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Submission date: 14-Jan-2022 09:56AM (UTC+0700)
Submission ID: 1741452820
File name: ng_Injection_and_Hormonal_Chemotherapy_-_Annisa_Hananingtyas.pdf (111.67K)
Word count: 3836
Character count: 20232

THE COMPARISON OF COGNITIVE FUNCTION IMPAIRMENT IN BREAST CANCER PATIENTS RECEIVING INJECTION AND HORMONAL CHEMOTHERAPY

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ABSTRACT

Introduction: Breast cancer is the most common malignancy in women. Chemotherapy is the main modality for treating breast cancer which affects the cognitive function. Chemotherapy increases the levels of cytokines, damage genetic material, or damage the brain's grey matter causing cognitive deficits and neurotoxicity. **Objective:** To determine the incidence of cognitive impairment before the first injection and after the third injection with an interval of 3 weeks in breast cancer patients receiving chemotherapy and hormonal therapy. **Methods:** This was an analytical observational study with a prospective cohort design of postoperative breast cancer patients receiving chemotherapy who met the inclusion and exclusion criteria. Cognitive function tests were carried out using the Moca-Ina questionnaire. Data analysis included descriptive statistics, Mann Whitney test, and Spearman's bivariate correlation test. The results were significant if the p-value <0.05. **Results:** A total of 40 breast cancer patients were included in this study. Cognitive impairment increased after the third injection of chemotherapy in the injection chemotherapy group compared to the hormonal therapy group. There was a significant difference between pre-chemotherapy and post-third injection of breast cancer patients who received chemotherapy compared to patients who received hormonal therapy (p=0.005). There was a correlation between cognitive impairment scores and neuropathic pain before (p=0.175; rho= -0.219) and after the third chemotherapy (p=0.017; rho= -0.377). **Conclusion:**Cognitive impairment increased after the third injection of chemotherapy. There was a significant difference between pre-post the third chemotherapy. There was also a correlation between cognitive impairment scores and neuropathic pain of breast cancer patients who received chemotherapy.

KEYWORDS Chemotherapy, Cognitive Function Impairment, Neuropathic Pain

Introduction

Breast cancer is the most common malignant disease in women, with an incidence of 43.1 / 100,000 people. In 2012, there were 1,617,149 new cases of breast cancer in the world, most of which occurred in developing countries, namely 882.9 cases per 100,000 population. In addition to the high morbidity rate, it has a standard mortality rate (ASMr) of 12.9 deaths per 100,000 cases, making it the second-largest cause of death after lung cancer, and the largest cause of death from cancer in women. Currently,

DOI:10.5455/IJMRCR.Cognitive-Function-Impairment-Breast-Cancer
First Received: October 28, 2020
Accepted: November 14, 2020
Associate Editor: Ivan Inkov (BG);
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the definitive therapy for breast cancer is surgery for stages 1 and 2, as well as chemotherapy, hormonal therapy, and radiotherapy as adjuvant and palliative therapy.[1] Chemotherapy is the main modality in treating breast cancer with one of its side effects being cognitive impairment.[2] It is estimated to occur in 13-70% of breast cancer patients who receive chemotherapy.[3] Several meta-analysis studies showed that cancer and in remission period-patients had impairments in the domains of memory, attention, executive function, processing speed, visual and verbal memory, and language when compared to people without cancer.[4–6] In chemotherapy or hormonal therapy, cognitive impairment usually affects executive function.[4,7] Several studies estimated that it was due to increased levels of cytokines, damage to deoxyribonucleic acid (DNA), or grey matter damage. They resulted in cognitive deficits and neurotoxicity due to chemotherapy-related to exposure to higher doses, also additive and synergistic effects of multichemotherapy.[8–10] Unlike chemotherapy, there were no significant difference in cognitive function in hormonal therapy (aromatase blockers) studies. This study aims to compare changes in cognitive function in breast cancer patients receiving chemotherapy and hormonal therapy using the MoCA-Ina instrument.

