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Review

Post-chemotherapy cognitive dysfunction in women with breast cancer

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Summary

Cancer-related cognitive dysfunction is an important clinical problem that can interfere with the daily functioning, work productivity, childcare, and other responsibilities of women with a history of breast cancer. Risks of cancer-related cognitive impairment include cancer and cancer treatment, as well as patient-related vulnerabilities. There is no established standard of neuroprotective care or treatment for breast cancer-related cognitive impairment.

Key words: cancer-related cognitive impairment, breast cancer, women

Introduction

Breast cancer is the most common malignancy in women, and its incidence is increasing in most countries of the world [1, 2]. Cognitive dysfunction in breast cancer patients has been reported since 1990. These reports are consistent with the increased use of adjuvant chemotherapy, especially in women who received very high doses of chemotherapy. Subsequent studies have documented cancer-related cognitive impairment (CRCI) in patients with a history of breast cancer, before cancer-targeted treatment, and in combination with other topical and/or systematic breast cancer treatments. These side effects of chemotherapy treatment of malignant tumors have been known as post-chemotherapy cognitive impairment (PCCI) or chemotherapy-induced cognitive impairment (CICI). In the era of more selective use of chemotherapy, cognitive dysfunction

symptoms continue to appear after cancer-targeted treatment, endocrine therapy, and in other situations, including radiation therapy and surgery [3–6].

Cognition is an important part of the quality of life for both healthy people and those suffering from malignant illnesses. Breast cancer is the most studied type of cancer in CRCI, but there is increasing literature data on the condition of patients with other types of cancer such as lymphoma, head and neck cancer, brain cancer, and those who have undergone stem cell transplantation. Cognitive impairment is also an independent prognostic factor for some malignant tumors [3–6].

There is no established standard of neuroprotective care against CRCI or the treatment of CRCI for breast cancer. Cognitive rehabilitation and behavioral therapy are the most promising interventions for CRCI. Physical activity is a promising intervention, but it has not been fully evaluated. Some drugs (psychostimulants, dementia drugs, etc.) have been studied without definitive efficacy and require further research [3–7].

There are several reports of short-term and long-term cognitive impairment and difficulties that these patients have experienced. This can last for years not only during treatment, but also after the end of treatment, and for many years after the end of treatment compared to the most commonly reported first breast cancer treatment.

Patients who develop cognitive impairment in the acute phase of breast cancer treatment may take months to a year to recover, and in some individuals, cognition, supported by reports of neuroimaging abnormalities, will never return completely to baseline. In the case of dementia, symptoms often impair function, work, and quality of life [4–7].

Many studies have confirmed that cognitive impairment is associated with negative emotions, the frequency, and intensity of which may be sufficient to meet the criteria for anxiety and mood disorders. This comorbidity reflects a feedback loop between physical symptoms and psychological/psychiatric difficulties [4–8].

The CRCI reported by breast cancer patients is common, but the frequency and type may vary depending on the population studied. The magnitude of cognitive impairment depends on the treatment that this patient's profile is receiving, and it is also important for the patient to be aware of the extent to which cognitive impairment is impaired. There is also a discrepancy between the scores obtained from the self-assessment scale and the scores obtained by the patient in the objective test of cognitive function/skills [3–6].

The main model of CRCI suggests that mechanisms and vulnerabilities overlap with cognitive aging and may represent accelerated aging. Based on clinical and preclinical studies, several possible mechanisms of CRCI have been hypothesized. Increased systemic inflammation occurs in response to cancer, chemotherapy, radiation therapy, and surgery. Chronic inflammation can cause neuroinflammation, which can lead to increased neurotoxicity and oxidative damage. Evidence also suggests neuronal mitochondrial dysfunction, as well as neurogenesis and neuroplasticity disorders. The potential cognitive effects of immunotherapy, a new breast cancer treatment, have been reported [7, 9–11].

Estrogen plays an important role in women's brain health, and down-regulating natural estrogen production and blocking its activity with endocrine therapies are associated with cognitive effects [3, 4, 7, 8].

Evaluation by cancer-related cognitive dysfunction

Neuroradiological (especially functional magnetic resonance imaging fMRI), neuropsychological, and neurophysiological methods were used to assess CRCI [11]. These methods certainly contribute to greater objectivity and

reliability of the results obtained, and provide deeper insight into the analysis and interpretation of the process of solving the task of testing cognitive function. Previous studies were inconclusive, and the author himself attributed it to the lack of sufficiently sensitive and practical measuring instruments that were not sufficient to detect minimal changes in cognitive ability [8].

