IOSR Journal of Nursing and Health Science (IOSRJ-JNHS)
e-ISSN: 2320–1959.p- ISSN: 2320–1940 Volume 6, Issue 4 Ver. VII (Jul. -Aug . 2017), PP 46-55
www.iosrjournals.org

Effect of Cognitive Training Program in Chemotherapy Treated Breast Cancer patients

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Abstract
Aim: *To evaluate the effect of cognitive training program in chemotherapy treated breast cancer patients.*
Research design: *A quasi-experimental "time series" research design was used.*
Subjects & Methods: Setting: *The study was carried out in Oncology outpatient facility in one of the University Hospitals in Cairo, Egypt.*
Study subjects: *It included two groups of 40 patients each: intervention and control group from the previously mentioned setting who met the inclusion criteria.*
Data collection tool: *A structured interview was utilized to gather data pertinent to the present study. It comprises two sections, A. Demographic and health characteristics data sheet B. Mini-Mental State Examination Scale (MMSE)*
Results: *The results showed improvement in the study group in follow up phase with statistically significant relation (p-value<0.001). Regression analysis specified training program as a single statistically significant independent positive predictor for the Mini-Mental State Examination (MMSE) score. While number of diseases, number of health problems and Hemoglobin level were negative predictors.* ***Conclusion:*** *Statistically significant improvement in the scores of MMSE of study group of chemotherapy treated breast cancer patients in follow up phase after their involvement in the cognitive training program.* ***Recommendations:*** *Further studies about cognitive interventions on larger scale and risk factors and predictors of chemotherapy-related cognitive changes need to be explored.*

Key words: *Breast cancer, Cognitive training, Chemotherapy, Patients, Program*

Date of Submission:08-08-2017 *Date of acceptance:05-09-2017*

1. Introduction

Globally, cancer is one of the main causes of morbidity and mortality, with approximately 14 million new cases in 2012 [1]. Breast cancer is the most common cancer in women worldwide, and is the most frequent cause of cancer among women in many countries. In developing countries the incidence has been expanding continuously [2]. Among females in Egypt, Breast cancer is considered to be the major cancer type [3].

Chemotherapy represents one of the most frequent methods of treatment [4]. Chemotherapy-induced cognitive impairment, also called "chemobrain" or "chemofog," is accepted as a relatively familiar adverse effect of chemotherapeutic agents typically given to treat various types of cancers, mainly breast, lung, prostate, and ovarian [5]. Among the growing body of literature some evidence suggests a relation between the chemotherapeutic agents and risk for exposure to cognitive impairment [6]. Diminished cognitive function is one of the most likely reported side effects of chemotherapy in patients with cancer [7]. Specifically, among patients with breast cancer cognitive impairment is a notable problem [8] and one of the most prevalent symptoms after treatment [9-10].

Cognitive function commonly includes a different skills, such as the ability to process information automatically (processing speed), the ability to react and decide automatically (response speed), attention, calculation, imagination, learning, memory and visuospatial abilities [11]. Most research reported that some patients seem to be susceptible to cognitive dysfunction even after completion of treatment and often have problems with multitasking, short-term memory, word finding, attention, or concentration [12].

From the literature it is clear that the consequences of cancer- and chemotherapy-related cognitive impairment were described as a significant clinical problem that inversely affect quality of life of many cancer survivors during and after treatment [13,6,14-15], hinder achievement of daily activities [16-17], has an important effect on self-perception, social network, and work ability [8] and interfere with independent life style of cancer survivors [18].

A number of studies demonstrate some aspects of the role of oncology nurses; such as provision of patient care that enhance or sustain cognitive function and quality of life in cancer patients [19], having an important role in the assessment and management of cancer-related cognitive impairment [20] recognizing cancer survivors with cognitive impairment [21], prepare them with knowledge[22], provision of education, support and advocacy for their patients through distinctive role of nursing in oncology team [23] and finally their vital role in early recognition and dealing with upsetting symptoms [24-25].

Significance of study:

Breast cancer is the most commonly occurring cancers in females globally, accounting for 1.67 million new cases in 2012 [26-27]. The estimated incidence of breast cancer worldwide is 1.7 million yearly and the five-year prevalence is 6.2 million. Both are increasing [28].