Methods

This was an observational analytic study with prospective cohort design carried out in an oncology outpatient ward, Dr. Kariadi Hospital, Semarang, from September 2019 to February 2020. The subjects were postoperative breast cancer patients who received injection chemotherapy and hormonal therapy. They were divided into two groups; the postoperative breast cancer group who received three injections of chemotherapy and the postoperative breast cancer group who received hormonal therapy for a period of 9 weeks that met the inclusion criteria, namely stage I and II breast cancer patients, post-partial mastectomy breast cancer patients, and agreed to participate in the study. At the same time, the exclusion criteria were a history of malignancies other than breast cancer and patients with metastases.

This study has received ethical approval from the Komisi Etik Penelitian No.368 / EC / KEPK-RSDK / 2019. Patients who were included in the inclusion criteria were asked for written consent on the informed consent sheet. They were examined for cognitive function using MoCA instruments with normal cognitive status if the score ≥26 and abnormal if the score <26. Cognitive function tests were compared with patients receiving hormonal therapy. The study was conducted in a period of 9 weeks per patient with an evaluation every 3 weeks. The injections consist of the first to the third injection.

The data were analysed using SPSS for Windows version 20. Data analysis included descriptive statistics and Mann Whitney hypothesis test. Bivariate correlation analysis using the Spearman test assessed the association between cognitive impairment scores and neuropathic pain scores. The p-value was considered significant if p <0.05.

Results

This study included 40 subjects who met the inclusion and exclusion criteria. There were no subjects who dropped out during the study. Table 1 showed the characteristics of the subjects with a predominance of under 60 years old (82.5%) with a mean age of 51.525 ± 9.41 years. The oldest age is 70 years, while the youngest age is 25 years.

Table 1 The characteristics of subjects

Variable	Group				p
	Injection chemotherapy		Hormonal therapy		
	N	%	n	%	
Age					
>60	4	20	3	15	1
≤ 60	16	80	17	85	
Education					
Elementary school	1	5	2	10	0.892
Junior high school	6	30	5	25	
SMASenior high school	9	45	10	50	
Undergraduate	4	20	3	15	
Occupation					
Housewives	5	25	8	40	0.06
Labor	0	0	3	15	
Private employee	12	60	5	25	
Enterpreneur	0	0	1	5	
Civil servant	3	15	1	5	
Retired	0	0	2	10	
Marital status					
Married	17	85	19	95	0.605
Widow	3	15	1	5	
Children					
>1	15	75	17	85	0.695
≤ 1	5	25	3	15	

Significant (p < 0,05); Chi square

Table 2 showed a decrease in the mean score from pre-injection chemotherapy to the first injection chemotherapy, 28.60 ± 2.21 and 28.25 ± 3.19, respectively and from pre-hormonal to the first pre hormonal, 28.75 ± 2.31 and 28.50 ± 3.05, respectively (p = 0.602). There was a decrease in the mean score, from pre-injection chemotherapy I to the first injection, 28.25 ± 3.19 and 27.20 ± 4.24, respectively and from pre hormonal I to pre hormonal II, 28.50 ± 3.05 and 28.25 ± 3.67, respectively (p = 0.285). We found a decrease in the mean score from pre-injection chemotherapy II to the third injection chemotherapy, 27.20 ± 4.24 and 25.25 ± 5.38, respectively and from pre-hormonal II to pre hormonal III, 28.50 ± 3.05 and 28.25 ± 3.67, respectively (p = 0.060). There was a decrease in the mean score on changes in cognitive function both pre (p = 0.634), post-therapy I (p = 0.602), post-therapy II (p = 0.285), and post-therapy III (p = 0.060).

Table 3 showed the difference in the scores in pre-post injection chemotherapy I and hormonal, -0.35 ± 1.09 and -0.25 ± 0.79, respectively (p = 0.938). There were a different score in

Table 2 The changes of cognitive function before and after chemotherapy I, II, III

Cognitive function	Group		p
	Injection chemotherapy	Hormonal therapy	
Pre	28.60 ± 2.21	28.75 ± 2.31	0.634
Post therapy I	28.25 ± 3.19	28.50 ± 3.05	0.602
Post therapy II	27.20 ± 4.24	28.25 ± 3.67	0.285
Post therapy III	25.25 ± 5.38	27.95 ± 4.40	0.06

*Mann Whitney

Table 3 The difference score of cognitive function before and after chemotherapy I,II, III

