AMERICAN UNIVERSITY OF BEIRUT

CHEMOTHERAPY AND COGNITIVE FUNCTION; AN EDUCATIONAL PROGRAM FOR NURSES

by
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AN ABSTRACT OF THE PROJECT OF

Najla Ghassan Moufarrej for Master of Science in Nursing
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Advancement in cancer treatments has increased the life expectancy of cancer patients. Despite the increase in life expectancy, the quality of life is not optimal due to chemotherapy induced cognitive impairment. Cognitive impairment (also known as chemo-brain) is estimated to occur in 15 to75% of breast and colorectal cancer patients which has been related to poorer quality of life.

In this project a review of the literature was conducted to examine the effect of chemotherapy and other related factors on cognition in cancer patients. Moreover, this paper includes a comprehensive review of the currently available evidence-based pharmacologic and non-pharmacologic treatments for chemotherapy associated cognitive impairment known to improve cognitive function and quality of life in thesepatients. The purpose of this project is to develop an evidence-based educational session for oncology nurses. This educational session will include the available pharmacologic and non-pharmacologic interventions for chemo-brain, in order for the nurses to educate the patients about the non-pharmacological interventions used to improve or prevent chemo-brain.

The clinical management, treatment approach and offerings, for chemotherapy induced cognitive decline at the American University of Beirut Medical Center were explored and a list of non-pharmacologic interventions that may improve cognitive performance in patients receiving chemotherapy was recommended. Based on these, an educational session for oncology nurses was prepared. This session aims to enhance the nurses' knowledge about cognitive impairment during chemotherapy and related evidence-based non-pharmacologic treatments. This session will serve as a guide for oncology nurses caring for patients receiving chemotherapy and complaining of cognitive impairment. The session will have a pre and post quiz about chemotherapy induced cognitive impairment for nurses. In addition, an immediate evaluation of the session, with a follow up evaluation at three months consisting of a scale of 1 to 10 rating will be performed. The evaluation will cover the nurses' benefit of the session and if their patients' reported self improvement after utilizing these non-pharmacologic interventions.

CONTENTS

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CHAPTER I

INTRODUCTION

Advancement in cancer treatments has increased the life expectancy of cancer patients; according to the United States ‘National Center for Health Statistics the mortality rate decreased from 215.1 -per 100,000 populations- in 1991 to 168.7 in 2011; with a rate of 22% decrease in deaths (Siegal, Miller,& Jamal, 2015). Despite the increase in life expectancy, the patients' quality of life is not optimal due to chemotherapy's hard to cope with and manage side-effect: cognitive impairment (Myers, 2012). Cognitive impairment is defined by the oncology nursing society (2015) as a "decline in function in one or multiple cognitive domains, including attention and concentration, executive function, information processing speed, language, visuospatial skill, psychomotor ability, and/or learning and memory" this is also referred to as chemo-brain.

The purpose of this project is to review the literature and to examine the non-pharmacological interventions for cognitive impairment associated with chemotherapy and propose an educational session for oncology nurses. A review of the literature was conducted to examine the currently available treatments for cognitive impairment associated with chemotherapy; pharmacological and non-pharmacological. Next, the oncology physicians and nurses at AUBMC were asked informally about their clinical observations working with cancer patients complaining about chemo brain. They were asked about their treatment approach and management plan. In addition, an evidence-based list of recommendation of non-pharmacological interventions to complement the treatment of cancer patients receiving chemotherapy in AUBMC was proposed. Finally, these recommendations were utilized to develop an educational session for oncology

nurses. This session includes information about possible cognitive dysfunction experienced by cancer patients taking chemotherapy and the currently available and researched non-pharmacologic interventions that can be used to improve or prevent chemo-brain. The objective of this educational session is to educate the nurses about chemo-brain; therefore, enhance their ability to educate their patients about the possible non-pharmacological interventions available to improve or prevent chemo-brain. Clinical Nurse Specialists (CNSs) play a unique role in delivering high standard evidence-based nursing care. Therefore, this educational session is within the scope of practice of CNSs and the expected role of clinical educators in oncology. On an oncology unit the CNSs will ensure that the nurses acquire the needed information to detect patients with chemotherapy related to cognitive impairment and plan their care accordingly to improve their outcomes.

CHAPTER II

BACKGROUND

Literature Review

Cognitive Impairment Associated With Chemotherapy

Chemotherapy induced cognitive dysfunction is being reported more than before because of the increase in life expectancy of cancer patients in general. Moderate cognitive dysfunction is reported in 75% of breast cancer survivors; this cognitive impairment is experienced during and after chemotherapy mostly in memory, executive function and attention (Christie et al., 2012; Kesler et al., 2013). The National Institutes of Health estimated in 2010 that the cost on society due to the difficulties that cancer and chemotherapy brings to the patient causing illness-related loss of productivity is around $20.9 billion US dollars. Cognitive difficulties are likely to be affecting these costs indirectly (Kesler et al., 2013).

With over 13 million cancer survivors in the United States alone, 4.5 million individuals may experience long lasting cognitive impairment. Chemotherapy induced cognitive impairment (Attention, concentration and memory problems) can persist long-term and can cause many undesirable behaviors. For example, it can influence the patients' adherence to treatment and decrease their ability to complete work tasks causing frustration and worsening their quality of life (Michelle C Janelsins, Kesler, Ahles, & Morrow, 2014).

In a publication by the National Institute of Health prepared by Ganz et al. (2014) entitled "Life after Cancer Treatment", cancer survivors shared their experience about the side effects they dealt with during and after completion of the treatment, and discussed

the few successful non-pharmacological interventions they used to mend the cognitive side effects related to chemotherapy. Most of the survivors mentioned in this manuscript, reported memory problems and concentration issues. For instance one of the survivors reported: “Not being able to concentrate the way I used to, has been the hardest for me. I’m hoping it doesn’t affect my work.”—JOSH (Ganz et al., 2014, p. 18).

Likewise, Dr. Lillian Nail a four time cancer survivor, a distinguished professor of nursing and a senior scientist at Oregon Health and Science University School of Nursing who was interviewed on the Ninth Annual cancer survivorship workshop of Cancer Care in 2011, stated that her memory and concentration were not as they used to be before the chemotherapy treatments. "I started engaging in sport activities, reading mystery books and taking on new computer games… I minimized my distractions by turning off music, closing the door… and staying away from window views… since my concentration was easily lost" she said. These anecdotes of survivors open a large panel of questions about chemo-brain, its etiology, impact and clinical management. For instance, Dr. Stewart Fleishman, a physician who gave his expert opinion during the Cancer Care workshop in 2006in Rockville, believes that the problem with chemo-brain is a "coding problem and not a memory problem" (audio from the Cancer Care Workshop, 2006).

In the following review of the literature, the studies' findings will demonstrate the major effect of chemotherapy on cognitive impairment. Other factors related to cognitive impairment in cancer patients will be explored as well.

Factors Related to Cognitive Impairment:

Chemotherapy:

Wefel et al. (2004) studied 84 women with breast cancer, stages I to IIIA, who underwent biopsy or mastectomy but no adjuvant chemotherapy yet. They all underwent extensive neuropsychological testing before the start of adjuvant chemotherapy and their results were compared to normative data. The results showed significant impairment in the following domains: 18% in verbal learning and 25% in memory function. Wefel et al. (2004) concluded that studies that did not have a baseline cognitive impairment test score may be falsely relating cognitive impairment solely to chemotherapy. Therefore, the authors conducted another study including 18 breast cancer patients, who had primary breast carcinoma with no metastasis; they underwent neuropsychological assessment that included a battery of cognitive tests and self-report questionnaires, before receiving adjuvant chemotherapy, then after stopping any medication that can have a neurological effect-extra pyramidal syndrome- such as those caused by an antiemetic approximately 6 months after baseline assessment and one year post chemotherapy (which was approximately 18 months from baseline assessment). At baseline 33% of the patients showed impairment in verbal learning and memory. At the short-term assessment about 6 months after chemotherapy, the percentage of women with cognitive decline increased to 61%: 34% experienced decline in attention, 12% in verbal learning and 11% in processing speed. Moreover, there was no significant difference in the quality of life of patients experiencing cognitive deficits compared to those having no deficits. However, patients who were still working while experiencing the cognitive dysfunction, in any of the domains mentioned earlier, reported higher difficulty at work compared to patients who did not experience cognitive dysfunction. Of the patients who experienced cognitive

decline at 6 months post-chemotherapy, assessed after one year, 45% showed improvement and 45% showed stable results compared to scores at 6 months. The remaining 10% had mixed results on the cognitive test scores of which improvement was detected in oral word association and stable test scores in verbal learning was seen compared to 6 months time point. On the other hand, self- reported ability to work showed improvement at one year post-chemotherapy. Though this study showed baseline cognitive decline, it was followed by a higher cognitive decline during and post-chemotherapy 6 months after the completion of chemotherapy cycles.

In line with Wefel et al. (2004), Jansen et al. (2011) conducted a prospective longitudinal study that portrayed changes in cognitive impairment in women with breast cancer taking AC (Doxorubicin and Cyclophosphamide) chemotherapy regimen alone or followed by Taxane (a mitotic inhibitor-chemotherapy agent such as Paclitaxel and Docetaxel). The women underwent neuropsychological testing and completed self-assessment questionnaires prior to taking any chemotherapy (at baseline), around one week after finishing four cycles of AC, around one week after the completion of the Taxane cycle, and 6 months after ending all chemotherapy types. The women were divided into two independent groups; the AC group of 22 women and the AC with Taxane group of 49 women. At baseline 23% of both groups of women had low scores in one or more of the cognitive fields before the start of chemotherapy. Of these 23%, 63% showed low scores in language, 50% in visuospatial memory, 50% in motor function, 13% in immediate memory, and 6% in attention. After completing all chemotherapy (6 months), 52% of both group participants had a decrease in one or more aspect of the tested fields; the decreased scores were seen mostly in the following cognitive domains (of the 52%): 71% had a low score in visuospatial skills, 43% in motor function, 34% in attention, 31%

in language, 26% in immediate memory, 26% in delayed memory, and 11% in executive function. Furthermore, at six months post completion of chemotherapy, 20% of both groups had a decline in one or two of the following domains on the test score from baseline scores: 39% of them scored lower in visuospatial, 21% in motor function, 18% in immediate memory, 14% in attention, and 7% in language. On the other hand, 7% had an improvement of cognition from their initial baseline. Of these 7%, 20% showed improvement in immediate memory, 20% in language, 20% in executive function, 20% in motor function, and 10% in attention. The remaining 73% had stable test scores compared to their baseline. These declines in cognitive domains showed statistical significance, and may have clinical implications. Impairments in these cognitive domains can hinder the patients' ability to perform routine activities at home and work (Jansen, Cooper, Dodd, & Miaskowski, 2011).Although the chemotherapy related cognitive impairment resolves in the majority of the patients when the chemotherapy cycles are completed, in this study, 20 % had residual cognitive problems that may have a long-term impact on their daily functioning. In addition, the percentage of patients who experienced chemotherapy related cognitive impairment during their treatment is high; these patients are the target of this project, they require additional nursing and medical attention to minimize the effect of chemotherapy on their cognitive function during treatment; consequently, their well-being and daily function. It maybe a combination of factors affecting chemo-brain, however, as seen in this study the decline is increased with chemotherapy (Jansen et al., 2011).

For further proof that chemotherapy alone, has a major impact on decreasing cognitive performance, 366 non-metastatic breast cancer patients who did not receive chemotherapy yet, underwent cognitive testing, their results were compared to the results

of an age matched sample of 366 healthy participants. The neuropsychological assessment was performed at baseline, one week before chemotherapy, then within 4 weeks post chemotherapy. The tested cognitive domains were; verbal memory, oral word association, word recall and backward counting to assess executive function. Breast cancer patients were found to have more chemotherapy induced cognitive impairment in all 4 domains, pre- to post-chemotherapy and performed worse on all measures of cognition compared to controls(Michelle Christine Janelsins et al., 2015).

Other researchers suspected that additional treatments received by most cancer patients concurrently with their chemotherapy might also have an effect on cognitive function; therefore, Anderson-Hanley et al. (2003) conducted a review of the literature examining other treatments that patients with cancer receive with their chemotherapy and its impact on cognitive performance. They compared the data from 838 patients originating from 29 different samples, with a mean age of 49 years and average amount of time from diagnosis or treatment was 86 weeks. The collected data included information on; chemotherapy, interferon alpha, radiation, total brain irradiation, and hematopoietic cell transplant, all of which showed significant medium to large association with a drop in the following cognitive domains; attention, information speed, verbal memory, visuospatial memory, visuospatial skill, executive function, and psychomotor skill. However, patients who were treated with chemotherapy alone scored worse on all the cognitive domains, compared to the control group of patients taking radiation alone, and compared to healthy individuals. Despite the fact that other factors may lead to cognitive impairment as well, chemotherapy seems to have the highest negative effect on cognitive function.

