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Cognitive-behavioral management of chemotherapy-related cognitive change

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Abstract

Adjuvant chemotherapy can produce mild cognitive decline among breast cancer survivors which adversely effects function and quality of life. However, no treatment to date has been proposed or developed for this problem despite large numbers of cancer patients who report post-treatment memory dysfunction. This paper presents data from a single arm pilot study of a brief cognitive-behavioral treatment aimed at helping breast cancer survivors manage cognitive dysfunction associated with adjuvant chemotherapy (Memory and Attention Adaptation Training; MAAT). Participants were twenty-nine women who were an average of 8 years post-chemotherapy for stage I and II breast cancer. All had reported complaints regarding memory and attention. Improvements in self-report of cognitive function, quality of life and standard neuropsychological test performance were observed at post-treatment, 2-month and 6-month follow-up. Participants also reported high treatment satisfaction and rated MAAT as helpful in improving ability to compensate for memory problems. Given these results, the treatment appears to be a feasible and practical cognitive-behavioral program that warrants continued evaluation among cancer survivors who experience persistent cognitive dysfunction.

Keywords

breast cancer; chemotherapy; cognitive dysfunction; cognitive-behavioral treatment; survivorship

Introduction

Standard and high dose cancer chemotherapies can have a deleterious effect on cognitive function [1,2]. Although subtle, chemotherapy-related changes in attention, verbal memory and executive function may be long-lasting (2–10 years post-treatment; [3]) and adversely affect cancer survivors' vocational and economic security, daily household management, or attainment of educational goals [4]. While the problem continues to be studied, little has been done to develop and evaluate treatment for cognitive dysfunction after chemotherapy for adult cancer survivors.

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Empirical study of cognitive remediation following cancer treatment is more advanced in pediatric than adult populations [5]. Many pediatric cognitive remediation approaches combine traditional 'repetitive drill and practice' to enhance memory [6,7] with behavioral adaptation strategies to improve function [8]. However, some pediatric approaches may be lengthy (e.g. 50 visits; [9]) and not practical for adult cancer survivors who are resuming career, familial or educational activity. In addition, many adult survivors may not have more severe cognitive deficits commonly observed in pediatric research. To address the need for a cognitive symptom intervention for adult chemotherapy recipients, we developed a brief cognitive-behavioral program that emphasizes instruction in memory and attention compensatory strategies applied to daily life. This article presents data on the first pilot study of this treatment approach.

Methods

Participants

Twenty-nine adult women who received adjuvant chemotherapy for stage I or II breast cancer comprised the final sample. Inclusion criteria were: (1) diagnosis of breast cancer; (2) three years post-cancer treatment (not including post-chemotherapy hormonal treatment such as selective estrogen receptor modulators); (3) complaint of memory and attention problems after chemotherapy; (4) no recurring disease; (5) greater than 18 years of age when diagnosed with cancer; (6) able to speak and read English; (7) able to provide informed written consent. Exclusion criteria were: (1) history of CNS disease; (2) previous CNS radiation or intrathecal therapy; (3) neurobehavioral risk factors such as traumatic brain injury with loss of consciousness, history of neurological disorder, substance abuse or learning disability; (4) current psychiatric disorder. Breast cancer surgery or non-CNS radiation treatments were not exclusionary criteria. The decision to include participants 3 years post-treatment was based on the finding that acute effects of chemotherapy, stress, depressive and anxiety symptoms, all influence cognitive function. But for many cancer patients, these acute effects appear to diminish within a year's time and cognitive function improves [3]. Therefore, we wanted to control for this recovery effect.

Participants were recruited from a rural, regional academic cancer center (Dartmouth-Hitchcock Medical Center) and private oncology offices in Northern New England. All were screened via telephone for eligibility and for psychiatric disorder using the Primary Care Evaluation of Mental Disorders PRIME-MD [10].

Sixty-six women inquired about the study. Twenty declined participation reporting cognitive symptoms were not troublesome and nine were ineligible for enrollment. Thirty-seven women enrolled and provided informed written consent approved by Dartmouth Medical School's Institutional Review Board. Seven enrolled participants dropped out citing personal reasons, relocation or travel inconveniences. These participants did not differ from the final sample on demographic or dependent variables. A final participant was excluded from final analysis due to severe poor and outlying neuropsychological test performance at baseline, skewing sample means.