The National Cancer Network Guidelines for Assessment and Management of CRCI suggest that strengthening patient education on CRCI is important. Many breast cancer patients are unaware of the potential for cognitive decline after treatment. Dementia screening tools are inadequate for CRCI assessment but screening for mood disorders and survival problems can identify cognitive symptoms. Careful assessment of cognitive impairment using the CRCI validated questionnaire can be used to track disability in the event of clinical suspicion. When patients voluntarily report these symptoms to their doctor, they should not be ignored. It is important to recognize the patient›s symptoms and perform a thorough examination. The first step is to assess and address potentially controllable comorbidities that are common and often co-occurring in this patient population, such as depression, sleep disorders, and fatigue. If CRCI symptoms do not improve, you should follow the referral of a neuropsychological assessment. It helps to characterize specific cognitive symptoms, provide targeted recommendations, and provide relief and information to patients who are concerned about developing dementia [8, 11].

Results of neuropsychological surveys

Berndt et al. show that person with breast cancer rate their memory as average, and point out that this negative self-reporting of mental function was almost consistently associated with higher levels of anxiety and depression. However, patients' scores on an objective measure of the degree of cognitive impairment did not correlate with their level of anxiety. In general, subjects in this study performed poorly on mental rotation tasks as an indicator of spatial cognition and memory-examining tasks. Author compared four groups formed by the type of treatment the patient received for general memory and verbal memory, and found that the treatment had a statistically significant effect. This means that memory loss in breast cancer patients is related to the type of treatment they receive, but in some cases memory may be normal or visibly impaired [12].

Chen et al. compared patients before and after chemotherapy and healthy subjects on various measures of cognitive performance. They found that these subjects were statistically tested for delayed recall and content recognition as an indicator of memory impairment, back-calculation as an indicator of concentration, and Stroop test. They have been found to have a significantly smaller effect on executive function. Subjects in this group also showed statistically significantly longer reaction times and diminished attention to the presented stimuli. However, when it came to assessing general cognitive performance, the treated subjects mentioned did not differ from the sample in the healthy population [13].

Henneghan et al. founded that objective and self-assessment of cognitive ability by breast cancer patients are moderately negatively correlated with perceived stress, anxiety, depression, loneliness, malaise, and sleep problems, and are statistically significantly correlated. On the other hand, the number of treatments and the time elapsed since the end of chemotherapy were not statistically significantly correlated with the objective and self-assessed cognitive function measurements in this group of cancer patients [14].

Hermelink et al. found that people with breast cancer generally show reduced cognitive

ability. However, only patients who received chemotherapy extended reaction time. Author found a small but statistically significant correlation between respondents› scores for an objective measure of cognitive performance and self-reporting of these types of abilities. In addition, post-traumatic stress disorder (PTSD) has been shown to have the potential to alleviate the association between breast cancer and cognitive impairment in these individuals [15].

Jung et al. found that breast cancer patients who received chemotherapy had statistically significantly lower scores on the language working memory test compared to healthy subjects. Chemotherapists showed statistically significantly higher deficiencies in the area of executive function not only in healthy individuals but also in breast cancer patients who did not receive chemotherapy. Interestingly, patients treated with chemotherapy and those not treated that way did not report statistically significantly greater cognitive impairment compared to healthy subjects. The level of anxiety and perceived stress was statistically significantly correlated with self-assessed memory loss. On the other hand, the association between anxiety and stress and patient scores on objective memory tests was not statistically significant. In addition to a neuropsychological examination, functional magnetic resonance imaging (fMRI) was also used in this study [8].

Kama et al. investigated connection with the electrophysiological aspects of cognitive impairment, and concluded that breast cancer survivors had statistically significantly more problems focusing attention on specific tasks or objects compared to healthy women. In addition, their response to visual stimuli appears to be less intense [11].

Kessler et al. compared the potential of functional magnetic resonance imaging with standard medical (patient-centric) testing to predict cognitive impairment in breast cancer patients one year after the end of chemotherapy. fMRI turned out to be a more accurate modality of this assessment, and the incidence of cognitive impairment in this patient profile was found to be 55% one year after the end of chemotherapy [7].

Lange et al. conducted a study of older women with breast cancer, and found that 49% of respondents have a cognitive impairment, which is primarily related to working memory, and 64% of respondents have problems in this area of cognitive function/skills. In addition, subjects who received chemotherapy were more likely to complain of cognitive impairment than those who received radiation therapy. Therefore, the subjective assessment of cognitive decline was higher [4].