Moreover, to investigate if conventional-dose of adjuvant chemotherapy is associated with long-term cognitive functioning; a study on 196 breast cancer survivors who received an adjuvant chemotherapy regimen 14-30 years prior to the study date. Neuropsychological tests were conducted to compare their scores to around 1500 women of the population with no history of cancer matched by age group. The results of this study showed that chemotherapy-exposed breast cancer survivors performed worse on several neuropsychological tests compared to the population with no history of cancer. The impaired cognitive domains were immediate and delayed verbal memory, processing speed, executive function and psycho-motor speed (Koppelmans, 2012). This study suggests that chemotherapy leads to long-term cognitive side effects, hence the need to integrate measures to overcome the chemotherapy effect on cognition early on, during the treatment.

Adjuvant chemotherapy has been used more often with more aggressive dosing, which increases survival rates; and allow patients to return to their normal occupational, academic and social life before chemotherapy (Wefel et al., 2004). Furthermore, current new studies are focusing on detecting functional and structural brain changes using functional MRI. It illustrates a decrease in white matter integrity which is linked to deterioration of attention and memory performance at 5 months following chemotherapy. The decrease in gray matter has been associated with subjective difficulties in executive function directly after chemotherapy (Hermelink, 2015). Chemotherapy induced cognitive impairment may have subtle changes that do not impair the patients daily living; therefore, using the functional MRI may be able to detect this problem. However, further research is needed to prove its ability to find chemo-brain results.

Most of the studies that examined cognitive performance in patients receiving chemotherapy were conducted on breast cancer patients, which limit the generalization of the results to all cancer patients. Nonetheless, a cross sectional comparative study, comparing the cognitive performance of 50 colorectal cancer survivors (after chemotherapy) to healthy controls was conducted. They all underwent a neuropsychological battery of tests covering the following domains of cognition: attention, cognitive control, memory function and associated self-report. After assessment, the group with colorectal cancer performed worse and reported more problems on tasks requiring attention and cognitive control compared to the healthy controls (Visovati et al., 2016). This study suggests that cognitive impairment is not limited to breast cancer patients.

Furthermore, in a study by Zimmer et al. (2015), on 30 B-cell non-Hodgkin Lymphoma patients after taking chemotherapy, objective and subjective neuropsychological tests were performed to measure cognitive functions and self-perceived status of cognition compared to healthy controls. Patients were assessed within the first three months after their chemotherapy ended. The objective neuropsychological tests showed a decline in executive function and attention in patients after chemotherapy compared to the healthy controls. As for the subjective tests, patients demonstrated significantly lower scores of subjective perception of their cognition compared to healthy controls.

Similarly Kam et al. (2016) examined breast cancer patients who self-reported cognitive problems three months up to three years post-chemotherapy treatment (n=19) compared to healthy controls (n=12). They were assessed on their ability for sustained attention and resource allocation. The breast cancer patients demonstrated decrease in

their ability to maintain attention and had a mind-wandering state compared to the healthy controls. In summary, there is cumulative evidence showing that chemotherapy is the leading factor causing cognitive impairment in cancer patients. Tables 1 (Appendix I) by Ahles et al., 2012 summarized most of the studies that showed cognitive decline after chemotherapy compared to baseline and control groups. Most of the studies found decrease in more than one cognitive domain. In this paper we updated Ahles et al., 2012 table to include studies conducted between 2012 and 2016 which were added separately in table 2. Other factors related to cognitive impairment in cancer patients receiving chemotherapy have been investigated and will be discussed in the next sections.

Fatigue:

Chemotherapy is known to induce fatigue this may exacerbate cognitive impairment. Johns et al. (2015) recruited 71 breast and colorectal cancer survivors with moderate-to-severe fatigue and assigned them into two groups: a group receiving mindfulness-based stress reduction exercises and another group receiving fatigue education and support. The mindfulness-based stress reduction exercises were proposed as indirect means to improve fatigue consequently cognition. The neuropsychological tests were used to assess cognitive function at baseline, after the 8-week intervention period, and 6 months later. The participants were recruited based on their response, to Fatigue Symptom Inventory, with a score higher than 4 representing chemotherapy related fatigue. Patients were excluded if they reported depressive or stress symptoms on the Patient Health Questionnaire. Eligibility of the participants was based on the presence of chemotherapy related fatigue and not chemotherapy related cognitive impairment. Participants receiving Mindfulness-Based Stress Reduction, (MBSR training included

instruction on formal mindfulness meditation practices, mindful movement featuring yoga poses, sitting meditation, and loving kindness meditation, and incorporated informal practices to cultivate present-moment awareness in everyday life), reported significantly greater improvement on the attention test at the assessment of 8 weeks and at 6 months compared to the education and support group (Johns et al., 2015). This study suggests fatigue as one of the possible reasons for chemo-brain. The significant recovery in attention, working memory, cognitive flexibility and control, and interpersonal effectiveness cognitive domains after implementing a stress reduction intervention indirectly improved fatigue and cognitive impairment.

Cognitive Reserve:

Another factor contributing to cognitive impairment during the chemotherapy is cognitive reserve. Cognitive reserve is defined as the differences in the cognitive processes or neural networks underlying task performance allow some people to cope better than others with cognition (Stern, 2009). Years of education, IQ, occupation, leisure activities and social networks all contribute to cognitive reserve. It is thought that patients who have a higher cognitive reserve at baseline may be able to score higher on cognitive tests than others who have lower cognitive reserve (AlEjielat, 2013). In addition, those who have higher cognitive reserve may have better cognitive function when receiving chemotherapy than those with lower cognitive reserve. A higher cognitive reserve may protect the patients' cognitive function when subject to the chemotherapy burden.

Genetics and Biological Factors:

Genetics:

There are many factors that can have an effect on cognitive impairment in cancer patients. However, if there is a genetic aspect behind it, healthcare providers may be able to identify the high-risk group before undergoing chemotherapy that may develop cognitive impairment. Therefore, healthcare providers may be able to improve cognitive performance decline associated with dosing and prolonged cycles (Mandelblatt, Jacobsen, & Ahles, 2014).

AlEjielat (2013) identified a group of target genes when studying genetic variations and its possible association with cognitive decline in a group of older adults. The identified target genes were AG genotype of the MPO463. This was associated with higher performance on executive function compared to the GG genotype. It was also associated with better performance on a test of memory and on measures of IQ. The GA genotype was associated with higher vocabulary subscale scores. This led the authors to conclude that the expression of MPO is associated with better cognitive performance. These results suggested that certain genetic predisposition might lead to higher cognitive impairment.

Therefore, another study by AlEjielat (2013) was conducted on 56 Non-Hodgkin Lymphoma patients aged above 45 years, who either have diffuse large B- cell lymphoma or grade 3 follicular lymphoma confirmed by a biopsy. Patient with CNS involvement or receiving brain radiation, or brain surgery were automatically excluded. Four neuropsychological tests were administered and saliva was used for DNA extraction. In the study the chemotherapy type was mentioned in details: doxorubicin or R-CHOP

(Rituxiab, cyclophosphamide, doxorubicin, vincristine, prednisone), or R-CHOP in addition to etoposide, or mitoxantrone, or R-CHOP cytarabine, and one received rituximab, cyclophosphamide, doxorubicin, vincristine, mitoxantrone and cytarabine. The neuropsychological tests were conducted at baseline before chemotherapy and 6 months after treatment, 78.4% of them completely responded to treatment, 9.8% had stable disease, 5.9% were not evaluated and the response to treatment was unknown in the remaining 5.9%. On the first neuropsychological test (assesses global cognition, with an emphasis on learning and memory) the baseline score compared to the follow up score at 6 months showed not statistically significant difference. However, when the baseline score and follow up score were compared to normative data with a mean score of 156 (database of healthy individuals who underwent the test before) the patients' performance was significantly worse with a mean score of 24.88. As for the genetic tests, none of the different genotypes showed any significant association with the first neuropsychological test scores. The second neuropsychological test (a self report measure including five cognitive domains: language, visual perceptual ability, verbal memory, visual spatial memory, and attention) showed no change in scores from baseline, only a minor decline in the verbal memory domain. However, the patients with the AA genotype of CYP3A4*1B performed worse than those with the AG genotype on this second test. The third neuropsychological test (covered different quality of life domains: Physical Well-Being, Social/Family Well-Being, Emotional Well-Being, and Functional Well-Being) results showed a statistically significant improvement from baseline after therapy. The domains that showed improvements were: Physical Well- Being, Emotional Well-Being, and Functional Well Being. In general there was no difference across the genotypes on this test; except for the TT genotype of Pg-p C3435T whom had a higher improvement

from baseline compared to the CC/CT genotype. On the fourth neuropsychological test (self report of their capability in physical functioning) the results were not statistically significant when comparing baseline to follow up. Also, no difference across genotypes was shown; however, a subgroup of patients with the GG genotype of carbonyl reductase showed a decline in function compared to the GT group who showed an improvement in function. These data suggest that a possible genetic difference, linked to cognitive performance, exists among cancer patients. A certain genotype may be neuro-protective during chemotherapy. With further research on the subject, detection of the cancer patients who are at high risk for cognitive impairment before starting chemotherapy to implement cognitive improvement interventions more rigorously on them may become possible in the future (AlEjielat, 2013).

Furthermore, breast cancer survivors (after finishing all chemotherapy) who had the ApoE E4 allele positive had higher cognitive impairment in visual-spatial and visual memory domains than those who had the ApoE E4 allele negative (Ahles, Root, & Ryan, 2012; Mandelblatt et al., 2013).

In addition, Small et al. (2011) studied the effect of being a COMT-valine carrier or a COMT- methionine homozygotes carrier on cognitive function in breast cancer patients. The patients were all diagnosed with stage II breast cancer and were assessed during and after the following treatments (51.52% of them on Anthracycline and Cyclophosphamide; 31.82% on Anthracycline, Cyclophosphamide, and Taxane; 9.09%on Cyclophosphamide, Methotrexate, 1.52%on 5-Fluorouracil; Anthracycline and Taxane; Anthracycline, Cyclophosphamide, 3.03% on 5-Fluorouracil; and Anthracycline, Cyclophosphamide, and 3.03% on 5-Fluorouracil and Taxane). A battery of neuropsychological tests was used to measure five cognitive domains: attention, episodic

memory, complex cognition, verbal fluency, and motor speed. The patients' DNA was used from their saliva for examining which COMT carriers they were. The patients were divided into two groups, 58 patients underwent radiotherapy alone, and 72 patients underwent chemotherapy with or without radiation and all were compared to 204 healthy control subjects. The COMT-methionine homozygotes performance on attention and verbal fluency cognitive domains was different than the COMT- valine group. Overall, the COMT-valine group receiving chemotherapy performed worse on all cognitive domains compared to the COMT-methionine homozygotes who received radiation alone and compared to the healthy controls. These are further evidence suggesting a genetic predisposition to cognitive impairment with chemotherapy; yet more studies are still required to support this evidence even more.

Moreover, as mentioned by Ahles et al. (2012) and Mendelbatt et al. (2014) genetic predisposition can play an essential role in the future to determine which cancer patient may experience a higher cognitive impairment and work on it before treatment and continue till after treatment.

Biological Factors:

The Blood Brain Barrier:

The Blood Brain Barrier (BBB) protects the brain from harmful toxins. However, a defect in transporters that usually prevent molecules from entering the cerebral spinal fluid, may allow chemotherapy to cross the blood brain barrier. The P-gp is expressed in the endothelial cells at the BBB and protects the brain by transporting toxic substances, including chemotherapeutic agents, outside of it. For this reason the level and functionality of Pg-p affects the levels of cytotoxic agents in the brain. Genetic polymorphisms in this gene can affect the functionality of the protein. Chemotherapy

drugs given to mice were associated with increased cell death of oligodendrocytes (myelin forming cells), the hippocampus, and the major white matter tracts, and persisted long term after repetitive drug exposure. The minimal amount of chemotherapy that crossed the blood brain barrier did not affect tumor growth; however, it led to neurological deficit. This study showed that systemic chemotherapy may cross the blood brain barrier; however, it needs to be repeated in other animals for confirmation(Cheung, Chui, & Chan, 2012; AlEjielat, 2013).