All participants were Caucasian (mean age 56.00 years; S.D.=7.81), reflecting the low minority representation in Northern New England. Participants on average had 15.40 (2.30) years of education and an estimated mean full scale IQ of 112.82 (6.18) based on demographic data [11]. The final sample had a variety of adjuvant chemotherapies but mainly had variations of cyclophosphamide/doxorubicin (AC or CAF) regimens or cyclophosphamide/methotrexate (CMF). No participants had a history of autologous bone marrow transplantation or whole-body radiotherapy. The mean years post-chemotherapy was 8.20 (4.40). All women were post-menopausal at the time of enrollment. Nine

participants in the final sample were taking antidepressant medications either for depressive symptoms or sleep enhancement (5 on SSRI compounds and 4 on tricyclic antidepressants). No participant met criteria for major depressive disorder and no changes in dosing or were reported during study participation.

Procedure

Intervention—Memory and Attention Adaptation Training (MAAT) consisted of a participant workbook, 4 individual monthly visits, with phone contacts once between visits for support and review—a total of 7 contacts. Visits were 30–50 minutes in length in which participants reviewed current knowledge of chemotherapy-associated memory problems, learned how to identify 'at risk' situations where memory failures arise, and learned and rehearsed compensatory strategies relevant to their unique difficulties. Application of strategies was the 'homework' between visits. Telephone contacts served as a means of assistance in applying strategies.

MAAT's four cognitive-behavioral components included: (1) Education on memory and attention; (2) self-awareness training; (3) self-regulation emphasizing arousal reduction through relaxation training, activity scheduling and pacing; and (4) cognitive compensatory strategies training. Compensatory strategies included self-instructional training (covert verbal 'self-guidance' during task performance), verbal rehearsal of auditory information, schedule making, external cueing and outlining written material. Each participant received a MAAT workbook with written information about chemotherapy and memory difficulty as well as step-by-step guides on how to practice and apply the compensatory strategies. The clinician (R.F.) followed a MAAT clinician's manual (Table 1).

Research design—Dependent measures included self-reported cognitive function, breast cancer survivor quality of life, measures of depressive and anxiety symptoms and standardized neuropsychological tests. Participants were assessed at 4 time-points: baseline, immediately after treatment, and at 2 and 6-month follow-up. A 1 (group) ×4 (time) repeated-measures factorial design was utilized. Because no control group was included in this preliminary evaluation, univariate analyses were used to detect differences in dependent measures across time and determine variability and probable effect size. The main hypothesis was that MAAT would produce significant improvement in self-reported cognitive function, quality of life and neuropsychological test performance over baseline. It was also predicted that participants would give MAAT high satisfaction ratings and rate it as helpful in compensating for chemotherapy- related memory dysfunction.

Measures—The principal outcome measures were self-report of daily cognitive function (The Multiple Ability Self-Report Questionnaire; MASQ; [12]) quality of life (Quality of Life—Cancer Survivors scale, [13]) and satisfaction with the treatment approach. Participants rated general satisfaction with MAAT using verbal anchors 'not at all satisfied,' (0) to 'completely satisfied' (8). Participants also rated how helpful MAAT was in *improving* memory and attention, and how helpful MAAT was in helping them *compensate* for memory and attention problems. Both items were rated on the same 0–8 scale with verbal anchors: 'not at all helpful,' (0), to 'completely helpful.' (8). Neuropsychological tests were selected on the basis that previous research demonstrated statistical discrimination between survivors treated with chemotherapy versus those treated with local therapy [3]. Tests included:

1. The California Verbal Learning Test-II (Alternate Forms; [14]);
2. Logical Memory I and II from the Wechsler Memory Scale, 3rd Edition [15];
3. Digit Symbol subtest from the Wechsler Adult Intelligence Scale III [16];

4. Trail-making tests A& B [17];
5. Stroop Color-Word Interference test [18];

Depression was assessed with the Center for Epidemiologic Studies-Depression Scale (CES-D) [19] and anxiety was assessed with the State-Trait Anxiety Inventory [20].

Results

All participants attended all 4 MAAT office visits with four participants missing one phone contact and one participant missing 2 phone contacts; 97.5% of all possible participant contacts were made.

Self-report of cognitive function

The main hypothesis that MAAT improves self-reported cognitive function in daily life (MASQ total score) was supported $F(3, 81) = 7.73$, $p<0.001$. Post hoc analysis utilizing the Student Newman–Keuls procedure demonstrated that participants reported significant improvement at post-treatment (Table 2; lower MASQ scores denote fewer cognitive problems) and improvements were sustained at 2-month and 6-month follow-up. In addition, similar patterns of significant post-treatment improvement were observed on several MASQ sub-scales: attention/concentration, spatial memory, verbal memory, and language.

