Residuals in post-chemotherapy, non-depressed patients with leukemia that is in remission

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Abstract

Debate persists regarding the occurrence and etiology of neurocognitive deficits associated with the utilization of chemotherapeutic agents, commonly referred to as "chemobrain". While some have previously attributed these features to other factors such as fatigue, emotional reactivity, etc., growing literature suggests that in fact chemotherapeutic agents may be the cause. Although research has investigated these deficits, greater investigation is warranted. The current study investigated the presence of residual neurocognitive deficits in non-depressed patients post-chemotherapy with a history of leukemia that was in remission in comparison to healthy controls. Methods: participants included 16 individuals with a history of leukemia post-chemotherapy, in remission and without depression and 48 healthy controls. Participants were assessed using the WJ-III with data from the first seven subtests entered for analysis. A multivariate analysis of variance revealed significant differences existed between groups. By way of a discriminant function analysis, subtest/domain specific discrepancies were noted. Specifically, participants with a history of leukemia who were post-chemotherapy and without depression were found to perform significantly worse on visual-auditory learning, concept formations, and sound blending than did healthy controls. Findings are seen as additional support of the idea that neurocognitive deficits do in fact occur following chemotherapy. However, they are particularly of interest as they are seen even in the absence of emotional distress and outside the

active treatment phase. Additional findings of importance and clinical relevance will be discussed.

Keywords: Oncology; Leukemia; Cancer

1. Introduction

Cross-sectional and longitudinal studies of cancer survivors have suggested detrimental effects of chemotherapy on cognitive performance (Brezden, Phillips, Abdolell, Bunston & Tannock, 2000; Ahles et al., 2002; Castellon, Ganz, Bower, Petersen, Abraham & Greendale, 2004; Shilling, Jenkins, Morris, Deutsch & Bloomfield, 2005). These changes are usually subtle with patients often showing mildly reduced functioning in comparison to healthy peers across an array of neurocognitive domains, including working memory, executive function, and processing speed (Ahles & Saykin, 2002; Anderson-Hanley, Sherman, Riggs, Agocha & Compas, 2003; Ferguson & Ahles, 2003; Tannock, Ahles, Ganz & van Dam, 2004).

Colloquially referred to as "chemobrain" or "chemofog," Chemotherapy-Induced Cognitive Impairment (CICI) is defined as the decrease in one's memory, learning, attention, reasoning skills, executive function, and visuospatial skills during and following chemotherapy (Argyriou, Ifanti & Kalofonos, 2010). Specifically, chemotherapy has resulted in functional and structural changes as follows: attention and concentration deficits in the frontal subcortical network, verbal memory impairments in the left hemisphere, remote memory deficits in the frontal and temporal lobes, episodic memory impairments in the temporal lobes and prefrontal cortex, working memory deficits in the bilateral prefrontal and parietal regions, executive function deficits in the bilateral prefrontal cortex, decreased processing speed in the frontal subcortical network, decreased motor speed in the bilateral frontal lobes and pyramidal tracts, visual memory deficits in the right hemisphere, visual-spatial impairments in the right parietal and bilateral frontal lobes, and decreased reaction time in the frontal subcortical network (Argyriou et al., 2010). The medical literature notes that the duration of CICI may range between two to ten years post-chemotherapy (Schagen, van Dam, Muller, Boogerd, Lindeboom & Bruning, 1999; Ahles et al., 2002).

Given the longstanding effects of chemotherapy on an individual's quality of life, it is critical to better understand what increases the likelihood of an individual experiencing these chemotherapy-induced impairments. While such deficits are most commonly noted during chemotherapy (Ahles

& Saykin, 2002; Ferguson & Ahles, 2003) research is still determining to what extent this impairment may truly be a result of neurophysiological changes from neurotoxicity, what is a result of prolonged fatigue, and what may be explained by other mitigating factors, such as emotional distress and hormone therapy (Brezden et al., 2000; Castellon et al., 2004; Wefel, Lenzi, Theriault, Buzdar, Cruickshank & Meyers, 2004; Jenkins et al., 2006; Mehlsen, Pedersen, Jensen & Zachariae, 2009). While the verdict is still out, there is stronger evidence in support for neurophysiological changes given that 20-40% of patients have persistent deficits in cognition post-treatment, even after controlling for psychological factors, fatigue, and confounding variables, including emotional distress and hormone therapy.