Patho- physiology of cancer:

Other factors that may lead to chemo-brain are oxidative stress and DNA damage. The individuals' capability of being affected by chemo-brain depends on the strength of their cellular repair mechanisms. Many chemotherapeutic agents are known to cause damage to normal and abnormal dividing cells (which causes nuclear DNA damage and cellular apoptosis). This damage is related to the release of cytokines and inflammation that has been associated with sickness- behavior; including weakness, decreased mobility, malaise, anorexia, inability to concentrate and a decreased ability to learn; which were similarly seen in chemotherapy induced cognitive impairment. In elderly patients who were diagnosed with mild cognitive impairment it was found that they had higher levels of oxidative damage in the blood and their brain after autopsy (AlEjielat, 2013 & Janelsins et al., 2014). Further studies on cancer patients are needed to confirm this, and give an over view of how it can be prevented.

Around 20-30% of patients may have low-test scores prior to chemotherapy. This was not related to stress or anxiety or depression, but to cancer pathways and inflammation, which in turn activate cytokine toxin release (Ahles et al., 2012 & AlEjielat, 2013). Therefore, this suggests that the disease itself; cancer may stress the

cognitive system in a way that overwhelms the compensatory mechanisms, allowing for a severe decrease in cognitive impairment during and after treatment (Wefel et al., 2004).

Hormone Dysfunction:

Few chemotherapeutic agents are known to affect changes in hormonal levels. Tamoxifen in particular, known to induce amenorrhea, causes a fast drop in estrogen, which has been associated with cognitive impairment in verbal memory in women with breast cancer (AlEjielat, 2013). Further studies are needed to evaluate the natural effect of hormonal changes on menopause women to have a clearer view of the significance of this change on cognition. Also, more studies exploring the hormonal effect on cognitive function in cancer patients receiving chemotherapy are needed.

Anemia and other factors:

Prolonged anemia the most common side effect associated with chemotherapy has been shown in renal failure studies that it may contribute to reduction in oxygen, causing ischemia, which in turn will affect cognition negatively if not corrected (AlEjielat, 2013).Moreover, thyroid function, vitamin B12 and folate deficiency are also associated with low cognitive functions.

Psychological:

Other factors contributing to cognitive impairment when the patients are receiving chemotherapy such as, anxiety, depression, and fatigue will be explored in the below section.

Depression, anxiety and stress are known to be negatively associated with cognitive performance; these may affect it in an indirect manner especially when the anxiety and depression are severe and chronic. Anxiety and depression tend to be highly prevalent among cancer patients (Herbst, 2015) and these two are known to affect

cognitive performance negatively(Barton et al., 2013; Moon, Kim, & Kim, 2011). However, it is not confirmed if the presence of high levels of depression and anxiety when receiving chemotherapy is directly associated to worsening of cognitive performance. Also, whether the treatment of anxiety and depression when receiving chemotherapy will improve the cognitive outcomes in cancer patient is yet to be determined (Wefel et al., 2004).

Self-regulation:

Four studies that checked if the subjects' perceived cognitive depletion depends on the person's ability to exert self-control and self-regulation were reviewed by Job et al. (2010). The studies' results showed that people who are able to exert self-control and self-regulation had a higher capacity to continue working on difficult tasks and increase cognitive processing. Therefore, people who believe that they have willpower and control about their resources can affect their perception of an exhausting task and enhance their performance. Furthermore, any exaggerated stereotypes and societal expectancies combined with stress and anxiety about the disease can decrease in self-regulatory, which decreases motivation, cognitive function and increases mental load and suppression. This aspect cannot be ruled-out, but measures to prevent its occurrence can be implemented (Arndt et al., 2014).

Literature Gaps:

Most of the reviewed studies did not have a large sample size and did not include a pre-treatment baseline cognitive assessment. In addition, most of the studies did not measure depression and anxiety to rule out any confounding effect on cognitive performance. Furthermore, most of the studies eliminated patients with Central Nerves System (CNS) tumors and chemotherapy and focused on non-CNS tumors (breast cancer

mostly) and on systemic chemotherapy. Moreover, different cognitive tests were used in different studies, which make the comparison of the results between studies difficult (Wefel et al., 2004). A remaining challenge in the cancer and cognition field has been defining and measuring chemotherapy induced cognitive impairment. Therefore, the International Cognition and Cancer Task Force (ICCTF) recommend the following measures as minimal assessment of cognitive function: the Hopkins Verbal Learning Test-Revised (HVLT-R), Trail Making Test (TMT), and the Controlled Oral Word Association (COWA). However, more studies using these measures are needed to compare studies' results (Wefel, Vardy, Ahles, & Schagen, 2011). Moreover, more studies are needed on hormonal therapy and Taxanes since the most significant drop in cognitive performance was seen with this type of treatment and in combination with chemotherapy (Cheung et al., 2012).

Furthermore, most of the studies were on breast cancer patients with very few including other types such as prostate and colon cancer, more emphasis should be placed on other types of cancer. In addition, studies should be able to assess the effect of time, length of exposure, doses of chemotherapy and a combination of cytotoxic drugs and if they differ in affecting cognition (Cheung et al., 2012).

In summary, the majority of the reviewed studies showed that chemotherapy is associated with cognitive impairment, in most studies participants may have pre chemotherapy cognitive impairment, but it may increase after receiving chemotherapy cycles. This calls for targeted measures and nursing interventions to identify patients who are at greater risk for cognitive impairment when taking chemotherapy to prevent further decline.

CHAPTER III

PHARMACOLOGICAL INTERVENTIONS

Few experimental studies have been conducted to examine the effect of certain drugs on cognitive function and whether they can be used to increase alertness and concentration post chemotherapy.

Stimulants:

In a randomized clinical trial, 68 breast cancer patients who received chemotherapy one month before entering phase one and phase two of the Modafinil clinical trial. Modafinil is a wakefulness promoting agent or stimulant usually used to treat narcolepsy and neurological fatigue. The results showed that all patients receiving Modafinil (200mg orally daily for 8 weeks) compared to those taking a placebo had a significantly greater improvement (pvalue=0.01 for Modafinil group vs. pvalue=0.054 for placebo) in speed of memory, quality of episodic memory and attention. Phases III and IV are needed for further confirmation (Kohli et al., 2007).

Moreover, Methylphenidate, a CNS stimulant, effect on cognitive performance was studied as well. 29 breast cancer patients received adjuvant chemotherapy and methylphenidate, and 28 patients on placebo. All patients were assessed at baseline, directly at the end of chemotherapy, and after 6 months of their last chemotherapy dose. No significance difference was found in terms of cognitive impairment in patients taking methylphenidate compared to patients taking placebo (Mar Fan et al., 2008).

Interestingly enough caffeine was studied as a stimulant to increase cognitive performance. The studies performed on it had mixed results, conducted mostly on healthy adults with only a few withdrawal side effects. However, the studies showed that

moderate intake of caffeine had a positive effect on improving cognition especially in word association, reaction time, short-term memory tasks, and attention (Lothes, 2009). Nonetheless, its efficacy in cancer patients receiving chemotherapy and other oral medications needs to be established.

Dementia medications:

Memantine is an Alzheimer's disease medication that acts by blocking NMDA receptor which controls synaptic plasticity and memory, has been found to delay cognitive impairment in brain metastasis patients receiving whole brain radiation. In a randomized, double-blind, placebo-controlled trial, 508 cancer patients who received whole brain radiation therapy were recruited to check Memantine's effect on cognitive function secondary to brain injury related to radiation. Patients taking Memantine had longer time to decline (2% on Memantine vs. 13% on placebo) in memory, executive function, and processing speed in preclinical trials. However, it still needs further studies for confirmation (Schagen et al., 2014; Von Ah, 2015).

Anti-depressants:

Fluoxetine has been studied in male rats for prevention of behavioral deficits associated with chemotherapy agents such as 5flurourecil (5FU); animals were divided into 3 groups 5FU and Fluoxetine and 5FU alone and Fluoxetine alone. All rats at baseline were exposed to two objects for familiarization and showed no significant difference in time for familiarization. Then after 40 days of 5FU administration and Fluoxetine, during the choice trial, the groups of rats receiving only fluoxetine and rats receiving both 5-FU and fluoxetine were able to perform the memory task, spending significantly longer time exploring the object in the novel location compared to the object in the familiar location. In contrast, rats treated with 5-FU only or 5-FU with fluoxetine in recovery showed no

object preference, and no significant difference in exploration time for either object, which indicated impairment in memory. The study showed that 5FU has long term effect on reducing hippocampal cell proliferation and can be counteracted when administering Fluoxetine during 5FU administration (Lyons, ELBeltagy, Bennett, & Wigmore, 2012). However, Fluoxetine has not been further studied with other animal models or human trials with no confirmation of preventing cognitive decline or if there is any negative interaction with drug absorption in combination with chemotherapy (Mandelblatt et al., 2014).

Erythropoietin:

Many studies have used erythropoietin stimulating factor (EPO) which was perceived as a neuro-protective medication, by increasing oxygen to the brain and treating chemotherapy induced anemia as mentioned earlier by AlEjielat, 2013. A study on 94 breast cancer patients undergoing chemotherapy were divided into two groups, group 1 receiving a placebo subcutaneously once per week, and group 2 receiving erythropoietin stimulating agent subcutaneously once per week. Both groups received the interventions at week 4 after chemotherapy till week 12. They were assessed with neuropsychological tests at baseline before chemotherapy and at the 4th cycle of chemotherapy and 6 months post chemotherapy. During chemotherapy the group taking erythropoietin performed better on the executive function test than the control group. However, after 6 months post chemotherapy no changes were seen in both groups (O'Shaughnessy et al., 2005).

In another study, 87 breast cancer patients were divided into two groups, group one received standard care and the second group received erythropoietin during chemotherapy. The neuropsychological tests were performed at 12 and 30 months post chemotherapy. The study showed no difference in cognitive function in both groups (Mar

Fan et al., 2008). However, erythropoietin has been shown to have a partial effect on promoting tumor growth. Therefore, more studies are needed to confirm this before considering its use to improve cognitive dysfunction in cancer patients (AlEjielat, 2013; Wu et al., 2012).

Antibiotics:

Mammalian target of Rapamycin MTOR is a protein kinase that controls cell growth, proliferation, and survival (regulates cellular metabolism) has been studied and showed that it may provide protective cognitive improvement, slows aging and decreases risk for Alzheimer's disease. The study was conducted on mice with cancer. Mice that received Rapamycin showed delayed in the aging process, which was illustrated after a brain autopsy (staining the brain for evaluating degeneration) compared to mice that did not receive Rapamycin (Schagenet al., 2014; Mandelblatt et al., 2014).

In summary, there are a number of emerging pharmacological agents that aim to improve cognitive performance during chemotherapy. A main concern would be the possible medication interaction with chemotherapy agents. However, there is no evidence so far of any interaction between these medications and chemotherapy. Moreover, these studies are still in their early stages, and are mostly based on the discoveries found from Alzheimer’s disease, depression and dementia. Pharmacologic agents that were found to be effective in these disorders are being tested on cancer patients to overcome the chemotherapy associated cognitive decline (McNeil, 2012; AlEjielat, 2013).

The evidence shows that cognitive impairment post chemotherapy is affected by multiple factors being biological interactions (cytokines, toxins, inflammation, genetics, and blood brain barrier transporters) and/or psychological (anxiety, fear, depression and support) and/or disease response to treatment (progression, location, doses administered,

number of cycles received and for how long) (Askren et al., 2014). Since a full understanding of the mechanisms leading to chemo brain is not yet attained, the development or use of a certain drug that targets it and improves cognitive function is not yet achieved. Pharmacological evidence is still inconclusive at this stage. Therefore, most of the focus of the clinical management has been on non-pharmacological interventions because of its safety and effectiveness (Ferguson & Martinson, 2011).

CHAPTER VI

NON- PHARMACOLOGICAL INTERVENTIONS

A number of studies focused on non-pharmacological approaches in minimizing or treating chemo-brain. Their focus was mostly on brain training and brain simulation activities before and after chemotherapy up to six months and years post chemotherapy (Kohli et al., 2007).

Brain Training:

Cognitive training exercises target processing speed, executive function, short-term memory, and visual-spatial memory. In the following few studies, home-based cognitive training that showed promising results in increasing cognitive performance after or during chemotherapy will be reviewed.