We compared the baseline MASQ total score to that of a healthy control sample enrolled in current research by our group. The healthy controls in that study ($n = 32$) reported a MASQ total score mean of 81.26 (S.D.=18.69). By comparison, the present sample reported substantially more cognitive symptoms at baseline ($m = 115.84$; S.D.=19.97). This is nearly 2 standard deviations higher than that reported by healthy (but demographically comparable) women.

Quality of life and treatment satisfaction

Qualtiy of life was improved (QOL-CS total score, $F(3, 82) = 2.86$, $p<0.05$) but post hoc analyses demonstrated improvement achieved statistical significance over baseline at 6-month follow-up (Table 2). Depressive symptoms did not change with MAAT; an expected result since CES-D scores were normal range at baseline ($m = 9.00$; S.D.=6.52). In addition, state and trait anxiety were within normal range at baseline with a trend toward reduction after MAAT ($p = 0.06$, 0.07, respectively).

Participants gave MAAT high general satisfaction ratings at post-treatment ($m = 7.14$, S.D.=1.09; 0–8 Likert-type rating scale). Participants also rated MAAT as helpful with *improving* memory and attention ($m = 5.86$, S.D.=1.53) and gave higher ratings to MAAT for helping participants *compensate* for memory and attention difficulties ($m = 6.63$, S.D.=1.34).

Neuropsychological test results

Univariate analyses demonstrated statistically significant improvement over baseline in verbal and executive function neuropsychological domains (see Table 2). With the exception of CVLT-II *T*-scores, neuropsychological test results were analyzed with raw scores. Conversion to standard and/or scaled scores indicated means presented here were within a normal range, despite participant complaints of cognitive problems.

Estimates of size of effect using Cohen's *d* corrected for repeated self-report and neuropsychological test measures are presented in Table 2. Each effect size presented is associated with each variable's relevant statistically significant difference from baseline. For

example, the effect size for the MASQ total score in Table 2 is the size of effect obtained from the difference between baseline and post-treatment MASQ total score. Moderate to large effect sizes observed in self-reported cognitive function (MASQ) suggests meaningful change over time for this dependent measure.

Discussion

Improvements in self-report of daily cognitive function, quality of life and neuropsychological test performance were observed among 29 long-term breast-cancer survivors who completed a brief treatment program aimed at managing cognitive symptoms associated with chemotherapy. Participants rated MAAT as helpful with respect to learning and using cognitive compensatory strategies and reported high treatment satisfaction. Results support MAAT as a feasible and possibly effective cognitive-behavioral, non-pharmacologic management approach to a common problem for many cancer survivors.

Participants showed gains in neuropsychological test scores with moderate effect sizes. However, because of the lack of a control condition, caution is urged with respect to observed neuropsychological results. Many neuropsychological test score gains can be due to effects of practice and repeat exposure to test materials. Results of this study require further evaluation of MAAT's effect on neuropsychological test performance by use of a more rigorous randomized control design. By the same token, MAAT's intent is to improve survivor coping through cognitive-behavioral self-management of cognitive problems and not to 'retrain' memory function. In this respect, it may be the self-report measure of daily cognitive function (MASQ score) is a more appropriate measure of MAAT's effectiveness. Further study should consider this matter of identifying the most appropriate outcome measure.

There are limits to the generalizability of MAAT with other populations. First, the present sample was highly educated and readily learned and applied MAAT strategies. Individuals with less education may require more time with a clinician. Future research should include individuals with a wider range of educational, ethnic or cultural backgrounds. Second, individuals with more profound cognitive dysfunction, such as those with executive function deficits due to previous stroke, brain injury or other cancer treatment, may have difficulty in this brief, 'guided self-help' approach. In view of these preliminary results, our group has initiated a second study utilizing a randomized wait-list control design to evaluate efficacy.