While fatigue has been perceived by patient's as leading to cognitive impairment evident in self-report measures, research has not shown a significant correlation between fatigue and abnormalities in objective neuropsychological testing (Castellon et al., 2004; Jenkins et al., 2006). As such, fatigue is believed to be strongly correlated with perceived, subjective cognitive functioning but not with objective cognitive functioning.

One pilot study evaluated the relative sensitivity of a number of neuropsychological tests to detect chemotherapy-induced cognitive impairments in a sample of individuals with breast cancer. Freeman and Broshek (2002) evaluated 15 neuropsychological tests and subtests based on their sensitivity to detect mild cognitive impairments in patients with head injuries. The sample in the cross-sectional study consisted of 17 patients with breast cancer, eight of whom were currently receiving standard-dose chemotherapy and nine survivors who had completed standard-dose chemotherapy treatment 6-12 months earlier. Significant differences between the two groups were found on only 2 of the 15 neuropsychological tests. Patients undergoing active cancer treatment demonstrated poorer performance on the visual construction subtest of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), whereas survivors demonstrated poorer performance on the Stroop Test.

Further, a meta-analysis was conducted to identify which neuropsychological tests have been used to evaluate chemotherapy-induced impairment in various domains of cognitive function in patients with breast cancer and to determine the sensitivity of each of these tests through estimation of effect size (Jansen, Miaskowski, Doss & Dowling, 2007). Four neuropsychological tests (d2 test, High Sensitivity Cognitive Screen [HSCS] attention subtest, and Wechsler Adult Intelligence Scale [WAIS] digit and spatial span subtests) were used in at least two studies to measure chemotherapy-induced impairments in attention and concentration. The digit span backward test produced the largest effect size, but none of the tests of attention and concentration produced

a significant effect size. Five neuropsychological tests (Booklet Category Test, Trail Making Test [TMT]-Part B, HSCS self-regulation and planning subtest, Stroop Test, and WAIS similarities subtest) were used in at least two studies to measure chemotherapy-induced impairments in executive function. Although the Booklet Category Test produced the largest effect size, none of the tests of executive function produced a significant effect size. Six neuropsychological tests (Fepsy binary choice, visual reaction, and visual searching subtests; Paced Auditory Serial Addition Test [PASAT]; TMT-Part A; and WAIS digit symbol subtest) were used in at least two studies to measure chemotherapy-induced impairments in information processing speed. Although the largest effect size was found with the PASAT and the visual reaction subtest of the Fepsy, none of the tests of information processing speed produced a significant effect size. Only two neuropsychological tests (HSCS language subtest and Controlled Oral Word Association) were used in at least two studies to measure chemotherapy-induced impairments in language. Only the language subtest of the HSCS produced a small but significant effect size (-0,43, p = 0,05). Four tests (Fepsy Finger Tapping Test, grooved pegboard, HSCS psychomotor subtest, and Haistein-Reitan Neuropsychological Battery [HRNB] finger tapping subtest) were used in at least two studies to measure chemotherapy-induced impairments in motor function. Significant effect sizes were found for two of the tests of motor function. The grooved pegboard produced a large effect size (-0.90, p = 0.05), and the Fepsy Finger Tapping Test produced a moderate effect size (-0.60, p = 0.05). Three tests (HSCS spatial subtest, Rey-Osterrieth Complex Figure Test [RCFT] copy, and WAIS block design subtest) were used in at least two studies to measure chemotherapy-induced impairments in visuospatial skill. Significant moderate effect sizes were found for two of the tests of visuospatial skill (RCFT copy -0.51, p = 0.05; block design subtest of the WAIS -0.55, p = 0.05). Four tests (Califomia Verbal Learning Test, HSCS memory subtest, Rey Auditory Verbal Learning Test, and Wechsler Memory Scale [WMS] logical memory subtest) were used in at least two studies to measure chemotherapy-induced cognitive impairments in verbal memory. Only the memory subtest of the HSCS produced a small but significant effect size (-0.45, p = 0.05). Two tests were used in at least two studies to measure chemotherapy-induced impairments in visual memory (RCFT delayed recall and WMS visual reproduction subtest). Although the largest effect size was found with the delayed recall of the RCFT, neither of the tests of visual memory produced a significant effect size.