Kesler et al., 2013 examined the effect of a home-based cognitive training program on cognitive performance in 41 breast cancer survivors (who were of stages I-IIIA) approximately 6 years after adjuvant chemotherapy. The studied program consisted of 4 sessions per week for 2 months from Lumosity; an online company that develops computer based cognitive training games that stimulate the brain cognitive function. The program can be accessed from home, and addressing the following cognitive domains: cognitive flexibility, working memory, processing speed, and verbal fluency. The cognitive domains were made into game forms consisting of; switching games (eg, based on the spatial location of the stimulus), mental rotation games (eg, navigate a rotating maze), memory games (eg, determine if the current picture or symbol matched the one shown before), spatial sequencing memory games (eg, recall the location of coins and then find them in the order),word stem completion games (eg, use various word stems

such as “cog” to be used to produce as many different words as possible by the patient), route planning (eg, navigate a maze by using the fewest number of moves), and rule-based puzzle solving (eg, determine if groups of figures follow an implicit rule). All the exercises used increase in difficulty by level depending on the patients' progress. All games had visual stimuli with auditory reinforcement and encouragement (Kesler et al., 2013). A baseline cognitive neuropsychological assessment was carried out three days before starting the sessions and then after finishing all the sessions and compared them to a wait-list group (control group) who did not undergo the session trainings. The group who received the cognitive training exercise showed significant improvement in performance on the following cognitive domains: cognitive flexibility, processing speed, and verbal fluency; as well as a major enhancement in self-rated executive behaviors and verbal memory. This approach showed a high adherence, 95% of the patients. It was easy to deliver and feasible, it required minimal preparations and was delivered to the patients in the comfort of their own home (Kesler et al., 2013).

Similarly, Bray et al. (2015) evaluated cognitive performance in cancer patients with cognitive symptoms. 243 adult breast and colorectal cancer patients, who completed adjuvant chemotherapy within 6-60 months and reported changes in memory and/or concentration on self report and neuropsychological testing, were randomized into a home web-based cognitive rehabilitation program group and usual care group for 15 weeks. The patients were assessed at baseline, post intervention and at 6 months later. At baseline, both groups showed no significant differences in cognitive performance. However, the group receiving a web-based cognitive rehabilitation program showed improvement on all neuropsychological and self-report tests at the assessment post

intervention; these results were sustained 6 months later as well when compared to the usual care group.

In another study 157 female breast cancer survivors were randomly allocated to either a home web-based cognitive training program with telephone support or a waitlist control. The cognitive training group received 30 training sessions over 6 weeks. Neuropsychological assessments were collected at baseline, post-intervention and at 5-month follow-up. No statistically significant difference was found post-intervention, however, statistically significant improvement was observed at 5-month follow-up in the cognitive training group on the following cognitive domains: verbal learning and working memory, indicating long-term effects of training. This intervention is important because it shows long-term improvement when using cognitive training exercises, in addition to its safety- no risk of adverse events- and its ability to be applied in a clinical setting (Damholdt et al., 2016).

Nature and Physical Exercise:

In addition to brain training, the effect of nature and physical exercise on cognitive performance after chemotherapy was studied in cancer patients. A study conducted by Cimprich & Ronis (2003) on 157 newly diagnosed breast cancer patients examined the effect of exposure to nature on cognitive performance. A battery of objective measures to assess attention was administered before surgery and after surgery. The patients were then randomly assigned to a home-based program that includes a 2-hour exposure to nature weekly. The intervention started after the first assessment and before any chemotherapy treatment and continued for the whole duration of treatment. The intervention group compared to controls and pre-adjuvant therapy group showed

significant therapeutic benefits. Weekly exposure to nature improved attention in newly diagnosed breast cancer patients on chemotherapy (Cimprich & Ronis, 2003).

Similarly, physical exercise (such as Yoga, Tai Chi and/or aerobic, walking exercises) is another possible non-pharmacological intervention that has been studied in cancer patients receiving chemotherapy suffering from various forms of cognitive impairment. Schmitz et al. (2010) believe that the goal of exercise prescription is to improve cognitive and psychosocial outcomes. In another study by Wolin et al., 2012, an expert panel developed a safe and efficient exercise program for cancer patients and survivors. This program suggested that the benefit of exercise is higher than the risk of exercise on the patient depending on the case. A case by case assessment for cancer survivors was recommended. For example, if a colon cancer patient has a colostomy they should avoid abdominal exercises (Wolin, Schwartz, Matthews, Courneya, & Schmitz, 2012). The American College of Sports Medicine and the Physical Activity Guideline for Americans for cancer patients and survivors, recommend that exercise starts at the time of diagnosis till the end of life. This includes at least 150min/week of moderate intensity or 75min/week of vigorous intensity, resistance training moderate to high intensity, moving all major muscles twice/week, aerobic exercise depending on age.

Five cancer patients reported that they were able to exercise during chemotherapy cycles and had a perceived improvement in cognitive performance. Another patient said she would leave work for 30-60min a day to work out and return with a better mental clarity (Myers, 2012). This suggests that exercise a non-pharmacological approach has an effect on cognitive performance in cancer patients.

In another study performed on thirty-three healthy adults of which, 17 were women with mild cognitive impairment of ages 55 to 85 years. Participants were

randomized either to a high-intensity aerobic group or a stretching control group. The aerobic group exercised with a fitness trainer and increased their heart rate to 75-85% for 45-60minutes/day four days a week for a total of 6 months. The control group did the same schedule but only increased heart rate to 50%. Cognitive tests were administered at baseline, after 3 months and 6 months. The results showed that the women after 6 months of aerobic exercise improved performance on multiple tests of executive function. As for the men, aerobic exercise increased their plasma levels of insulin-like growth factor I. This study suggests that aerobic exercises may have differences in sex- based responses. However, it did show a potential for use as a non-pharmacologic intervention that improves executive control processes for older women at high risk of cognitive decline. Therefore, aerobic exercise can be studied on cancer patients in the future for proof of effectiveness in improving cognitive impairment (Baker et al., 2010).

Moreover, after establishing safety guidelines and recommendations, the goal is to develop an exercise schedule to prescribe to cancer patients as a non-pharmacological intervention to improve chemo-brain side-effects. Nonetheless, further clinical research studies are needed to establish the validity related to prevention or improving chemo-brain cognitive side effects with physical exercise.

Other forms of exercises that were studied on cancer patients include Tai Chi Chuan and yoga, which are considered mindfulness-based exercises. A pilot study was performed on 23 women with history of cancer, who had previously received chemotherapy for breast cancer treatment. They received a Tai Chi program of 60minutes two times per week for 10 weeks. They underwent neuropsychological testing on memory, executive function, language and attention before and after the intervention. After the 10-week Tai Chi sessions, patients were compared to their baseline and found

a decline in neuropsychological complaints and a 26.1% enhancement in neuropsychological function especially in the following domains: immediate and delayed memory, verbal fluency, and executive functioning(Reid-Arndt, Matsuda, & Cox, 2012; Mustian, Sprod, Janelsins, Peppone, & Mohile, 2012).

Another randomized control trial explored the effect of Yoga on cognitive performance. 200 post-treatment breast cancer survivors were randomized to receive a Yoga session twice per week for a total of 12 weeks and into a wait list control group. Neuropsychological tests were administered at baseline, directly after the intervention at 12 weeks, and 3 months after the end of the Yoga sessions. Immediately after intervention and at 12 weeks, there were no significant changes observed between the two groups compared to baseline. However, at 3 month follow up the breast cancer group who received the Yoga session had an average of 23% lower cognitive complaints than the wait list. This showed that Yoga may have a long-term benefit on decreasing cognitive complaints; this study suggests that Yoga and other forms of exercise decrease symptoms of chemo-brain (Derry et al., 2015).

Moreover, a study performed on rodents, which allows investigators to control for genetic factors and use rodents that do not have cancer. These rodents received chemotherapy alone, which allows a better understanding of chemotherapy induced cognitive impairment since, in humans many factors may come together and cause cognitive impairment. Tests completed before and after chemotherapy showed that in these rats, chemotherapy increased cell death in the corpus callosum and denate gyrus 10 days after treatment. Also, a decrease in cell division was witnessed 6 weeks post treatment. Exercise and an enriched environment showed an increase in learning, and neurogenesis (seen in the hippocampus, the major structure that mediate the processes of

learning and memory) and facilitated their recovery, by improving performance on tests such as the Morris water navigation or the object location recognition test (Hall, 2014). This study on cancer-free rodents illustrates that chemotherapy on its own has a negative effect on cognitive function and that exercise and enriched environment improved cognitive performance.

Antioxidants and Dietary Interventions:

Ginkgo Biloba, a herbal supplement, was studied in a two-arm randomized, placebo-controlled, double-blind, phase III trial on breast cancer patients who were about to receive adjuvant chemotherapy. They were randomized to receive 60 mg of Ginkgo Biloba or a matching placebo twice daily. The study agent was to begin before their second cycle of chemotherapy and to be administered throughout chemotherapy and one month beyond completion. Objective and subjective neuropsychological data were collected at baseline and at intervals throughout and after chemotherapy, up to 24 months after completion of adjuvant treatment. The study showed no significant improvement in cognitive function (Barton et al., 2013).

Some evidence supports the use of antioxidants in obstructing possible pathological behavioral (attention, concentration and memory) and physiologic result of chemotherapy by preventing chemotherapy-induced oxidative stress and cognitive deficits when administered prior to and during chemotherapy (Fardell, Vardy, Johnston, & Winocur, 2011). Increasing antioxidants from dietary intake, such as Mediterranean diet, which is high in whole grains, fruits, vegetables, olive oil, and lean protein, in animal models has shown to have a protective effect on cognitive function, oxidative stress, and neurogenesis (de Ruyter, 2012; Mandelblatt et al., 2014; Janelsins et al., 2014; Gordon, 2014). However, they may not be the best treatment option yet because

concerns are arising that they may decrease the efficacy of chemotherapy by interacting with the absorption (Ahles et al., 2012).

Curcumin is now known to exert antioxidant and anti-inflammatory effects as well, specifically down regulating IL-6, IL-1, and TNF-alpha, all of which have been linked to impaired cognition. In addition, since a few studies have associated the inflammatory pathways with cognitive function; therefore, Curcumin may be able to decrease cognitive decline. However, more studies are needed to support this theory in animal models and human trials, eventually trials on cancer patients (Belcaro et al., 2014).

Vance et al. (2016) showed the before and after results of various cognitive interventions (the types of tests, exercises or games used) and its effect on cognitive performance post chemotherapy in Table 3 (see appendix I). Another table carried out in this project after the review of literature updated the information with Vance et al., 2016 tables, and was added separately in table 4 (see appendix I).

Cognitive Behavioral Therapy Programs:

A 6-week psycho-educational program, a cognitive behavioral program (also known as emerging from the Haze) was developed to help cancer survivors after chemotherapy and who are complaining of cognitive problems. In this program the patients meet once a week for 2 hours for 6 weeks. The leading neuropsychologist covers material such as guided relaxation, behavioral strategies for automatic/negative thoughts, compensatory strategies for attention and memory, executive functioning, pacing, and balance. Neuropsychological assessment was performed on the first day, on the last day of the series, 3 months, 6 months and 1 year after. The first 110 survivors with various cancer types that have completed the program demonstrated statistically significant improvements in perceived cognitive impairment and perceived cognitive abilities based

on a before and after comparison on the neuropsychological tests. A multi-disciplinary psycho-educational clinical program that addresses cognitive changes and adjusts for difficulty depending on the patients needs appears to have a positive effect on the patients' perceived cognitive functioning (Bailey, Asher, & Jo, 2016). However, this program does not accommodate patients who are unable to attend the sessions. Therefore, a home-based extension of this program is needed for future studies.

Based on the reviewed literature, the non-pharmacological interventions have shown promising results. The brain training, nature, physical exercise, and the anti-oxidants, are being used as an attempt to prevent cognitive impairment related to chemotherapy in cancer patients. In this project we acquired these literature recommendations and placed them in Table 5, as a list of Evidence-Based recommendation of non-pharmacological interventions known to help improve chemotherapy induced cognitive dysfunction in cancer patients.

CHAPTER V

EDUCATIONAL PLAN

As an oncology nurse working with physicians, fellows and nurses, I asked them informally about their clinical experience dealing with patients receiving chemotherapy and exhibiting signs of chemo-brain;"Are your patients complaining of cognitive impairment? If yes, what do you do about it?" The four oncology fellows asked reported that they did not come across any patient who complained of cognitive problems who didn't have brain metastasis. However, the four oncology attending physicians asked stated that many of their patients complain about difficulty concentrating, becoming forgetful, and being tired all the time. Nonetheless, they did not intervene unless it was severe. As for the eight oncology nurses, they reported hearing patients say: "Wow I am being very forgetful, do you think it is from the chemotherapy?" after which the nurses inform the primary physician who in turn informs the patient that it is expected with the treatment. Moreover, if the reported symptoms were severe, a CT or MRI brain is usually performed to rule out metastasis, followed by a referral to the neurology team. Currently, in AUBMC and worldwide there is no protocol or set guidelines that have been established to target this problem, only expert opinions and recommendations have been proposed based on scattered research. Therefore, based on this informal needs assessment that identified a gap in the plan of care of the patients and knowledge deficit among the nurses, an educational session for nurses was planned and proposed. After the extensive literature review, scattered recommendations of non-pharmacologic interventions were gathered; these recommendations will be disseminated in this educational session targeting oncology nurses.