Cognitive function	Group		p
	Injection chemotherapy	Hormonal	
Pre – post I	-0.35 ± 1.09	-0.25 ± 0.79	0.938
Pre – post II	-1.40 ± 2.16	-0.50 ± 1.40	0.085
Pre – post III	-3.35 ± 3.50	-0.80 ± 2.14	0.005*

*Mann Whitney

pre-post injection chemotherapy II and hormonal, -1.40 ± 2.16 and -0.50 ± 1.40, respectively (p = 0.085). There was a difference in scores in pre-post injection chemotherapy III and hormonal, -3.35 ± 3.50 and -0.80 ± 2.14, respectively (p = 0.005). There was a significant difference between pre-post injection chemotherapy III compared to hormonal therapy in breast cancer patients (p = 0.005).

In the pre-therapy group, there was no abnormal number of cognitive impairments on injection chemotherapy and hormonal therapy. In the post-therapy I group, there was no any abnormal number of cognitive impairments either on injection chemotherapy and hormonal therapy. In the post-therapy II group, we found an abnormal number of cognitive impairments (5 subjects) in injection chemotherapy and no abnormal numbers were found on hormonal therapy. In post-therapy III, we also found an abnormal number of cognitive impairment (8 subjects) in injection chemotherapy and no abnormal number on hormonal therapy. There was an increase in the number of cognitive impairment in breast cancer patients with injection chemotherapy II and III, 5 and 8 subjects, respectively. The number of cognitive function impairment before and after hormonal therapy did not increase (Table 4).

Table 4 The frequency of cognitive impairment before and after 9 weeks in injection chemotherapy and hormonal group

Cognitive impairment	Group			
	Injection chemotherapy		Hormonal	
	Yes (%)	No (%)	Yes (%)	No (%)
Pre	2 (10%)	18 (90%)	2 (10%)	18 (90%)
Post I	2 (10%)	18 (90%)	2 (10%)	18 (90%)
Post II	5 (25%)	15 (75%)	2 (10%)	18 (90%)
Post III	8 (40%)	12 (60%)	2 (10%)	18 (90%)

*Mann Whitney

Table 5 showed the insignificant association between a cognitive function with neuropathic pain in pre-chemotherapy (p <0.175; rho -0.219), the first chemotherapy (p <0.224; rho -0.196), and the second chemotherapy (p <0.103; rho -0.261). On the other hand, there was a significant association between cognitive function and neuropathic pain in the third chemotherapy (p <0.017; rho -0.377). There were also significant associations between cognitive function and neuropathic pain in the second chemotherapy (p <0.034; rho -0.336), in the third chemotherapy (p <0.006; rho -0.424). While there was an insignificant association between cognitive function and neuropathic pain in the first chemotherapy (p <0.05; rho -0.305). We can conclude that there was a significant association between cognitive function and neuropathic pain in the third chemotherapy (p <0.017; rho -0.377).

Discussion

The intrinsic risk factor for breast cancer in women is the age at first diagnosis. Breast cancer is most often found in menopausal women (> 45 years). The incidence of breast cancer increases significantly with age and peaks at menopausal age and then decreases with age.[11] A Polish study found a linear increase in a group of women aged 40 to 59 years, then the incidence rate persisted until around age 70, and decreased slightly after that.12 Epidemiological study in central Africa found the same demographic condition as the age group was predominantly 45-54 years old (29.53%) with a mean age of 45.83 ± 13.55 years, education level was dominated by a primary and secondary school.[13]

It is estimated that 13-70% of cancer patients who receive chemotherapy have measurable cognitive impairment.[3] Decreased cognitive function in breast cancer patients who received chemotherapy is appropriate with a study by Val Shilling et al., which showed a significant decrease in cognitive function compared to the control group (OR 2.25).[14] Cognitive disorders associated with cancer therapy commonly called chemotherapy-induced cognitive impairment or chemo brain.[15] The mechanisms underlying age-related cognitive decline overlap with cognitive decline due to cancer. These mechanisms include DNA damage, chronic inflammation, mitochondrial dysfunction, and oxidative stress. Most chemotherapy agents cause neuronal and