Chemotherapy-related cognitive impairment constitutes an important problem to patients with cancer and its rate ranged between 17%-75% [29] and needs to be considered for attentive care [30]. Enhancing a cancer survivor's ability to function can reduce cancer-related occupational disability costs for individuals and society [31]. Despite this, earlier research findings suggest that evidenced-based interventions are scarce [32]. Ongoing and future researches to test interventions are required [33]. Similarly, prior studies have emphasized the need to investigate new strategies [34]. Lately, other findings recommended further studies to test the efficacy of such cognitive interventions [35-36].

Nurses are frequently reported to be the preferred provider to deliver survivorship care but there is little literature documenting their efficacy [23]. The benefits of cognitive rehabilitation are still to be confirmed [37]. Investment in education and competent planning among nurses and other health care workers either in hospital or community are suggested to improve cancer patient services [38]. So, the present study attempts to provide insight to symptoms management and draw attention for potential nursing strategies that can improve those symptoms.

Aim:
To evaluate the effect of cognitive training program in chemotherapy treated breast cancer patients

Research hypothesis:
Mini-Mental State Examination (MMSE) scores of study group of chemotherapy treated breast cancer patients improve after participation in the cognitive training program.

II. Subjects and methods

2.1 Research design:
A quasi-experimental research design (time series design) was used to achieve the aim of the study.

2.2 Setting:
The study was conducted in oncology outpatient clinic at one of the University Hospitals in Cairo.

2.3 Study subjects:
The study involved intervention and control group. Women were consecutively recruited according to the following inclusion criteria:
Females, 25 to 60 years old, had completed at least 6 years of education, newly diagnosed with breast cancer , starting the same chemotherapy protocol after mastectomy for the first time for at least 3 months,

Exclusion criteria:
No previous history of breast cancer, not having Hematologic cancer (leukemia) or lymphomas or brain tumor, had no history of dementia, had no prior diagnosis of cancer or neurologic illness and no history of hospitalization for psychiatric illness within the previous 2 years.

The sample size:
Is estimated to detect the difference between the rate of abnormal MMSE before (p1=60%) and after (p2=90%) the intervention with a 95% level of confidence (α error = 5%), and a study power of 80% (β error=20%). Using the equation for the difference between two proportions (Epi-Info 6.04), the estimated sample size is 38 subjects per group. After adjustment for a dropout rate of about 5%, the sample size is 40 per group.

2.4 Data collection tool:

Structured interview consists of two sections was used to collect data pertinent to the current study.

A. **Demographic and health characteristics data sheet**: It includes age, education, job and marital status, residence, presence of chronic diseases, health problems and hemoglobin level.

B. **The Mini-Mental State Examination Scale (MMSE):** A brief screening tool to provide a quantitative assessment of cognitive impairment and to record cognitive changes over time in adults. The scale developed by Folstein, Folstein & McHugh [39]. It consists of 11 simple questions or tasks grouped into 7 cognitive domains; Orientation to time, Orientation to place, Registration of three words, Attention and calculation, Recall of 3 words, Language, Visual construction. A perfect score is 30 points. Levels of impairment have been classified as: None: score = 24-30, Mild: score = 18-24, Severe: score = 0-17[40].

2.5 Tool validity and Reliability:

For the content validity, the scale was translated into Arabic using the translation-back-translation method to ensure its validity. As well as, a three nursing faculty experts were tested the readability of the questionnaire, accuracy, question sequence comprehensiveness of the questions and relevance of the items in the scales and completion time. The reliability analysis was done .The analysis yielded an average Chronbach's alpha of 0.724 for the entire scale, indicating sufficient internal consistency.

2.6 Pilot study:

A pilot study was carried out on 10% of the sample size of the study to test the study tool in terms of clarity, applicability and the time required for each patient interview. The pilot sample was not included in the main study sample.

2.7 Procedure for data collection

Upon clearance of necessary permissions, patients who match the inclusion criteria and who did not meet any of the above-mentioned exclusion criteria were informed about the aim of the study and were invited to participate. Patients were assigned to either study or control group in an alternating way. The fieldwork started in August 2013 and ended in February 2014. The researchers then started the actual research scheme, which contains the following phases.

Assessment phase:

Baseline data were obtained from patients in the two groups (study & control) using the designed tool. The time required for completion of the questionnaire ranged from 20 to 30 minutes. Patients were helped by the researcher to fill out the questionnaire.