Clinical Nurse Specialists (CNSs) play a major role in clinical education. The CNS practice has evolved with changes in healthcare systems delivery models. CNSs are essential in providing clinical academic education and ensuring life-long learning opportunities for registered nurses as well as patients. Moreover, they are important in providing evidence-based practice and following up on its benefits for the nurses and patients(Specialists, 2004). The CNSs are also involved in initiating multidisciplinary guideline development in health care settings, therefore, for future recommendations; the CNS can assist in providing a guideline for chemo-brain prevention or treatment.

As an oncology CNS, this proposed educational session aims to guide the nurses caring for patients complaining of chemotherapy induced cognitive impairment. At the end of the session the nurses will be able to identify them and propose non-pharmacological interventions that the patients can benefit from. The CNS will act as a clinical educator in disseminating the new information about cognitive impairment in cancer patients receiving chemotherapy to the oncology unit nurses. Moreover, the session will provide them with evidence-based recommendations of non-pharmacological interventions to use to prevent or improve cognitive dysfunction related to chemotherapy. Also, the CNS will be viewed as a resource for the nurses to help them identify patients suffering from chemo-brain and may undergo one to one session with the CNS for a comprehensive assessment. The CNS will collaborate with physicians, nurses and patients about their plan of care and best way to incorporate the proposed interventions to improve the patients' cognition, and follow up on their progress (Specialists, 2004).

The educational session will be administered after the approval of the unit nurse manager and in collaboration with the Clinical Professional Development Center (CPDC). With the CPDC, the PowerPoint slides of the session, additional resources and

reading material about chemo-brain will be made available online for the nurses to access at their own pace. Moreover, these educational materials will be a resource for the nurses when the CNS is not available which can improve outcomes.

The goal of this informational session is to help the oncology nurses educate their patients about chemo-brain and informing them about the best methods they can use to improve cognition during chemotherapy sessions. The objectives of this session are: At the end of the session the oncology nurse will be able to:

1) State the chemotherapy related cognitive impairment signs and symptoms.
2) Identify patients who are at high risk for chemo-brain
3) Explain the possible non-pharmacological intervention options to instruct patients about them.

The session will begin with the definition of chemotherapy related cognitive impairment, its' risk factors, impact on quality of life, importance of early detection and assessment, followed by possible pharmacological and non-pharmacologic interventions that are based on the extensive literature review. The focus of the educational session will be on four non-pharmacologic intervention with the most evidence to improve cognitive function; Yoga, nature and physical exercise and brain games.

The information will be disseminated in the form of a PowerPoint lecture. The learning will be assessed before and after the session (see appendix II). Emphasis is placed on the importance of these non-pharmacologic interventions. These nurses will be encouraged to instruct their patients about these methods and evaluating their benefits with their patients. After the session, it is expected that the oncology nurses will be able to use these methods and have the skills needed to address the urgent cognitive problems their patients will complain of. The duration of the session is 50 minutes and will be

administered twice weekly (8AM and 2PM) for one month to accommodate all the oncology unit nurses. The nurses will be given an evaluation sheet, directly after the session, to evaluate it, and will be asked if there is any information they would like to know more about. Later, three months, post-educational session, the oncology nurses will be asked again to evaluate the progress with their patients (see appendix II). They will be asked if the session was useful to them and whether they incorporated the gained knowledge in their care plans. They will also be asked about their patients' self-report of improvement if any. It will be a written evaluation; they will be asked to:

Rate on a scale of 1-10 (1 being the lowest and 10 being the highest) how much the education session on chemotherapy induced cognitive impairment benefited their experience and contributed to their patients' improvement; and they will be asked to give an example about one patient they cared for who benefited from their recommendations. This evaluation contains five questions for rating and one narrative question that asks about a patient’s self-report of improvement after using the non-pharmacological interventions recommended by the oncology nurses (see appendix II).

The educational session as well as any online resources will be updated periodically with the help of the CPDC onto Moodle. These will be kept as a reference for the nurses to access at their own pace.

CHAPTER VI

CONCLUSION

In conclusion, after exploring the possible factors that can cause chemo-brain, we reached an understanding that chemotherapy has the highest effect on chemo-brain. Therefore, cancer survivors who received chemotherapy exhibit difficulty in cognition during and after the completion of their treatment. This can hinder their return to normal life. Other than chemotherapy a few risk factors have been addressed of which are genetics, cancer related pathways, anemia, psychological distress, cognitive reserve, blood brain barrier, hormonal changes and fatigue. All of which were linked in one way or another to cognitive impairment in cancer patients. However, most of the studies that had a pre-chemotherapy and post-chemotherapy assessment showed a higher decline in cognition after chemotherapy. Providing an enhanced understanding that chemo-brain is affected mostly by chemotherapy.

A few pharmacological drugs have been mentioned earlier that may have a future in improving cognitive dysfunction in cancer patients (stimulants, dementia related drugs, erythropoietin, anti-depressants and antibiotics). However, most drugs have not been systematically tested with cancer patients and hence their use in practice is not supported by evidence. More studies are needed to address chemotherapy related cognitive impairment and the use of pharmacologic interventions.

Other than pharmacologic interventions, non-pharmacologic interventions have been studied, that showed safer and faster promising results in improving cognitive performance. Such as physical exercise and nature, mental exercises, yoga, and brain

training which have shown to be a potential for use as a treatment of chemo-brain in the near future.

The aim of this project was to use the literature to combine non-pharmacologic recommendations for improving chemotherapy related cognitive dysfunction in one education session for nurses. An education session was developed based on evidence-based literature to educate nurses about chemo-brain. The education session includes a pre-post quiz about chemo-brain with focus on the non-pharmacologic interventions. The nurses in turn will educate their patients about it, and incorporate this knowledge into their care plan. A follow up evaluation in three month will be administered to check for the benefit of this session for the nurses as well as their patients. This project was carried out based on an informal needs assessment that indicated that the nurses were not well prepared to address the complaints they hear from the cancer patients about memory and concentration problems when they receive chemotherapy. In addition, at AUBMC the physicians had their concerns about chemo-brain because to date there is no guideline for the treatment of chemo-brain to base their clinical management on and inform their patients about.

The review of literature identified a significant need for more randomized clinical trials consequently a guideline for the clinical management to be used concurrently with chemotherapy for all cancer patients to prevent and improve cognitive dysfunction. More research in the field and more suggested interventions will allow the patients to withstand longer cycles and higher doses without complaining of major cognitive impairment. It allows for an increase in adherence to treatments and prolonging chemotherapy cycles to increase survival rate and quality of life.

In the future, a survey will be administered to gather information from the patients receiving chemotherapy (before and during chemotherapy) about their cognitive function. This will guide the development of targeted interventional research studies. Also, an educational package about chemo-brain signs and symptoms and possible non-pharmacologic interventions specifically for cancer patients will be designed.

APPENDIX I

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TABLES

Tables 1: Literature review on chemotherapy related cognitive impairment in Breast Cancer Patients (Ahles et al 2012)

Study	Participants	Assessment Schedule	Cognitive Domains	Outcomes
Wefel et al[7]	Chemotherapy (n = 18; mean age, 45.4 years)	Baseline, 3 weeks postchemotherapy, and 1 year postchemotherapy	Attention, processing speed, learning, memory, executive function, visuospatial function, and motor skills	Decline in attention, learning, and processing speed
Mar Fan et al[8]	Adjuvant chemotherapy (n = 104); healthy controls (n = 102)	Baseline and 1 and 2 years after adjuvant chemotherapy	Memory, language, attention/concentration, visual motor, spatial, psychomotor speed, and executive functions	Moderate to severe cognitive dysfunction decreased from 16% to 4% over 2-year follow-up; no difference in cognition between ER-positive patients who started hormonal therapy (mainly tamoxifen) after chemotherapy and ER-negative patients who did not
Schilling et al[9]	Patients to receive chemotherapy and patients receiving radiotherapy and/or endocrine therapy (n = 50; mean age, 51.1 years); healthy controls (n = 43; mean age, 52.3 years)	Baseline, 4 weeks after completion of chemotherapy (6 months for controls), and 18 months	Intelligence, verbal memory, visual memory, working memory, executive function, and processing speed and vigilance	Decline in cognitive performance compared with controls
Bender et al[10]	Chemotherapy only, chemotherapy and tamoxifen, and no chemotherapy or tamoxifen (n = 46; mean age, 42.57 years)	T_1, postsurgery, before starting adjuvant therapy; T_2, within 2 weeks of completing chemotherapy; T_3, 1 year after T_2	Attention, learning, memory, psychomotor speed, mental flexibility, executive function, visuoconstructional ability, and general intelligence	Chemotherapy plus tamoxifen group declined in visual memory and verbal working memory; chemotherapy alone group showed decline in verbal working memory only
Hurria et al[11]	Chemotherapy only (age > 65 years; n = 31; mean age, 71 years)	Before and after chemotherapy	Attention, verbal memory, visual memory, and verbal, spatial, psychomotor, and executive functions	Women who received CMF (91%) declined in visual memory, spatial function, attention, and psychomotor function
Jenkins et al[12]	Chemotherapy (n = 85; mean age 51.49 years); endocrine therapy and/or radiotherapy (n = 43; mean age, 58.93 years); healthy controls (n = 49; mean age, 51.90 years)	Baseline, postchemotherapy or 6 months postbaseline, and 18 months postbaseline	Intelligence, verbal memory, visual memory, working memory, executive function, and processing speed and vigilance	Treatment regimens were not found to affect cognitive performance at group or individual level
Schagen et al[13]	High-dose chemotherapy (n = 28; mean age, 45.5 years); standard-dose chemotherapy (n = 39; mean age, 45.2 years); stage I disease, not receiving chemotherapy (n = 57; mean age, 50.5 years); healthy controls (n = 60; mean age, 48.8 years)	High- and standard-dose groups, before and 6 months after chemotherapy (12-month interval); stage I disease with no chemotherapy, baseline and 12-month interval; healthy controls, baseline and 6-month interval	Attention, working, verbal, and visual memory, processing speed, executive function, and verbal and motor function	Patients who received CTC chemotherapy declined in cognitive performance
Hermelink et al[14]	Chemotherapy (n = 101; mean age, 48.6 years); standard dose (n = 48); dose intense (n = 53)	Before neoadjuvant chemotherapy and toward end of neoadjuvant chemotherapy	Verbal memory, attention, working memory, information processing speed, and executive function	Before chemotherapy, subgroup showed cognitive decline; during chemotherapy, most remained stable; subgroup declined (27%) and another improved (28%); no effects were associated with treatment arm

(continued on following page)

Study	Participants	Assessment Schedule	Cognitive Domains	Outcomes
Stewart et al[15]	Adjuvant chemotherapy (n = 61; mean age, 57.5 years); adjuvant hormonal therapy (n = 51; mean age, 57.9 years)	Baseline (before any adjuvant treatment) and follow-up (after last chemotherapy cycle or equivalent time point in hormonal group)	Executive function, language function, motor, processing speed, verbal learning and memory, visual learning and memory, visuospatial function, and working memory	Chemotherapy patients were 3.3x more likely to show reliable cognitive decline; working memory was most vulnerable to chemotherapy
Collins et al[16]	Postmenopausal patients: chemotherapy (n = 53; mean age, 57.9 years); hormone therapy only (n = 40; mean age, 57.6 years)	After surgery but before adjuvant chemotherapy, within 1 month of completing chemotherapy or 5-6 months after baseline (T_2), and 1 year after T_2 (T_3)	Executive function, language function, motor, processing speed, verbal learning and memory, visual learning and memory, visuospatial function, and working memory	Chemotherapy plus hormone therapy group performed more poorly on measures of processing speed and verbal memory at T_3
Hermelink et al[17]	Premenopausal (n = 11); induced menopause at T_3 (n = 31); postmenopausal (n = 49; mean age, 48.4 years); received one of two neoadjuvant chemotherapy regimens; received tamoxifen or AIs (n = 62)	Before start of cancer therapy, toward end of neoadjuvant chemotherapy, and 1 year after baseline	Verbal memory, attention, working memory, information processing speed, psychomotor function, and executive function	No effects of treatment-induced hormonal changes on cognitive functioning
Mehlsen et al[18]	Patients with breast cancer (n = 34; mean age, 48.6 years); cardiac patients hospitalized with MI (n = 12; mean age, 50.4 years); healthy controls (n = 12; mean age, 39.3 years)	Baseline; patients with cancer, 0-7 days before chemotherapy; cardiac patients, 4 days after hospitalization; follow-up (25 weeks later for patients with cancer; 3 months later for cardiac patients); healthy controls, 12-16 weeks between assessments	Processing speed, working memory, visuospatial ability, visual memory, verbal memory, verbal fluency, and response inhibition	No differences in cognitive performance between three groups
Quesnel et al[19]	Chemotherapy and radiotherapy (n = 41; mean age, 50.3 years); radiotherapy only (n = 40; mean age, 57.7 years); healthy controls matched to those receiving chemotherapy and radiotherapy (n = 23; mean age, 47.9 years); healthy controls matched to those receiving only radiotherapy (n = 22; mean age, 55.0 years)	Before and after adjuvant chemotherapy and/or radiotherapy and 3 months post-treatment; healthy controls at baseline only	Verbal and visual memory, attention, concentration, executive functions, speed of information, and verbal fluency	At baseline, patients showed lower performance on attention measures compared with healthy controls; both patient groups declined in verbal memory; chemotherapy group also declined in verbal fluency
Vearncombe et al[20]	Standard-dose adjuvant chemotherapy with or without endocrine treatment and radiotherapy (n = 138; mean age, 49.4 years); no adjuvant chemotherapy (n = 21; mean age, 53.9 years)	After surgery but before chemotherapy (T_1) and 4 weeks after last cycle of chemotherapy (T_2); no-chemotherapy group assessed at matched intervals	Verbal learning and memory, visual memory, working memory, processing speed, attention, executive function, and motor coordination	Declines in verbal learning and memory, abstract reasoning, and motor functioning were seen in 16.9% after chemotherapy; decline in hemoglobin and increased anxiety over course of chemotherapy predicted impairment in ::: two cognitive domains

