Life Sciences 93 (2013) 617–622

Contents lists available at ScienceDirect

Life Sciences

journal homepage: www.elsevier.com/locate/lifescie

A randomized trial of cognitive rehabilitation in cancer survivors

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ARTICLE INFO

Article history:
Received 4 October 2012
Accepted 19 August 2013

Keywords:
Cancer
Cognition
Cognitive rehabilitation
Controlled trial
Attention
Working memory

ABSTRACT

Aims: The second most frequently reported post-treatment symptom in cancer survivors are concerns about impaired cognition. Despite numerous studies demonstrating significant impairments in a portion of survivors, information on effective treatments remains an emerging area of research. This study examined the effectiveness of a group-based cognitive rehabilitation intervention in cancer survivors.
Main methods: This study was a randomized, controlled study of a 7-week cognitive rehabilitation intervention delivered in group format. Participants were evaluated with subjective symptom questionnaires and objective neurocognitive tests prior to and following treatment.
Key findings: Twenty-eight participants (mean age 58 years) with a median of 3 years (±6 years) post-primary/adjuvant treatment and various cancer sites (breast, bladder, prostate, colon, uterine) completed the study. Compared to baseline, the treatment group demonstrated improvements in symptoms of perceived cognitive impairments ($p < .01$), cognitive abilities ($p < .01$) and overall quality of life with regard to cognitive symptoms ($p < .01$) as measured by the FACT-Cog. The treatment group also improved on objective measures of attention ($p < .05$) and a trend toward improvement on verbal memory. Significant improvement was not observed on all cognitive tests.
Significance: A group based cognitive rehabilitation intervention in cancer survivors was effective for improving attention abilities and overall quality of life related to cognition. Results suggest that group based cognitive rehabilitation may be an effective intervention for treating cognitive dysfunction in cancer patients and should be further studied in a larger trial with an active control condition.

Introduction

Millions of cancer survivors live with residual symptoms of impaired cognition severe enough to interfere with basic activities of daily living and work (Cavanna et al., 2011). Although some studies indicate persistent cognitive deficits in cancer survivors related to chemotherapy or use of tamoxifen (Debess et al., 2010; Koppelmans et al., 2012), findings in this regard are equivocal.(Du et al., 2010; Harrington et al., 2010; Pedersen et al., 2009) Despite numerous studies demonstrating significant cognitive impairments in a portion of survivors, research into effective treatments for cognitive difficulties is an emerging area of enquiry (Loiselle and Rockhill, 2009; Marín et al., 2009; Vardy, 2009; Wefel et al., 2010). Cognitive rehabilitation has been utilized successfully for many years in the context of brain injury programs (Sohlberg and Mateer, 2001). Cognitive rehabilitation and cognitive training have also been shown to be effective in helping children with cancer achieve school success (Butler et al., 2008) and more recently to improve cognition in older adults with mild cognitive impairment (MCI), multiple-sclerosis, schizophrenia and brain tumor patients (Gehring et al., 2010; Hassler et al., 2010; Haut et al., 2010; Mattioli et al., 2010; Poppelreuter et al., 2008; Pyun et al., 2009). In cancer survivors, cognitive behavioral treatment can be effective for improving memory and attention problems (Ferguson et al., 2007, 2012). In general, studies indicate some success for goal development as well as over learning or repeated practice approaches, as well as an indication that a deficit specific approach can be useful. See Rajeswaran for a comprehensive review (Rajeswaran, 2013).

In this preliminary study, we examined a randomized, controlled trial of a 7-week, group based cognitive rehabilitation intervention for cancer survivors. We selected cognitive rehabilitation techniques that addressed the most common complaints from survivors: memory and attention difficulties. These included memory techniques such as method of loci and attention techniques such as chunking and repetition. We hypothesized that treatment would result in improvements in quality of life related to cognition as well as objectively measured memory and attention performance.

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http://dx.doi.org/10.1016/j.lfs.2013.08.011

Materials and methods

Subjects

Participants were adult cancer survivors recruited from the area through referral from providers or via response to flyers. Inclusion criteria were: 1. Subjective concern about declines in cognitive functioning related to a diagnosis of cancer and/or cancer related treatment. This was obtained by asking participants the question "do you have concerns about your memory or other thinking abilities following cancer treatment?". Participants were required to answer yes to this question to meet this inclusion criteria. Additional details on the nature and severity of these difficulties were obtained using the FACT-cog to allow for quantification and comparison among participants. 2. Age greater than 18 years and less than 90 years. 3. Completion of active treatment for cancer (e.g., chemotherapy, radiation therapy and surgery) 6 months or more in the past. 4. Able to read English and participate in informed consent process. Exclusion criteria were: 1. Ongoing treatment for cancer (e.g., chemotherapy, radiation, surgery, etc.). 2. Unstable medical problems (such as unstable or untreated heart disease or hypertension, diabetes in poor control, respiratory disease complicated by hypoxia or hypercapnia, infectious illnesses, unstable thyroid dysfunction, and/or currently hospitalized). 3. History of, or current symptoms of, serious psychiatric disorder requiring antipsychotic medications or hospitalization. Mild symptoms of depression or stable anti-depressants, and anti-seizure medications were acceptable. Due to adverse effects of benzodiazepines on cognition, this class of anti-anxiety medication was not allowed (Ghoneim and Mewaldt, 1990). 4. Current substance abuse as defined by consuming 4 drinks or more per day or binge drinking (6 or more drinks in one night) within the past week. 5. History of or current neurological illness that significantly impacts cognition (e.g. stroke, multiple sclerosis, Parkinson's disease, Alzheimer's disease, head injury, epilepsy). 6. History of a central nervous system tumor, due to known site specific cognitive deficits and variability of treatment modality effects that would require selection and study arm balance efforts beyond the scope of this preliminary study (Alomar, 2010; Gregor et al., 1996; Hahn et al., 2009; Harder et al., 2004; Salander et al., 1995) 7. A score of 25 or more on the Patient Health Questionnaire (PHQ-9) a measure of depression (Wittkampf et al., 2009). 8. A score of 26 or below on the Mini Mental Status Exam (MMSE) a screening measure of cognition (Folstein et al., 1975).