Intervention phase:

All patients were kept on their routine care and regular chemotherapy. The patients in study group were provided individualized training sessions to enhance cognitive function. Each patient had two sessions, before starting their chemotherapy. Each session was 45 minutes long, which covers contents of training program. All patients were instructed about different types of exercise to perform them at home one time a day for 9 weeks. In addition, the researcher met the participants every three weeks to follow their practice of exercises.

The researchers prepared a guide booklet and delivered it to patients to help them in complying with the program.

The training program consisted of two main parts:

- **The first part** covered early symptoms of cognitive impairment and healthy lifestyle that can enhance brain functions including healthy diet, physical activity, rest and sleep, listening to music, reading books, using sense, exposure to nature, social contacts and co-morbidities.
- **The second part** contains eight simple brain games that planned to strength memory, concentration, attention and perception: (1) select a specific color and observing all things of the same color in patient's daily life and try to retrieve colored objects in her imagination ,at the end of the day, each patient were asked to record those objects. The same exercise was repeated in the next day for the same color to observe the new things and underline forgotten items. (2) Choose a column in the newspaper and read it with normal speed and mark specific letter (for example letter B) with a blue pen in all words, then read the same column at a slower speed and mark the same letter with a red pen in all the words to identify forgotten letters, then the patient put the newspaper aside and immediately record everything she remembers from the column. (3) For 5 minutes, patient writes her full name with the opposite hand (4) Draw a star and color it by looking at the mirror, (5) For 5 minutes, patient were asked to calmly and patiently concentrate on the movement of the seconds hand dial of a clock, (6) Select a particular image and focus on it for enough time,

then close her eyes, and remember the details, (7) simple mathematics (ascending/ descending counting, counting in pairs (8) start each word for each of animal, plant, object and country with selected letter and (9) Try to remember the details of what happened each day.

Evaluation phase:
The evaluation was done immediately after implementing the training (after 9 weeks) and repeated after three months as a follow up by using the same tool of data collection.

2.8 Ethical considerations:

After obtaining official permissions, all patients were informed about the aim, tools, procedures, and length of the study and consented to participate. They were given full explanations about the benefits of the study. They were also reassured that they were able to stop participation in the study at any time without giving reasons and without consequences on their care. Moreover, the information obtained during the study will be confidential and used for the research purpose only.

2.9 Statistical analysis:

Data entry and statistical analysis were done using SPSS 20.0 statistical software package. Chronbach's alpha coefficient was calculated to assess the reliability of the developed tool through their internal consistency. Qualitative categorical variables were compared using chi-square test. Whenever the expected values in one or more of the cells in a 2x2 tables was less than 5, Fisher exact test was used instead. Spearman rank correlation was used for assessment of the inter-relationships among quantitative variables and ranked ones. In order to identify the independent predictors for Mini-Mental State Examination (MMSE) score, multiple linear regression analysis was used, and analysis of variance for the full regression models was done. Statistical significance was considered at p-value <0.05.

III. Results

Table (1): Socio-demographic characteristics of patients in the study and control groups

Item	Group				X^2 test	p-value
	Study (n=40)		Control (n=40)			
	No.	%	No.	%		
Age:						
▪ <50	26	65.0	26	65.0		
▪ 50+	14	35.0	14	35.0	0.00	1.00
Range	25.0-60.0		29.0-60.0			
Mean±SD	44.8±9.0		45.1±8.6		U=0.01	0.91
Median	44.50		45.50			
Education:						
▪ Basic	13	32.5	17	42.5		
▪ Intermediate	12	30.0	10	25.0	0.86	0.65
▪ High	15	37.5	14	32.5		
Job status:						
▪ Housewives	29	72.5	29	72.5		
▪ Working	11	27.5	11	27.5	0.00	1.00
Marital status:						
▪ Unmarried	4	10.0	3	7.5		
▪ Married	36	90.0	37	92.5	Fisher	1.00
Residence:						
▪ Urban	30	75.0	29	72.5		
▪ Rural	10	25.0	11	27.5	0.06	0.80

(U) Mann Whitney test

The age of 65% of patients in the study and control groups was less than 50 years old. Studied patients' age ranged between 25 and 60 years in the study group and between 29 and 60 in the control group with median of 44.5 and 45.5 years respectively. Also, 37.5% of the study group had high education whereas, 42.5% of the control group had basic education. Furthermore, most of both groups (study & control) were housewives (72.5%). On the other hand, majority of study group (90%) and control group (92.5%) were married and most of them were from urban areas (75 & 72.5 % respectively).