Neurotoxicity caused by chemotherapeutic agents is a frequently observed side effect (Verstappen, Heimans, Hoekman & Postma, 2003). Cancer patients may experience a wide range of neurological symptoms due to chemotherapy, such as cognitive deficits, seizures, cerebellar dysfunction,

psychiatric symptoms and extrapyramidal disorders (Verstappen et al., 2003; Dietrich, Monje, Wefel & Meyers, 2008). The development of these harmful effects may have an acute, subacute, or delayed course, and may be reversible or partially irreversible (Ahles et al., 2002; Schagen et al., 2002; Verstappen et al., 2003). The incidence of central neurotoxicity of chemotherapy depends on the chemotherapeutic drug used, the frequency of administration, the dosage prescribed, the route of administration and concomitant cranial irradiation (van Dam et al., 1998; Verstappen et al., 2003; Boogerd et al., 2004; Schagen, Muller, Boogerd, Mellenbergh & van Dam, 2006; Dietrich et al., 2008).

Although research has examined these deficits (e.g. Ahles & Saykin, 2007), greater investigation is warranted. The current study investigated the presence of residual neurocognitive deficits in patients post-chemotherapy with a history of Leukemia and currently in remission in comparison to healthy controls as a means of providing greater evidence in support of chemotherapy-induced cognitive decline.

2. Methods

Data was collected via a standardized administration of neuropsychological tests as part of clinical examination through a mid-western hospital. IRB approval was granted for the secondary analysis of the data. Data of interest included scores on the Woodcock-Johnson III-Tests of Cognitive Abilities (WJ-III), which represents the cognitive portion of the Dean-Woodcock Neuropsychological Assessment System. The WJ-III provides information on an individual's cognitive performance across four indices: verbal comprehension, perceptual organization, working memory, and processing speed as well as an overall IQ score. Participants included 16 children and adolescents; 8 male and 8 female. During the course of this study, subjects were between the ages of 93 ad 737 months (*mean* = 258.75 months, *SD* = 285.202 months), with an education between 1.5 and 20 years (*mean* = 6.3, *SD* = 8.17052). Twelve (75%) of the subjects were right-handed.

3. Results

A multivariate analysis of variance revealed significant differences existed between groups. No within-cell outliers at $a = .001$ were found. Assumptions of normality, linearity, homogeneity of variance-covariance matrices,

and multicollinearity were met. Using Wilks' Lambda criterion, results demonstrated that significant differences between groups did, in fact, exist $F(7, 56) = 2.865$, $p < .05$. In finding significant differences between groups, a Discriminant Function Analysis (DFA) was performed using the selected WJ-III-Cognitive subtests as predictors of diagnostic group membership (*Table 1*). A significant discriminant function resulted, $\chi^2(7) = 14.257$, $p < .05$. Interpretation of variables with a loading factor of .3 or above revealed participants with a history of Leukemia that received chemotherapy performed significantly worse on visual-auditory learning, concept formations, and sound blending. Group outcomes including means and standard deviations are depicted in *Table 2*. Specifically, participants with a history of Leukemia who were post-chemotherapy and without depression were found to perform significantly worse on visual-auditory learning, concept formations, and sound blending than did healthy controls.

Table 1. Discriminant Function Analysis – Structure Matrix

Visual-Auditory Learning	.605
Concept Formation	.391
Sound Blending	.310
Numbers Reversed	.250
Visual Matching	-.141
Verbal Comprehension	.090
Spatial Relations	-.089

Table 2. Neurocognitive Outcomes on the Woodcock Johnson Test of Cognition, Third Edition

WJ-III Outcomes	Chemo-treated Leukemia	Normal Controls
Verbal Comprehension**	102.63 (15.12)	103.95 (12.78)
Visual-Auditory Learning	94.72 (11.86)	101.48 (9.54)
Spatial Relations	100.87 (11.71)	99.81 (10.64)
Sound Blending**	95.54 (14.19)	100.41 (14.32)
Concept Formation**	95.36 (12.74)	101.57 (14.99)
Visual Matching**	99.36 (15.81)	97.74 (10.88)
Numbers Reversed**	97.16 (15.01)	101.3 (15.33)

Note: ** = significant effects.

4. Discussion

The results of this study are consistent with previous findings suggestive of neurocognitive deficits post-chemotherapy. Following cancer treatment, individuals are at an increased likelihood of experiencing psychosocial and affect-related difficulties. These deficits are highly related to poor quality of life perceptions by cancer survivors. As such, neuropsychological services for this population are of the utmost importance. Specifically, services should emphasize consideration of a variety of appropriate treatment and rehabilitation regimens. Furthermore, continued care and monitoring of individuals psychological, emotional, and social functioning during and following cancer treatment may be beneficial for better long-term functioning. Future research may want to consider assessing various treatment and rehabilitation programs to determine the healthiest and most beneficial options.

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