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Table 1

Outline of MAAT content

Memory and attention adaptation training schedule	
Visit	**Content**
Visit 1	• Treatment overview, instruction in self-monitoring of memory failures in daily life and progressive muscle relaxation training instruction with practice
Phone Contact 1	• Review of workbook and answering any participant questions • Review of self-monitoring of memory failures to identify specific problems of memory and attention in daily activities (i.e. 'at risk' situations) • Review relaxation practice and ability to identify application to daily activity
Visit 2	• Quick relaxation instruction with practice • Identify 'at risk' memory failure situations with self-monitoring data • Learn behavioral memory and attention skill or compensatory strategy. This is tailored to the participant's specific cognitive problems that arise in specific activity (i.e. using 'memory routines' at the work place to improve productivity and reduce forgetting where items are placed)
Phone Contact 2	• Review of workbook, self-monitoring of memory failures and relaxation • Review the application of the memory and attention skill and modify if necessary
Visit 3	• Learn a new behavioral memory and attention skill • Activity scheduling
Phone Contact 3	• Review of applying relaxation and memory skills and activity scheduling
Visit 4	• Establish a 'behavioral maintenance plan' to assure maintenance of the newly learned and applied attention and memory skills • Wrap-up with answering final questions

Table 2

Self-report of cognitive function (MASQ), quality of life results and neuropsychological test outcomes ($N = 29$)

Measure		Baseline	Post-Tx	2-Month f/u	6-month f/u	Effect Size: Cohen's
MASQ						
MASQ Total Score	$p<0.001$	115.84_a (19.97)	109.71_b (17.45)	107.07_b (18.31)	106.08_b (19.75)	BL v. Post =0.57
MASQ Attention/Concentration	$p<0.0001$	19.57_a (4.30)	18.23_b (3.70)	17.62_b (3.64)	17.58_b (4.05)	BL v. Post =0.67
MASQ Spatial Memory	$p<0.05$	16.74_a (4.43)	15.59_b (4.37)	15.66_b (4.25)	15.22_b (4.47)	BL v. Post =0.55
MASQ Verbal Memory	$p<0.001$	21.94_a (3.90)	20.89_b (3.56)	19.85_b (3.86)	19.95_b (4.14)	BL v. Post =0.47
MASQ Visual Perceptual	$p<0.05$	13.45_a (3.81)	13.45_a (3.69)	12.58_b (3.88)	12.53_b (3.71)	BL v. 2-month f/u 1 =0.63
MASQ Language	$p<0.001$	19.15_a (3.84)	17.69_b (3.41)	17.17_b (3.63)	17.44_b (3.92)	BL v. Post =0.66
Quality of Life—Total Score	$p<0.05$	7.06_a (1.05)	7.22_a (1.05)	7.24_a (1.13)	7.26_b (1.11)	BL v. 6-month f/u 2 =−0.51
CES-D		9.0 (6.5)	9.1 (7.6)	9.7 (8.6)	9.0 (8.0)	
State Anxiety	$p = 0.06$	34.07 (7.67)	33.28 (9.80)	30.66 (6.93)	30.41 (9.48)	
Trait Anxiety	$p = 0.07$	35.14 (7.98)	32.18 (8.34)	33.25 (9.15)	33.93 (9.31)	
Neuropsychological Measures-Verbal						
CVLT Total Score	$p = 0.0001$	54.90_a (8.62)	55.10_a (8.80)	61.59_b (9.23)	59.56_b (10.35)	BL v. 2-month f/u = 1.12
Logical Memory I	$p<0.0001$	44.14_a (8.44)	47.93_b (8.05)	53.48_c (8.43)	56.22_d (8.65)	BL v. Post =−0.90
Logical Memory II	$p<0.0001$	28.62_a (6.66)	32.41_b (7.37)	35.66_c (6.52)	37.52_d (6.05)	BL v. Post =−0.95
Neuropsychological Measures-psycho-motor						
Digit Symbol	$p<0.0001$	12.66_a (2.50)	13.76_a (2.42)	14.28_b (2.40)	14.67_b (2.88)	BL v. 2-month f/u =−1.23
Stroop Color-Word Test: Interference	$p<0.0001$	57.05_a (9.96)	54.11_b (8.25)	51.65_b (8.14)	51.40_b (7.46)	BL v. Post =0.59
Trail-Making—A	$p = 0.001$	27.08_a (7.84)	24.87_a (8.44)	22.53_b (4.96)	22.36_b (5.23)	BL v. 2-month f/u =0.90
Trail-Making—B	$p = 0.01$	60.13_a (21.86)	61.08_{ab} (18.66)	54.31_{ac} (14.35)	52.64_c (17.42)	BL v. 6-month f/u =0.55

Lower MASQ scores indicate fewer cognitive problems. Means with differing subscripts indicate significant differences (Student Newman–Keuls post hoc test).