Table (2): Health characteristics of patients in the study and control groups

Item	Group				X^2 test	p-value
	Study (n=40)		Control (n=40)			
	No.	%	No.	%		
Have chronic disease:						
▪ No	28	70.0	27	67.5		
▪ Yes	12	30.0	13	32.5	0.06	0.81
Diseases:[@]						
▪ Hypertension	7	17.5	10	25.0	0.67	0.41
▪ Diabetes	8	20.0	6	15.0	0.35	0.56
▪ Hyperlipidemia	1	2.5	0	0.0	Fisher	1.00
▪ Ischemic heart	1	2.5	0	0.0	Fisher	1.00
Total number of diseases:						
▪ Range	0.4±0.7		0.4±0.6			
▪ Mean±SD	0.0-3.0		0.0-2.0		U=0.02	0.90
▪ Median	0.00		0.00			
Health problems:[@]						
▪ Fatigue	29	72.5	30	75.0	0.06	0.80
▪ Sleep disorders	10	25.0	11	27.5	0.06	0.80
▪ Stress	9	22.5	9	22.5	0.00	1.00
▪ Depression	7	17.5	5	12.5	0.39	0.53
Total number of problems:						
▪ Range	0.0-4.0		0.0-3.0			
▪ Mean±SD	1.4±1.1		1.4±1.0		U=0.02	0.90
▪ Median	1.00		1.00			
Hemoglobin:						
▪ <12	34	85.0	36	90.0		
▪ 12+	6	15.0	4	10.0	0.46	0.50
Range	8.2-13.0		8.5-12.6			
Mean±SD	10.7±1.1		10.8±0.9		U=0.06	0.81
Median	10.80		10.80			

(@) Not mutually exclusive (U) Mann Whitney test

Table (2): Indicates that patients in both study and control group had chronic diseases (70 & 67.5% respectively). Across these diseases, diabetes was primarily reported in study group (20%) followed by hypertension (17.5%) whereas, hypertension constituted 25% of reported diseases in control group followed by diabetes (15%). Also, fatigue represents the highest reported health problem in study and control group (72.5 &75% respectively) followed by sleep disorder and stress, while the lowest percentage was related to depression (17.5 & 12.5 respectively). Furthermore, 85% of study group and 90% of control group had hemoglobin less than 12 g%.

Table (3): Mini-Mental State Examination (MMSE) scores among patients in the study and control groups throughout the intervention

Item	Group				X^2 test	p-value
	Study (n=40)		Control (n=40)			
	No.	%	No.	%		
Pre MMSE:						
▪ Abnormal (<24)	6	15.0	6	15.0		
▪ Normal (24+)	34	85.0	34	85.0	0.00	1.00
▪ Total score: Mean±SD/Median	26.8±2.3	27.0	26.8±2.3	27.0	U=0.02	0.90
Post MMSE:						
▪ Abnormal (<24)	16	40.0	16	40.0		
▪ Normal (24+)	24	60.0	24	60.0	0.00	1.00
▪ Total score: Mean±SD/Median	23.7±3.6	26.0	24.1±3.4	26.0	U=0.93	0.33
FU MMSE:						
▪ Abnormal (<24)	4	10.0	16	40.0		
▪ Normal (24+)	36	90.0	24	60.0	9.60	0.002*
▪ Total score: Mean±SD/Median	27.0±3.1	28.0	23.1±3.9	26.0	U=31.53	<0.001*

(*) Statistically significant at p<0.05 U) Mann Whitney test

As regard to Mini-Mental State Examination (MMSE) scores among patients in the study and control groups throughout the intervention **(table 3)** the findings revealed improvement in the study group in follow up phase with statistically significant relation (p-value<0.001)

Table (4): Correlation between MMSE scores and patients' characteristics

Item	Spearman's rank correlation coefficient	
	Study group	Control group
▪ Age	-0.09	0.03
▪ Educational level	0.04	-0.11
▪ No. of diseases	-0.32	-0.01
▪ No. of problems	-0.15	-0.19
▪ Hemoglobin level	-0.16	-0.14

Table (4) displays no statistically significant correlation can be detected between MMSE scores and patients' characteristics in study and control groups.

