mood, or age at baseline or at 1 month post chemotherapy. However, given the small sample size employed in the current study, these findings should be

considered tentative.

The finding of transient neuropsychological deficits following cisplatin-based chemotherapy was consistent with previous reports of transient neurotoxicity following the same therapy. Whereas the most common side effects of cisplatin include nausea and vomiting, more serious effects have been seen, including nephrotoxicity, myelosuppression, ototoxicity, peripheral neuropathy, and such reversible focal cerebral disorders as seizures and cortical blindness.^{28–31}

A published case report also detailed a case of reversible posterior leukoencephalopathy syndrome following cisplatin therapy.³² Reported onset of encephalopathy has varied from 6 hours to 3 months after the start of treatment,²⁹ but this effect appears to be reversible in most cases.^{29–32} The etiology of these reversible CNS effects is unclear. Unfortunately, clinicopathologic evidence offers few explanatory data—although cisplatin accumulation appears to be highest in the dorsal root ganglia of the spinal cord (perhaps accounting for peripheral neuropathy), central structures of the brain and spinal cord appear to be relatively well protected from platinum accumulation.³³

The present study, like most, employed combination chemotherapy. Thus, it is not possible to independently evaluate the effects of either chemotherapeutic agent used. In both clinical and research settings, use of different drug combinations and additional chemotherapeutic agents continues to be explored. It is of great importance for patients, especially those with potentially curable NSCLC, to understand the potential short- and long-term risks of chemotherapy on cognitive function.

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