Manning et al. found that patients in their sample who received chemotherapy and endocrine therapy reported statistically significantly weaker physical and social functions than healthy subjects [10]. However, subjects in these two groups did not show a statistically significant difference in self-assessment of cognitive function. However, an objective test of their cognitive abilities revealed that the group of subjects who received chemotherapy and hormone therapy for breast cancer had statistically significantly greater cognitive impairment than healthy subjects. Another result of this study is related to a statistically non-significant difference in IQ levels between breast cancer subjects and a group of healthy subjects. However, this difference was not large enough to declare it to be statistically significant [10]. In another study the authors used fMRI to observe the neurophysiological correlation of cognitive impairment in patients treated with chemotherapy and endocrine therapy. They found that performing tasks designed to test executive function resulted in high parietal lobe activation in patients, reflecting the cognitive load generated by solving such tasks. The correlation of this phenomenon was patient complaints about fatigue, physical dysfunction, and cognitive dysfunction. The authors explained this phenomenon by disrupting the integration of

processes in the brain, due to the potential neurotoxicity of the treatment the patient received [16].

Paquet et al. found that differences in the subjective assessment of cognitive function between breast cancer subjects and healthy subjects could be explained by increased fatigue and depression in the first group of subjects. Both groups reported that forward-looking memory was worse than backward-looking memory. However, self-assessment of forward and backward memory did not statistically significantly correlate with objective measurements of these two types of memory. In addition, one group of patients achieved statistically significantly lower scores in objective measurements of both forward and backward memory, compared to healthy subjects. The subjective assessments of forward and backward memory were also strongly correlated with each other. Patients' results on objective measurements of forward and backward memory were also statistically significant, but still poorly correlated [17].

Lamar found that the development of cognitive impairment in breast cancer patients was statistically significantly associated with chemotherapy compared to other therapies: radiation therapy, endocrine therapy, immunotherapy, etc. in subjects who were not anxious at the time of diagnosis. In addition, the authors found that 38% of the women in the sample reported clinically significant levels of anxiety, and that incidence of cognitive impairment one year after the diagnosis of breast cancer is 8.1%, which is significantly lower than in other studies [18].

Two studies observed the greatest cognitive impairment in the combination of chemotherapy and hormone therapy for breast cancer. The three findings are positive, which can be concluded from the statistically significant difference in size between groups of patients treated differently, namely the degree of cognitive impairment. On the other hand, none of the results of the studies included in the meta-analysis were negative [10, 16]. In addition, six studies found that breast cancer patients (most commonly when receiving some available treatments) had statistically significantly worse cognitive function compared to healthy subjects. However, in three studies, these differences were not statistically significant. In a study conducted by Manning et al., patients complained of cognitive problems more than healthy individuals, but objective tests showed that these differences were not statistically significant. There were no results that general intelligence could decline but in contrast, the study by Manning et al. gave negative results [16]. Attention and concentration appear to be a mental function that is impaired in breast cancer patients, and we observed two positive and no negative findings [11, 13].

Four studies gave statistically significant results suggesting different memory deficits in breast cancer patients, but this effect was not seen in two studies. Interestingly, in one study, this cognitive deficiency was identified by an objective measurement (test), but in the same study, when self-assessment was measured, the patient was unaware of such a deficiency, and this can be due to the nature of the measurements used. Patients may know that they must control their problems and difficulties without admitting that their abilities and skills are weakened. Memory impairment includes three major flaws: working memory problems, problems related to retrospective memory, and future memory problems, and these are more pronounced than the problem of retrospective memory [12].

In two studies, Chen et al. and Henneghan et al. found that cognitive problems in women with breast cancer are often associated with discomfort and anxiety, sadness and depression, higher levels of stress, and a type reaction similar than post-traumatic stress disorder (PTSD). These findings were conducted in seven analyzed studies (i.e. more than half of the studies included in the meta-analysis),

and negative findings were conducted in two studies [13, 15].

In two studies conducted by Berndt et al., and Jung et al., there should be noted that the assessment of depression and anxiety is mostly self-reported, and herefore, this finding is not surprising [8, 12].

Results of neuroimaging surveys

There is compelling evidence from imaging studies showing cognitive changes associated with cancer treatment in some people. Several neuroimaging studies have, for example, described brain changes comparable to aging, such as compensatory overactivity during cognitive tasks and gray matter reduction [19].