Table (5): Best fitting multiple linear regression model for the MMSE score

Item	Unstandardized Coefficients		Standardized Coefficients	t-test	p-value	95% Confidence Interval for B	
	B	Std. Error				Lower	Upper
▪ Constant	33.14	2.56		12.953	<0.001	28.10	38.18
▪ Training program	1.18	0.43	0.17	2.728	0.007	0.33	2.03
▪ No. of diseases	-0.69	0.32	-0.13	-2.127	0.034	-1.33	-0.05
▪ No. of problems	-0.50	0.23	-0.14	-2.200	0.029	-0.94	-0.05
▪ Hemoglobin level	-0.46	0.23	-0.13	-1.989	0.048	-0.91	0.00

r-square=0.10
Model ANOVA: F=5.88, p<0.001
Variables entered and excluded: age, education, marital status, residence, job status

In multivariate analysis, training program was the only statistically significant independent positive predictor for the MMSE score. While number of diseases, number of health problems and Hemoglobin level were negative predictors. The model explains 10% of the variation as indicated by r-square.

IV. Discussion:

As for worrying, the results of the current study revealed that, the age of nearly two thirds of patients in the study and control groups was less than 50 years old. Studied patients' age ranged between 25 and 60 years and between 29 and 60 in the control group. Also, about one third of the study and control group had high education. By contrast, other literatures pointed out that the incidence of cancer rises dramatically with age [2]. Also, most breast cancers are found in women who are 50 years old or older [41]. Other study showed that breast cancers occur among women who are aged 65 years or older [42]. This discrepancy is likely to be related to need for greater understanding of factors that influence risk susceptibility especially environmental role and enhance efforts of prevention among Egyptian females.

However, there are growing findings in Egypt that point to young Egyptian patients with breast cancer should be given focus [43-4. Also, findings from a study at the South Egypt showed that the age of studied female patients diagnosed with breast cancer was ranged between 26-86 years and more than half of them were in the premenopausal age [45]. Meanwhile, a total of 144 of female patients who presented with locally advanced breast cancer in Sudan ranging in age from 25 -71 years and they were presented at a younger age and lack of education [46]. Furthermore, a study for analysis of demographic characteristics for breast cancer patients in India found that studied patients' age ranged between 24-88 years and one third of them were premenopausal [47]. On the other hand, a higher risk of malignant disease was among those in the lowest educational attainment category [48].

The present study results showed that most of the study and control group were housewives. Interestingly, majority of them were married. On the other hand, most of them were from urban areas. It was observed that the current findings are inconsistent with other studies; a study in Iran demonstrates that employed women were at a higher risk of breast cancer compared with those who were homemaker [49]. Another study finding from Iran that investigate risk factors in breast cancer showed that never married women demonstrated a higher risk of breast cancer than the others (married, divorced/widowed) 50. Other findings in Egypt and more recently in India indicated that rural areas were prevalent in their studies [45, 47]. These inconsistent results could be attributed to exposure to other risk factors such as stress or carcinogens and provision of awareness and facilities for early diagnosis in urban area.

Generally, the current study findings go in the same line with study findings in Egypt and Iraq which reported that most of women with breast cancer were married [45,51]. Also, in Sudan, majority of breast cancer patients were married and more than half of them were from the urban area [46]. Moreover, women in urban communities associated with greater risk of breast cancer versus rural ones [52].

The present study findings indicated that diabetes was primarily reported chronic disease in the study group (less than one quadrant) whereas; hypertension was dominant in control group. The average of diabetes was nearly similar to those found in a previous study [53]. Congruent with other studies, diabetes can be considered as a risk factor for breast cancer [54-56]. In addition, the most prevalent comorbidities associated with breast cancer are hypertension [57]. Findings of meta-analysis demonstrate that hypertension is associated with increased risk of breast cancer, especially among postmenopausal women [58]. In contrast, arthritis was the most common chronic conditions noted in breast cancer survivors [59].

Fatigue represents the highest reported health problem in study and control group (more than two thirds) followed by sleep disorder (one quadrant of the study group) and less than one quadrant of the study group reported stress and depression. These findings are consistent with other studies which reported that fatigue is the most common symptom experienced by cancer patients [60-61]. Moreover, fatigue and sleep disturbances manifest as a symptom cluster in breast cancer patients [62].