Study	Participants	Assessment Schedule	Cognitive Domains	Outcomes
Ahles et al[21]	Chemotherapy (n = 60; mean age, 51.7 years); no chemotherapy (n = 72; mean age, 56.6 years); healthy controls (n = 45; mean age, 52.9 years)	Before chemotherapy and 1, 6, and 18 months postchemotherapy; no-chemotherapy group and healthy controls assessed at matched intervals	Verbal ability, verbal memory, visual memory, working memory, processing speed, and executive function	Chemotherapy patients who were older and had lower baseline cognitive reserve had slower processing speed; in no-chemotherapy group, negative effect of tamoxifen on processing speed and verbal memory; healthy controls and no-chemotherapy group improved in verbal ability over time; chemotherapy group improved at 6 and 18 months
Debess et al[22]	Patients with stage I-III disease identified after surgery (n = 124): chemotherapy (n = 75; mean age, 47.2 years); chemotherapy and tamoxifen (n = 26; mean age, 56.2 years); not receiving chemotherapy or tamoxifen (n = 19; mean age, 49.7 years); healthy controls (n = 208; mean age, 48.1 years)	Baseline and after 6 months of chemotherapy	Concentration, episodic memory (intermediate and long-term memory), simple and complex attention, cognitive speed and flexibility, visual scanning, and executive functioning	No differences in cognitive functioning
Tager et al[23]	Postmenopausal women: adjuvant chemotherapy (n = 30; mean age, 60.3 years); no adjuvant chemotherapy (n = 31; mean age, 61.1 years)	Before adjuvant chemotherapy, 6 months after adjuvant therapy, and 6 months after second evaluation	Motor, language, attention/concentration/working memory, visuospatial, verbal memory, and visual memory	Time by treatment interaction with slower motor functioning among women treated with chemotherapy (but possibly result of peripheral neuropathy)
Wefel et al[24]	Patients with stage I-III disease (n = 42; mean age, 48.8 years)	Before adjuvant chemotherapy, during and shortly after adjuvant therapy, and 1 year after chemotherapy	Attention, processing speed, learning and memory, and executive function	Decline most common in learning and memory, executive function, and processing speed; before chemotherapy, 21% had cognitive decline; 71% exhibited continuous decline; 29% had new-onset decline
Hedayati et al[25]	Chemotherapy (n = 18; mean age, 52 years); hormone therapy (n = 45; mean age, 61 years); no adjuvant therapy (n = 14; mean age, 61 years); healthy controls (n = 69; mean age, 51 years)	Before diagnosis (T_1), after surgery and before adjuvant treatment (T_2), 6 months after start of adjuvant treatment (T_3), and after another 3 months of follow-up (T_4)	Response speed, processing speed, memory, and attention	Memory was lower for patients than controls; memory and response speed were lower after chemotherapy and remained low at T_4; processing speed and attention improved consistent with practice effect

Study	Participants	Assessment Schedule	Cognitive Domains	Outcomes
Jansen et al[26]	Patients divided by regimen (n = 71; mean age, 50 years): AC alone (n = 22); AC followed by a taxane (n = 49)	Before chemotherapy, 1 week after AC chemotherapy, 1 week after completing all chemotherapy, and 6 months after completing all chemotherapy	Attention, immediate memory, delayed memory, visuospatial, language, motor, and executive function	23% had impairment before chemotherapy; decreases after chemotherapy but improvement in visuospatial ability, attention, and delayed memory 6 months after completing chemotherapy; deficits in motor function almost exclusively in patients receiving taxane (likely result of peripheral neuropathy)
Biglia et al[27]	Patients (n = 40; mean age, 51 years)	Before and after 6 months of chemotherapy	Attention, verbal fluency, verbal memory, processing speed, and global intelligence	Decline in selective attention and global cognitive functioning postchemotherapy; processing speed improved (attributed to practice effect)

Abbreviations: AC, cyclophosphamide and doxorubicin; AI, aromatase inhibitor; CMF, cyclophosphamide, methotrexate, and fluorouracil; CTC, cyclophosphamide, thiotepa, and carboplatin; ER, estrogen receptor; MI, myocardial infarction.

Note. From "Cancer- and Cancer Treatment–Associated Cognitive Change: An Update on the State of the Science ", by Ahles et al., 2012, Journal of Clinical Oncology, p.2-5.

Table 2: Updated Literature Review on Chemotherapy Related Cognitive Impairment.				
Study	Participants	Assessment Schedule	Cognitive Domains	Outcomes
Visovati et al., 2016	50 colorectal cancer patients receiving chemotherapy	One cross sectional assessment	Attention, cognitive control, memory function	Performed worse on all the cognitive domains compared to the control group
Kam et al., 2016	19 breast cancer survivors	3 years following breast cancer adjuvant chemotherapy compared to healthy controls	Ability to maintain attention over time	The breast cancer survivors reported higher mind wander and decrease in attention compared to the healthy control
Zimmer et al 2015	30 patients with B-cell non Hodgkin lymphoma	Over a period of 18 months. All patients were assessed within the first 3 months after their chemotherapy ended	Objective cognitive function test in combination with serum parameters (IL-6 and BDNF concentrations of serum samples were analyzed). Self-perceived status of cognition, fatigue and emotional functioning	Patients had significantly lower correct answers than the control group on executive function and attention. Patients' subjective report on cognition, fatigue and emotional wellbeing was significantly lower than those of the control group. Cytokine IL-6 was higher in the patient group which showed significant impairment compared to control group.

(Visovati et al. 2016; Kam et al. 2016 and (Zimmer et al., 2015)

Tables 3: Literature review on cognitive intervention studies for cognitive deficits in breast cancer survivors (Vance et al., 2016)

Table • Cognitive Intervention Studies for Cognitive Deficits in Breast Cancer Survivors

Author, Date, and Title	Participants	Design and Procedure	Findings	Strengths and Limitations
Cognitive Training Interventions				
Von Ah et al,[24] 2012 Advanced Cognitive Training for Breast Cancer Survivors: A Randomized Controlled Trial	82 chemotherapy-treated BCSs • 3 Randomized groups: 1. Memory training (n = 26, M_{age} = 55 y, $M_{months\ posttreatment}$ = 59.5 mo) 2. Speed of processing training (n = 27, M_{age} = 57 y, $M_{months\ posttreatment}$ = 78 mo) 3. Wait-list control (n = 29, M_{age} = 57 y, $M_{months\ posttreatment}$ = 59 mo)	• BCSs in the training protocols received ten 1-h training sessions over a 6- to 8-wk period • Outcome measures consisted of a cognitive battery administered at baseline, immediately posttest, and at a 2-mo follow-up	• BCSs in both the memory and speed of processing training groups improved on the cognitive battery both immediately postintervention and at the 2-mo follow-up • The memory training group showed significant improvement on memory testing at the 2-mo follow-up • The speed of processing training group showed significant improvement in both speed of processing and memory at both time points	**Strengths** • Relatively large sample size • Both interventions were effective and satisfactory to participants **Limitations** • Limited diversity of sample • No attention control group
Kesler et al,[26] 2013 Cognitive Training for Improving Executive Function in Chemotherapy-Treated Breast Cancer Survivors	41 chemotherapy-treated BCSs • 2 Randomized groups: 1. Cognitive training (n = 21, M_{age} = 55 y, $M_{months\ posttreatment}$ = 72 mo) 2. Wait-list control (n = 20, M_{age} = 56 y, $M_{months\ posttreatment}$ = 72 mo)	• BCSs completed online exercises (Luminosity games) at home • 48 sessions lasting 20-30 min were conducted over 12 wk • Outcome measures consisted of a cognitive battery administered at baseline and within 3 d of intervention completion	• BCSs in the intervention group demonstrated some transfer to verbal memory and showed improved cognitive flexibility, speed of processing, set shifting, and verbal fluency compared with the control group • BCSs in the intervention group self-reported improvement in executive behaviors	**Strengths** • Demonstrates efficacy of a home-based training program for cognitive deficits in BCSs **Limitations** • No attention control group • No extended follow-up • No auditory component
Compensatory Strategies With Cognitive Training Interventions				
Dolbeault et al,[27] 2009 The Effectiveness of a Psychoeducational Group After Early-Stage Breast Cancer Treatment: Results of a Randomized French Study	203 BCSs treated with radiation or radiation and chemotherapy • 2 Randomized groups: 1. Psychoeducational (n = 102, M_{age} = 55 y) 2. Wait-list control (n = 101, M_{age} = 52 y); time posttreatment ranged from 15 d to 1 y	• Psychoeducational group intervention program • BCSs in the intervention group received 8 weekly 2-h sessions led by 2 therapists • Outcome measures consisted of a set of questionnaires administered preintervention, immediately following the intervention, and 1-mo postintervention	• BCSs showed no statistical significance for improvement in cognitive function • BCSs showed significant reduction in anxiety	**Strengths** • Relatively large sample size • Randomized controlled trial **Limitations** • No attention control group • Mixed treatment regimens

Table • Cognitive Intervention Studies for Cognitive Deficits in Breast Cancer Survivors, Continued

Author, Date, and Title	Participants	Design and Procedure	Findings	Strengths and Limitations
Ercoli et al,[28] 2013 Assessment of the Feasibility of a Rehabilitation Intervention Program for Breast Cancer Survivors With Cognitive Complaints	27 chemotherapy-treated BCSs (M_{age} = 54 y, $M_{months\ postdiagnosis}$ = 33.6 mo)	• BCSs participated in a manual guided 5-wk cognitive intervention • Outcome measures consisted of a cognitive battery administered preintervention, immediately following the intervention, and 2- and 4 mo postintervention	• BCSs showed significant improvement on tests of speed of processing and executive functioning • Significant reductions in self-reported cognitive deficits were found immediately postintervention and were greatest for memory deficits • Reductions in self-reported deficits of executive functioning became apparent at the 4-mo follow-up	**Strengths** • Combined cognitive training with use of compensatory strategies • Extended postintervention follow-up **Limitations** • No control group
Ercoli et al,[29] 2015 Cognitive Rehabilitation Group Intervention for Breast Cancer Survivors: Results of a Randomized Clinical Trial	• 2 Randomized groups of BCSs with self-reported cognitive deficits: 1. Intervention group (n = 32, M_{age} = 54.5 y, $M_{months\ postdiagnosis}$ = 34 mo) 2. Wait-list control (n = 16, M_{age} = 52.4 y, $M_{months\ postdiagnosis}$ = 34.8 mo)	• The intervention consisted of manual guided 5-wk group sessions (1 session/wk) to complete exercises in the areas of attention, executive function, and memory • Outcome measures consisting of neuropsychological testing and self-report questionnaires were collected at baseline, immediately postintervention, and at a 2-mo follow-up	• BCSs in the intervention group showed significant improvement on an assessment of their own functioning immediately following the intervention which was sustained at 2-mo follow-up The intervention group, but not the wait-list control group, also showed significant improvement on neuropsychological tests of memory	**Strengths** • Randomized design • Incorporation of exploratory EEG measures **Limitations** • No attention control group • 2:1 randomization • Longer-term follow-up required
Ferguson et al,[30] 2007 Cognitive-Behavioral Management of Chemotherapy-Related Cognitive Change	29 chemotherapy-treated BCSs (M_{age} = 56 y, $M_{months\ posttreatment}$ = 96 mo)	• Memory and Attention Adaptation Training (MAAT) with workbook • BCSs attended 4 individual monthly visits of 30–50 min, and phone calls • Outcome measures consisted of self-rating questionnaires and a cognitive battery administered at baseline, immediately postintervention, and at 2- and 6-mo follow-up	• BCSs self-reported improved cognitive functioning from baseline to immediately posttreatment, which was sustained at 2 and 6 mo follow up • Improvement on measures of executive function, verbal skills, and quality of life was also sustained	**Strengths** • High intervention satisfaction **Limitations** • No control group