Study procedures

The study design was a randomized, controlled trial of a group based cognitive rehabilitation program. Participants underwent a phone screening followed by an in-person screening session (visit 1), including neurocognitive tests and symptom questionnaires, and a second baseline assessment (visit 2) of neurocognitive tests. The in-person screening visit (visit 1) began with the informed consent process and all participants signed a written consent form. All study procedures and materials were approved by the University of Washington/Fred Hutchinson Cancer Research Center Institutional Review Organization. Symptom questionnaires included those that assess the frequency and severity of cognitive, mood and physical symptoms.

Symptom measures included a quality of life scale related to cognition, the Functional Assessment of Cancer Therapy-Cognition (FACT-Cog) (Jacobs et al., 2007). The FACT-Cog has three subscales: symptoms of perceived cognitive impairments with higher indicating fewer symptoms, perceived cognitive abilities in which a higher score indicates a rating of better cognitive abilities, and overall quality of life with a higher score indicating better quality of life as it relates to cognition. Additional measures include a depression symptom measure, the Patient Health Questionnaire (PHQ-9), for which a higher score indicates more symptoms of depression (Wittkampf et al., 2007), an anxiety symptom measure Beck Anxiety Inventory (BAI), in which a higher score indicates endorsement of more and/or more severe anxiety symptoms (Stanley et al., 1996), and a measure of fatigue symptoms, Functional Assessment of Chronic Illness Therapy — Fatigue (FACIT-Fatigue), with higher scores indicating a better quality of life and fewer fatigue symptoms (Cella, 1997).

The neurocognitive battery was comprised of standard objective measures of attention, memory, and executive functions using published versions along with modified, equivalent alternate versions to control for practice effects. Measures included Wechsler Adult Intelligence Scale—III (WAIS-III) subtests digit span and digit symbol (Wechsler, 1997). Digit span is a task of attention and working memory and involves hearing a series of digits and recalling them in the same order (forward) or in the reverse order (backward). A score is given for both forward and backward and a total score is generated with a higher score indicating better performance. Digit symbol is a task of psychomotor coordination, visual tracking, and working memory and involves rapid completion of a series of symbols according to a visible key, with higher scores indicating better performance. The Stroop test is considered a task of executive function and involves reading text, naming color blocks and the interference trial in which the pre-potent response of reading must be inhibited to name ink color. Time to complete is recorded so that a lower score is better performance (Delis et al., 2001). The Rey Auditory Verbal Learning test (RAVLT), is a task of verbal memory in which participants hear a word list and must recall it after several presentations and a short delay (Schmidt, 1996). Total recall across trials as well as the delay are recorded with a higher score indicating better verbal memory. Participants were also given a questionnaire (using a five point Likert scale) to assess their experience and satisfaction with the workshops.

The neurocognitive measures were administered twice prior to the start of the intervention or control periods to help reduce practice effects. Only the baseline (visit 2) was used for analysis.

After the screening visit, and determining eligibility, participants were randomized to active treatment (TX) or control (CL) (delayed treatment). However, participants were not informed of the randomization process and therefore they were blind to their treatment condition until completing the study. All participants were told that they would undergo treatment. Study personnel were aware of their assignment, however, study personnel who were involved in the assessment of cognition and administration of questionnaires were not involved in administering the treatment.

Treatment (TX) included seven consecutive workshop sessions lasting 1 h and delivered over seven consecutive weeks. Content of the workshops included memory aids (e.g. calendar, reminders, note-taking, study aids) as well as development of memory skills (e.g. habit formation, method of loci, chunking, learning names) and one session on mindfulness meditation. Group sessions typically involved a didactic portion in which new concepts were introduced, a practice portion in which participants could try out the new skills with other group members and a portion of time devoted to review of previous concepts. Participants were also given assignments to work on the outside of the group sessions (i.e. homework) that encouraged them to practice the skills learned in class. The control condition (CL) involved no intervention. Participants in the control condition were informed that a group was not readily available and that they would be assigned to a group at the next possible opening. All participants underwent a post-condition evaluation with neurocognitive measures and symptom questionnaires. For participants in the TX group, post-test was scheduled one to two weeks after completion of the group workshops and for the CL group this was scheduled 7–8 weeks after their baseline evaluation (visit 2).

Statistical analysis

Data was entered into SPSS statistical software and double checked for accuracy. Mixed model (group by time) repeated measure