Miao et al. in their study found that the functional connectivity of the anterior cingulate cortex (ACC) was significantly lower in patients with breast cancer treated with chemotherapy than in healthy subjects. We have known that functional connectivity of ACC was significantly correlated with executive function. These results provide evidence that these changes in functional connectivity may be the pathophysiological basis for long-term chemotherapy-related cognitive dysfunction, as well as executive dysfunction, in breast cancer patients [20]. Zheng et al. localized brain region with increased amplitude of low-frequency fluctuation in patients treated with breast chemotherapy 1 month after therapy: lower left inferior temporal gyrus, right medial temporal gyrus, left medial and superior temporal gyrus, and the anterior precuneus on both sides. After conventional chemotherapy for breast cancer patients, memory, attention, executive function, and processing speed also decrease in the short term. Chemotherapy alters neural activity in the resting, local brain regions, and primarily, there is an increase in the bilateral activity of the middle temporal gyrus and the anterior cuneiform gyrus, where the brain region constitutes the standard network [21].

Li et al. in their study found that gray matter density was reduced in the inferior frontal gyrus, right middle frontal gyrus, right fusiform region, and bilateral in cerebellar region in breast cancer patients compared to healthy controls. Also, a decrease in gray matter density in the right medial frontal gyrus may mediate the effect of chemotherapy on speech fluency performance. These results indicate that the dose-response relationship between chemotherapy and cognitive impairment may be dependent on a decrease in gray matter density in the frontal cortex structure [22].

In some post-treatment cross-sectional studies, using magnetic resonance imaging, gray matter reduction has been proven mainly in the frontal cortical structure and hippocampus, and also white matter in cancer survivors treated with chemotherapy. However, negative results have also been documented [23–28]. Similar results have been reported in longitudinal studies. Gray matter density decreased in bilateral frontotemporal, temporal (including hippocampus), cerebellar region, and right thalamus one month after chemotherapy, with only partial recovery one year after therapy compared with no significant changes in gray over time in cancer group patients without chemotherapy or healthy controls. Also, there was reduced frontal, parietal, and occipital white matter integrity in patients exposed to chemotherapy, and there was no change in the non-chemotherapy group or the healthy controls after treatment [29, 30].

Cross-sectional studies of cancer survivors using functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), have showed areas of reduced activation during the performance of cognitive task in the area similar to the structural differences described, in survivors exposed to chemotherapy compared to controls. McDonald's et al. in longitudinal studies using fMRI, found frontal lobe hyperactivity to support pretreatment work memory tasks, reduced activation

one month after chemotherapy, and pretreatment hyperactivity one year after treatment [31–36].

Cimprich et al. studied selective attention and working memory in women using functional magnetic resonance imaging before chemotherapy for localized breast cancer. Compared to healthy controls, these patients have bilateral brain activation in demanding tasks, adoption of additional components of attention / working memory circuits, and less accurate and slower task execution. These results show cognitive dysfunction before chemotherapy [37].

Scherling et al. also reported over-activation in memory tasks in cancer patients during pretreatment compared to healthy controls, consistent with reports of neuropsychology test. This over-activation in pretreatment period is an attempt to compensate for the pre-existing deficit. However, over the years, patients lose the ability of that compensation as a result of exposure to cancer treatment and/or age-related changes in the brain [38].

Conclusion

CRCI is an important clinical issue and can interfere with the daily functioning, work productivity, childcare, and other responsibilities of patients with a history of breast cancer. Risks for CRCI include type of cancer and cancer treatment, as well as patient-related vulnerabilities. Treatment recommendations include treating the symptoms reported by the patient with a thorough symptom-based assessment. Cognitive and behavioral therapies are primarily recommended interventions.

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Kognitivna disfunkcija nakon hemoterapije kod žena oboljelih od karcinoma dojke

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Kognitivna disfunkcija povezana sa karcinomom je važan klinički problem koji može ometati svakodnevno funkcionisanje, radnu produktivnost, brigu o djeci i druge odgovornosti žena sa istorijom karcinoma dojke. Rizici od kognitivnih oštećenja povezanih sa karcinomom uključuju karcinom i liječenje karcinoma, kao i ranjivosti pacijenata. Ne postoji utvrđen standard neuroprotektivne njege ili liječenja kognitivnih oštećenja povezanih sa karcinomom dojke.

Ključne riječi: kognitivno oštećenje uzrokovano karcinomom, karcinom dojke, žene