Table • Cognitive Intervention Studies for Cognitive Deficits in Breast Cancer Survivors, Continued

Author, Date, and Title	Participants	Design and Procedure	Findings	Strengths and Limitations
Ferguson et al,[31] 2012 Development of CBT for Chemotherapy-Related Cognitive Change: Results of a Waitlist Control Trial	40 chemotherapy-treated BCSs • 2 Randomized groups: 1. MAAT (n = 19, M_{age} = 55 y) 2. Wait-list control (n = 21, M_{age} = 57 y) • All BCSs were >18 mo posttreatment	• MAAT with workbook • BCSs attended 4 individual monthly visits of 30–50 min, and phone calls • Outcome measures consisted of self-rating questionnaires and a cognitive battery administered at baseline, immediately postintervention, and at 2- and 6-mo follow-up	• BCSs in the MAAT group showed significant improvement on a test of verbal memory • BCSs in the MAAT group reported significantly improved spiritual well-being on a quality of life questionnaire • BCSs in the MAAT group did not show the expected improvement on a questionnaire of daily cognitive problems	**Strengths** • High intervention satisfaction • Only 4 visits required • Randomized controlled trial **Limitations** • Sample was small, highly educated, and prescreened for anxiety and depression • No active control group • Inadequate quality of life measures for MAAT
Pharmacological Interventions				
Lower et al,[33] 2009 Efficacy of Dexmethylphenidate for the Treatment of Fatigue After Cancer Chemotherapy: A Randomized Clinical Trial	154 chemotherapy-treated cancer survivors • 2 Randomized groups: 1. Methylphenidate (n = 76, BCSs = 59, M_{age} = 53 y, $M_{months\ postchemotherapy}$ = 28 mo) 2. Placebo control (n = 78, BCSs = 59, M_{age} = 53 y, $M_{months\ postchemotherapy}$ = 25 mo)	• 1-wk single-blind placebo run-in period followed by randomized double-blind trial • Treatment phase lasted 8 wk • Primary outcome measure consisted of change from baseline on Functional Assessment of Chronic Illness Therapy–Fatigue Subscale • Secondary outcome measure was change from baseline on High-Sensitivity Cognitive Screen	• There was no significant change on the High-Sensitivity Cognitive Screen in either group as compared with baseline. The High-Sensitivity Cognitive Screen is a brief test with items testing 6 neuropsychological domains including memory, language, attention, visual skills, spatial skills, and executive function	**Strengths** • Randomized double-blind design • Improvement in fatigue compared with placebo group **Limitations** • Adverse effects • Low dose • Non-BCS participants • High-Sensitivity Cognitive Screen is known for practice effects
Mar Fan et al,[36] 2008 A Randomised, Placebo-Controlled, Double-blind Trial of the Effects of d-methylphenidate on Fatigue and Cognitive Dysfunction in Women Undergoing Adjuvant Chemotherapy for Breast Cancer	57 BCSs undergoing chemotherapy • 2 Randomized groups: 1. Methylphenidate (n = 29, M_{age} = 50 y) 2. Placebo control (n = 28, M_{age} = 51 y)	• BCSs in intervention group received methylphenidate throughout chemotherapy • Primary outcome measure consisted of proportion of BCSs with moderate to severe cognitive dysfunction on the High-Sensitivity Cognitive Screen at the end of chemotherapy and 4-6 mo postintervention	• There was no significant group difference on the High-Sensitivity Cognitive Screen at any time point	**Strengths** • Randomized placebo-blind design **Limitations** • Small sample size • High-Sensitivity Cognitive Screen is known for practice effects

Table • Cognitive Intervention Studies for Cognitive Deficits in Breast Cancer Survivors, Continued

Author, Date, and Title	Participants	Design and Procedure	Findings	Strengths and Limitations
Escalante et al,[37] 2014 A Randomized, Double-blind, 2-Period, Placebo-Controlled Crossover Trial of a Sustained-Release Methylphenidate in the Treatment of Fatigue in Cancer Patients	33 BCSs undergoing chemotherapy (M_{age} = 57 y)	• BCSs undergoing chemotherapy received sustained release methylphenidate for 2 wk and placebo for 2 wk • Cognitive performance measures administered at baseline, crossover, and final visit • Primary outcomes of interest were scores on tests assessing fatigue, depression, sleep, and mood	• BCSs performed significantly better on tests of verbal learning, memory, visual perception, and scanning speed in the methylphenidate condition	**Strengths** • Double-blind, 2-period, placebo-controlled crossover trial **Limitations** • Small sample size • Short treatment period • Low dose of methylphenidate • No long-term follow-up testing
Kohli et al,[34] 2009 The Effect of Modafinil on Cognitive Function in Breast Cancer Survivors	68 chemotherapy-treated BCSs • 2 Randomized groups: 1. Modafinil (n = 34, M_{age} = 52 y, $M_{months\ posttreatment}$ = 22.1 mo) 2. Placebo control (n = 34, M_{age} = 56 y, $M_{months\ posttreatment}$ = 22.1 mo)	• All 68 BCSs participated in an open label 4-wk trial of modafinil and had initial good response on fatigue • In a post–open label-trial, BCSs received either 4 wk of modafinil or placebo • Cognitive assessment was administered prior to any modafinil treatment, after the 1st 4 wk of treatment, and after the 2nd 4 wk of treatment	• The modafinil treated group showed significant improvement compared with the placebo group on speed and quality of memory and attention after 4 wk of treatment • Treatment of 8 wk resulted in greater improvement than 4 wk on some measures	**Strengths** • Fewer adverse effects than other stimulants **Limitations** • Secondary data analysis • Lack of prechemotherapy baseline
O'Shaughnessy et al,[35] 2005 Feasibility of Quantifying the Effects of Epoetin Alfa Therapy on Cognitive Function in Women With Breast Cancer Undergoing Adjuvant or Neoadjuvant Chemotherapy	94 BCSs undergoing chemotherapy • 2 Randomized groups: 1. Epoetin alfa (n = 47, M_{age} = 53 y) 2. Placebo control (n = 47, M_{age} = 54 y)	• BCSs received either epoetin alfa or a placebo subcutaneously once per week at the beginning of 4 wk of chemotherapy lasting for a total of 12 wk • Cognitive function was evaluated with the EXIT25 and clock drawing tasks at baseline, 1 wk before chemotherapy cycle 4, and 6 mo postchemotherapy	• BCSs treated with epoetin alfa during chemotherapy performed better than a placebo control group on a questionnaire of executive functioning • There was no difference between the 2 groups 6 mo posttreatment	**Strengths** • Randomized double-blind placebo-controlled trial • Epoetin alfa was well tolerated **Limitations** Performance on the clock drawing task was near ceiling at baseline

Table • Cognitive Intervention Studies for Cognitive Deficits in Breast Cancer Survivors, Continued

Author, Date, and Title	Participants	Design and Procedure	Findings	Strengths and Limitations
Mar Fan et al,[38] 2009 The Influence of Erythropoietin on Cognitive Function in Women Following Chemotherapy for Breast Cancer	87 BCSs undergoing chemotherapy • 2 Randomized groups: 1. Epoetin alfa (n = 45, M_{age} = 53 y) 2. Placebo control (n = 42, M_{age} = 50 y)	• BCSs received either epoetin alfa during chemotherapy or standard care • High-Sensitivity Cognitive Screen, Revised Hopkins Verbal Learning Test, and fatigue and quality of life questionnaires were administered 12-30 mo postchemotherapy	• There was no group effect on either of the 2 cognitive tests • The epoetin alfa group reported a higher overall quality of life than the standard-care group	**Strengths** • Examined long-term effects of erythropoietin on cognition **Limitations** • Only BCSs with moderate-severe impairment were considered to have cognitive deficits • Substudy design precluded randomization
Complementary and Integrative Medicine Interventions				
Milbury et al,[43] 2013 Tibetan Sound Meditation for Cognitive Dysfunction: Results of a Randomized Controlled Pilot Trial	42 BCSs undergoing hormonal therapy • 2 Randomized groups: 1. Tibetan sound meditation (n = 18, M_{age} = 53 y) 2. Wait-list control (n = 24, M_{age} = 54 y)	• The BCSs in the meditation intervention group attended twice-weekly 60-min sessions for 6 wk and were also encouraged to practice at home • BCSs completed a self-report assessment prior to, immediately following, and 1 mo postintervention • Cognitive performance measures were administered at baseline and at the 1-mo follow-up	• BCSs in the intervention group reported fewer cognitive deficits than BCSs in the wait-list control group immediately postintervention but not at the 1-mo follow-up • BCSs in the intervention group showed a trend to perform better than the wait-list control group at the 1-mo follow-up on tests of verbal and short-term memory and processing speed	**Strengths** • Randomized controlled trial • High intervention satisfaction • Intervention feasible for patients suffering from physical limitations or fatigue **Limitations** • No attention control group • Small effect sizes did not reach significance
Reid-Arndt et al,[46] 2012 Tai Chi Effects on Neuropsychological, Emotional, and Physical Functioning Following Cancer Treatment: A Pilot Study	24 chemotherapy-treated cancer survivors (BCSs = 16, M_{age} = 62 y, $M_{months\ postchemotherapy}$ = 78 mo)	• Cancer survivors participated in a 1-h biweekly tai chi class for 10 wk • Cognitive tests and a questionnaire of self-reported cognitive function were administered prior to and within 1 mo following the intervention	• Statistically significant improvement was found on tests of immediate and delayed memory, verbal fluency, and executive functioning, as well as on the self-report questionnaire of cognitive function	**Strengths** • Potential for cognitive improvement following tai chi intervention **Limitations** • No exercise control group • Small sample size with heterogeneous cancer types

Table • Cognitive Intervention Studies for Cognitive Deficits in Breast Cancer Survivors, Continued

Author, Date, and Title	Participants	Design and Procedure	Findings	Strengths and Limitations
Oh et al,[44] 2012 Effect of Medical Qigong on Cognitive Function, Quality of Life, and a Biomarker of Inflammation in Cancer Patients: A Randomized Controlled Trial	81 Cancer survivors (65% postchemotherapy, 34% undergoing chemotherapy) • 2 Randomized groups: 1. Medical qigong (n = 37, BCSs = 12, M_{age} = 65 y) 2. Usual care control (n = 44, BCSs = 13, M_{age} = 61 y)	• Participants in the medical qigong group attended at least 1 (with the option of a second) 90-min class per week for 10 wk • Two measures of self-reported cognitive function were administered at baseline and following the 10-wk intervention	• As compared with the control group, the medical qigong group showed significant improvement on 2 questionnaires of self-reported cognitive function	**Strengths** • Pilot study of potential cognitive improvement following medical qigong intervention **Limitations** • No exercise control group • Small sample size with heterogeneous cancer types
Galantino et al,[48] 2012 Longitudinal Impact of Yoga on Chemotherapy-Related Cognitive Impairment and Quality of Life in Women With Early Stage Breast Cancer: A Case Series	4 BCSs undergoing chemotherapy (M_{age} = 55 y)	• BCSs attended a modified Iyengar yoga program twice a week for 6 wk and then once a week for 6 wk • Cognitive testing consisted of a questionnaire of self-reported cognition and a computerized cognitive battery and was administered before onset of chemotherapy, 6 and 12 wk into chemotherapy, and 1 and 3 mo postchemotherapy	• Performance on the computerized cognitive battery was variable and fluctuated over time	**Strengths** • Pilot study of potential cognitive improvement following yoga intervention both during and postchemotherapy **Limitations** • No exercise control group • Series of 4 case studies
Culos-Reed et al,[49] 2006 A Pilot Study of Yoga for Breast Cancer Survivors: Physical and Psychological Benefits	38 chemotherapy-treated cancer survivors (BCSs = 32, M_{age} = 51 y, $M_{months\ postdiagnosis}$ = 56 mo) • 2 Randomized groups: 1. Yoga (n = 20) 2. No-contact control (n = 18)	• Participants in the yoga group attended one 75-min class per week for 7 wk • Outcome measures consisted of a set of psychological and physical questionnaires and physiological and fitness measurements administered pre-intervention and immediately following the intervention	• As compared with the control group, the yoga group showed a reduction in confusion as measured by the POMS concentration subscale immediately post intervention	**Strengths** • Randomized controlled trial **Limitations** • Small sample size with heterogeneous cancer types • Short program duration