Anemia can damage any tissue or organ and cognitive dysfunction and neurological injury have been reported in cases of severe anemia, indicating that the brain is susceptible to anaemia induced injury [63]. Many patients with breast cancer suffer from anemia, as a consequence of the disease itself or its treatment [64]. Chemotherapy regimens for breast cancer result in high incidences of anemia [65]. In this regards, the current study findings showed that most of study and control group had hemoglobin less than 12 g%. Similar to studies in other countries, a survey of Austrian patients with breast cancer receiving chemotherapy found that less than half of the patients developed anaemia during adjuvant chemotherapy [66]. The European Cancer Anemia Survey indicated that the incidence of anemia was found to be more than half of studied patients with breast cancer receiving chemotherapy [67]. In Japan, the majority of cancer patients undergoing chemotherapy develop anemia during their treatment [68].

Nurses are in a key position to provide patient education regarding cognitive impairments caused by cancer and cancer treatment. Therefore, nurses must have an understanding of the current evidence as the science continues to evolve. Patient education needs may differ along the continuum; however, patients desire information and validation of problems [21]. Although interventional research is scanty, non-pharmacological strategies such as cognitive training programs show the greatest promise [22]. Current evidence does not favour the pharmacologic management of cognitive alterations associated with breast cancer treatment. Approaches of cognitive training and physical activity appear promising [69].

In this respect, findings of multivariate analysis indicate that intervention was the only statistically significant independent positive predictor for the cognitive function. It is to be noted that, the study findings revealed improvement in the study group after intervention in follow up phase with statistically significant relation. The reason could be inverse relation with number of diseases, number of problems and hemoglobin level of studied patient therefore their cognitive functions didn't show immediately improvement in post- test phase. Consistent with earlier studies, a study about management of chemotherapy-related cognitive change found significant improvements over baseline in verbal and executive function, self-reported cognitive function, and quality of life, but without control group [70]. Also, online cognitive training in long-term breast cancer survivors led to significant improvements in cognitive flexibility, verbal fluency and processing speed, with slightly significant downstream improvements in verbal memory [71]. In addition, interventions were associated with improvements in perceived cognitive functioning, symptom distress and quality of life in breast cancer survivors [72]. Furthermore, results of a pilot study reported that compensatory cognitive training significantly improved the objective and subjective cognitive functioning of breast cancer patients [73]. On the other hand, other findings failed to note significant intervention effects for training program for breast cancer patients after chemotherapy [74]. Lastly, findings of web-based cognitive training for breast cancer survivors show no statistically significant change in primary or secondary outcome at follow-up in either group [75].

The findings of present study showed that number of diseases, number of health problems and Hemoglobin level were negative predictors for the cognitive function. Studies conducted in other countries, found that there is evidence that psychological and health factors may increase vulnerability to cognitive dysfunction after chemotherapy for breast cancer [76]. Furthermore, treatment for hypertension was identified as having a significant negative impact on verbal fluency and working memory performance in breast cancer patients, and treatment for diabetes mellitus, was found to detrimentally influence executive functioning and reaction speed [77]. One year post-diagnosis, breast-cancer survivors with higher chronic disease burden had lower physical and social functioning than survivors without additional health conditions [7]. Comorbidity was strongly associated with cognitive impairment among patient with breast cancer [79].

Congruent with other studies, cognitive changes were exacerbated by fatigue and stress [80-81]. Co-occurring symptoms are associated with cognitive changes in women with breast cancer [82]. Moreover, Fatigue had the greatest effect as a predictor of cognitive decline in patients with cancer undergoing chemotherapy [30]. In addition, declines in hemoglobin were significantly related to greater increases in fatigue duration and disruptiveness and more negative changes in performance on cognitive tasks. [83]. In a Korean study about

predictors of symptom experience in patients undergoing chemotherapy, the findings pointed out that higher symptom experience was significantly associated with lower hemoglobin levels [24]. Anemia is a prevalent complication in patients with breast cancer who undergo chemotherapy which affects the health status and quality of life in these patients [84].

V. Conclusion & Recommendations:

Current results suggest that cognitive training program seems promising; they support the study hypothesis that there was statistically significant improvement in the scores of MMSE of study group of chemotherapy treated breast cancer patients after participation in the cognitive training program. However, this improvement was achieved in in follow up phase.

Further studies are required to establish efficacy with a larger sample and after a longer follow-up period. Also, risk factors and predictor of chemotherapy-related cognitive changes need to be explored.

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Eman Mohammed Abd El-Aziz . "Effect of Cognitive Training Program in Chemotherapy Treated Breast Cancer patients." IOSR Journal of Nursing and Health Science (IOSR-JNHS) , vol. 6, no. 4, 2017, pp. 46–55.