Table • Cognitive Intervention Studies for Cognitive Deficits in Breast Cancer Survivors, Continued

Author, Date, and Title	Participants	Design and Procedure	Findings	Strengths and Limitations
Derry et al,[45] 2014 Yoga and Self-reported Cognitive Problems in Breast Cancer Survivors: A Randomized Controlled Trial	200 BCSs • 2 Randomized groups: 1. Yoga (n = 100 (59 treated with chemotherapy), M_{age} = 52 y, $M_{months\ posttreatment}$ = 16.3 mo) 2. Wait-list control (n = 100, 53 treated with chemotherapy, M_{age} = 51 y, $M_{months\ posttreatment}$ = 18.3 mo)	• BCSs in the yoga intervention group attended 24 twice-weekly 90-min sessions, and were also encouraged to practice at home. • BCSs completed a symptom checklist prior to, immediately following, and 3-mo postintervention	• Participants in the yoga condition did not differ from wait-list control participants on self-rated cognitive complaints at baseline or immediately following the intervention • At the 3-mo follow-up, BCSs in the treatment condition reported significantly fewer cognitive symptoms • There was a significant correlation between practice frequency and reduction in cognitive symptoms	**Strengths** • Randomized controlled trial • Differences remained significant after controlling for mood, fatigue, and sleep quality • High retention • Home practice was tracked **Limitations** • No exercise control group • Mixed treatment regimens
Miki et al,[50] 2014 Feasibility and Efficacy of Speed-Feedback Therapy With a Bicycle Ergometer on Cognitive Function in Elderly Cancer Patients in Japan	78 chemotherapy-treated cancer survivors (55% BCSs) • 2 Randomized groups: 1. Speed-feedback therapy (n = 38, M_{age} = 73 y, $M_{months\ postdiagnosis}$ = 56.6 mo) 2. No-contact control (n = 40, M_{age} = 75 y, $M_{months\ postdiagnosis}$ = 68.9 mo)	• Cancer survivors in the speed-feedback therapy intervention group participated in 4 weekly sessions	• Intervention participants showed significantly greater improvement at week 4 on the Frontal Assessment Battery, which consists of cognitive tests associated with executive functioning	**Strengths** • Randomized controlled trial • Highly acceptable intervention **Limitations** • No exercise control • No extended follow-up
Alvarez et al,[47] 2013 The Effect of EEG Biofeedback on Reducing Postcancer Cognitive Impairment	23 chemotherapy-treated BCSs ($median_{age}$ = 56 y, $median_{months\ postchemotherapy}$ = 24 mo)	• BCSs participated in a 10-wk wait-list control period followed by a 10-wk neurofeedback intervention • Neurofeedback sessions (20 sessions) occurred twice a week for 10 wk • Questionnaires were administered 3 times during each 10-wk session (wait-list and intervention) and once at 4 wk postneurofeedback	• Significant improvement was observed on all 4 domains of the Functional Assessment of Cancer Therapy–Cognitive Function over the course of the 10-wk intervention	**Strengths** • Pilot study of potential cognitive improvement following biofeedback intervention • Delay in administration of questionnaires • No adverse effects **Limitations** • Control condition did not include sham EEG

Abbreviations: BCSs, breast cancer survivors; EEG, electroencephalogram; M, mean; POMS, Profile of Mood States.

Note.From "Interventions for Cognitive Deficits in Breast Cancer Survivors Treated With Chemotherapy ", by Vance et al., 2016, Cancer Nursing, p. 4-10.

Table 4: Updated Literature Review on Cognitive Intervention Studies for Cognitive Deficits in Cancer Survivors			
Author	Participants	Design and procedure (cognitive training exercises)	Findings
Bray et al., 2015	243 breast and colorectal cancer patients who completed adjuvant chemotherapy within 6-60 months.	One group receiving web-based cognitive rehabilitation program and the other group receiving usual care for 15 weeks. Neuropsychological assessment tests were performed at baseline, post intervention directly and at 6 months.	The group who received web-based cognitive rehabilitation showed improvements on all neuropsychological and self-report assessment; the results were sustained at 6 months.
Damholdt et al., 2016	157 breast cancer survivors,	Received 30 cognitive training sessions for 6 weeks.Randomly assigned into a group receiving web-based cognitive training and another telephone support (waitlist) Neuropsychological assessments were collected at baseline, post-intervention and 5 months follow up.	The group who received cognitive training session showed improvement on their verbal learning and working memory compared to the waitlist group.

(Bray et al. 2015 and Damholdt et al. 2016)

Table5: Recommended Cognitive Interventions Based on Literature Review

Interventions	Target Group	Details of Intervention	Study Results	Reference
Exercise Walking, Resistance training	Randomized control trial of 479 patients receiving chemotherapy	Six weeks of a home-based daily walking and resistance training program	Significant improvement in FACT-Cog* overall scores	Mustain et al., 2013 Janelsins et al., 2012
Yoga	Randomized control trial of 328 Cancer survivors	Four-week yoga program (2 times/week, 75 min sessions)	Reduced self-reported memory impairments by 19.2% in participants who practiced yoga compared to 5.4% in controls receiving standard care. Patients receiving chemotherapy showed significant cognitive improvement.	Janelsins et al., 2012 Derry et al., 2015
Relaxing exercises Tai Chi	23 women with history of cancer	Tai Chi sessions of 60minutes two times per week for 10 weeks	Significant improvement in the following domains; immediate and delayed memory recall, verbal fluency, and executive function.	Reid-Arndt et al, 2012 Mustianet al., 2013

Education on memory and attention, self-awareness training, Self-regulation emphasizing arousal reduction through relaxation training, activity scheduling and pacing.	29 breast cancer survivors	Memory and Attention Adaptation Training (MAAT), 30-50 minutes for 4 months	Improvement in verbal memory, attention, and executive psychomotor function	Herbst 2015 Von Ah *et al*. 2015 Ferguson et al., 2012
cognitive compensatory strategies training, verbal rehearsal of auditory information	157 female breast cancer survivors	Web-based cognitive training 30 training sessions over 6 weeks	Improvement in the following cognitive domains verbal learning and working memory	Damholdt et al., 2016
Brain games (training exercises) crossword puzzles, word games, Sudoku, computer games, learning new skills, or languages, reading books	Cancer survivor anecdotes expert opinions		The survivors reported improvement in their daily function	Herbst 2015 Von Ah 2015 Kesler et al., 2014 Myers 2012 Cancer Care Workshop 2006
Writing things down (to do list, meetings and appointment schedule)	Cancer survivor anecdotes expert opinions		The survivors reported improvement in their daily function	Von Ah 2015 Gordon 2014 Myers 2012 Cancer Care Workshop 2006

Enough rest and sleep Eating vegetables Trying to keep a routine schedule and putting things in the same place. No multitasking (focus on one thing at a time and minimize distractions)	Cancer survivor anecdotes expert opinions Close doors, turn off music do not sit in front of a window	The survivors reported improvement in their daily function	Gordon 2014 Von Ah 2015 Myers 2012 Cancer Care Workshop 2006

* Functional assessment of cancer therapy cognitive function (FACT-COG) is a self-report questionnaire, with potential to be used in standard clinical practice as a tool for evaluating patients' cognitive function: before, during and after chemotherapy.

APPENDIX II

EVALUATION FORMS

Immediate Evaluation Form

American UniversityofBeirut MedicalCenter
NursingServicesClinical&ProfessionalDevelopmentCenter
EducationalOfferingEvaluationForm

ActivityTitle: **Date:**

Pleaseratethecriteriaforevaluationaccordingtothefollowingscale:

Excellent…4 Good …3 Fair …2 NeedsImprovement…1

CriteriaforEvaluation	**NameoftheSpeaker**

1. Presenter knowledge ofthesubject.	
2. Learningobjectiveswere met.	
3. Benefitofthe sessiontoyou.	
4. Clarityofcontent.	
5. Appropriatenessoftheteachingstrategies.	
6. Qualityofaudiovisuals/handoutsused.	
7. Teaching-learningenvironment.	
8. Responseofthespeakertoyourquestions.	
9. Overallorganizationof thesession.	

Areasforimprovement:

Futurerecommendations:

Comments:

Three Months Evaluation Form

After 3 months of implementing the educational session for nurses they will be asked the following questions:

Date:

Please rate on scale of 1 to 10.

1). How beneficial was the session on chemotherapy related cognitive impairment to you:

1 2 3 4 5 6 7 8 9 10

Not beneficial Very Beneficial

2). How often did you care for a patient with cognitive impairment and you used information you acquired from the session in your care plan

1 2 3 4 5 6 7 8 9 10

Never Always

3) How often did you recommend non-pharmacologic intervention to your patients complaining of cognitive impairment?

1 2 3 4 5 6 7 8 9 10

Never Always

4) How often did you check to the online resources for more information on cognitive impairment and recommendations for patients?

1 2 3 4 5 6 7 8 9 10

Never Always

5) Based on your practice, was the information you received of benefit to your patients?

1 2 3 4 5 6 7 8 9 10

Not beneficial Very Beneficial

Give an example of a patient who reported benefit from your recommendations.

Pre and Post Session Quiz

Pre-post quiz on chemo-brain:
American University of Beirut Medical Center

Name:
Years of experience:
Date:

Please choose one correct answer and circle it on the paper:

Part I: True or False questions

1) Chemotherapy induced cognitive impairment is also known as chemo-brain.

   True False

2) Chemotherapy is the major factor leading to cognitive impairment in cancer patients

True False

3) Severe anxiety and depression contribute to the cognitive impairment seen in cancer patients receiving chemotherapy.

True False

Part II: Multiple choice questions

4) A 38 year old patient with breast cancer is coming in for her 4th cycle FAC, she tells you that she has been feeling "fuzzy" lately; she is unable to focus and is being forgetful. As her primary nurse, what do you tell her?

a) I will inform your physician about this. But, research has shown that in some patients chemotherapy may induce cognitive impairment, I will explain to you about a few interventions you can use to prevent or improve your symptoms.

b) Tell me more, since when are you feeling dizzy? Do not worry I can explain to you a few tips you can use that can help prevent your symptoms and I will inform your physician about this.

c) I will inform your physician about this, he may request a scan for you just to be sure all is well, don’t worry it is probably nothing.

d) Ask her if there is anyone in the family who has memory loss or history of Alzheimer. Ask her how long was this happening and if she told anyone about it. I will inform your physician about it.

5) What are the adverse signs that you as a nurse will see on the patients complaining of chemo-brain?

a) Increased questioning
b) Forgetfulness
b) Hallucinations
c) Mistrust

6) If your patient called you to their room to ask a question; however, 5 minutes later when you enter the room the patient tells you "No I didn’t call for you". His wife shocked tells him: "What's wrong with you, you just told me that you wanted to ask your nurse what time is your chemotherapy!" Your response to this is:

a) We will start your chemotherapy at 5pm today, for 2 hours and then you will be discharged.

b) Oh it's okay maybe you (to the wife) are the reason he is forgetting things, you mesmerize him.

c) Is this his first time he is being forgetful? Or it happened before? We will start your chemotherapy at 5pm today, for 2 hours and then you will be discharged.

d) I will inform your physician about this, and he will explain this to you better.

Part III: Please match the following options in column A to the correct interventions in column B they can be more than one answer to each intervention.

7)

Column A	Column B
Puzzles_____	A. Brain training
Sudoku_____	B. Physical Exercise
Yoga_____	C. Mental Exercises
Self-regulation and Self-control_____	
Learningnew games/procedures_____	
Keeping track with a schedule _____	

Part IV: In the following part you will be given a question with multiple answers, list these answers from most important to least important write the numbers from 1(most important) and 5 (least important) beside each question:

8) As a nurse what do you look for in your patient to assess for chemotherapy induced cognitive impairment?

   a) The patient is receiving chemotherapy_____

   b) The patient has finished his chemotherapy cycles_____

   c) The patient is complaining of headache_____

   d) The patient is complaining of forgetfulness_____

   e) The patient's family is complaining that he is losing his things frequently_____

9) Your patient is considered possibly at lower risk for developing chemo-brain if they : (rank the following, 1 lower risk to 5 higher risk)

   a) They have a PhD _____

b) They walk for one hour daily_____

c) They finished their chemotherapy sessions_____

d) They eat healthy _____

e) They are house wives_____

10) If your patient tells you he/she is not able to minimize distractions at work, and that his/her concentration is poor. What would your response be?

a) Work with another coworker

b) Close the door and sit away from a window

c) Ask for assistance

d) Sleep

e) Write things down