Table 5 The association between cognitive function score and neuropathic pain

Cognitive function – neuropathic pain	p	rho	Note
Pre Cemotherapy	0,175	-0,219	Not significant
Post Chemotherapy I	0,224	-0,196	Not significant
Post Chemotherapy II	0,103	-0,261	Not significant
Post Chemotherapy III	0,017	-0,377	Significant, negative, weak
pre – post chemotherapy I	0,056	-0,305	Not significant
pre – post chemotherapy II	0,034	-0,336	Significant, negative, weak
pre – post chemotherapy III	0,006	-0,424	Significant, negative, moderate

Note : Spearman correlation

non-neuronal mitochondrial damage, which increases the production of Reactive Oxygen Species (ROS) and thereby increases oxidative stress.[16] Studies have found evidence of oxidative DNA damage in peripheral blood lymphocytes after chemotherapy for breast cancer and increased numbers of mitochondrial DNA point mutations in patients with multiple diagnoses of cancer treated with chemotherapy with or without radiation therapy.[17] Therefore, the logical mechanism for chemotherapy-induced cognitive changes is DNA damage affecting the central nervous system.[18] Harrison et al. reported that decreasing capacity to repair mitochondrial DNA damage was associated with increased apoptosis in nerve cell cultures.[19]

The theory regarding the mechanism of chemotherapy-induced cognitive dysfunction can also be explained by some evidence supporting the idea that chemotherapy regimens cross the blood-brain barrier giving a direct neurotoxic effect that can lead to both grey and white matter atrophy. Standard chemotherapy agents, when administered in clinical doses, are more toxic to progenitor cells and oligodendrocytes in the central nervous system than cancer cells, leading to reduced death and cell division.[20] Brain atrophy and white matter damage have been observed after chemotherapy in patients with breast cancer. Longitudinal studies have shown a reduction in the volume of grey matter, especially in the bilateral frontal area and hippocampus in breast cancer patients after more than 20 years. The change in the volume of grey matter in total is equivalent to four additional years of aging.[21]

Cytokine neurotoxicity has been discovered during the early stages of cancer and triggered by chemotherapy. The chemotherapy agents used to stop cancer cell apoptosis through DNA damage can also affect normal cells.[21]

Aromatase plays a role in the conversion of adrenal androstenedione into estrone which is the main source of estradiol in postmenopausal women. Apart from adipose tissue, aromatase is also expressed in many areas of the brain, although little is known about its function and implications for cognitive function. The IBIS II and TEAM studies provided good evidence that there was no cognitive impairment effect of aromatase inhibitors when compared to placebo.[22]

Our study also showed that there was an effect of the amount of therapy on cognitive function, especially in patients who are given chemotherapy rather than hormonal therapy. Elevated levels of cytokines, DNA damage, or white matter damage can contribute to cognitive deficits and the risk of chemotherapy-induced neurotoxicity associated with exposure to higher doses, the additive and synergistic effects of multi-agent chemotherapy.[21]

This was in accordance with the study by Val Shilling et al. who concluded that chemotherapy could affect cognitive impairment, where the administration of relatively low chemotherapy giving the possibility that little or no cognitive impairment would be seen, whereas higher dose chemotherapy might cause more severe and persistent disturbances. In addition, the 'standard' regimen may have different effects on cognitive function; for example, it is important to investigate possible differences between six and eight cycles of the same chemotherapy combination.[14]

In addition, we did not find any abnormal number of cognitive impairments either after the first, second, or third hormonal therapy in breast cancer patients who received hormonal therapy. This was consistent with a study by Phillips et al., where there was no evidence that the administration of hormonal therapy (oral adjuvant) substantially affected the cognitive function of patients with breast cancer.[23] Van Dyk K et al. and Le Rhun E, et al. also found no significant difference in administration hormonal therapy or adverse effects on cognitive function.[24,25]

The limitations of this study are using the observational design and not analysing the drugs given to the subject because of the healthcare system limitations. In addition, our study did not consider comorbid factors such as anxiety and depression scale as suggested in previous studies.

Conclusion

There was an increase in cognitive impairment after the third injection of chemotherapy, a significant difference in the pre-post therapy III, and a correlation between cognitive dysfunction scores and neuropathic pain in breast cancer patients who received chemotherapy.

Conflict of Interest

The authors have no conflicts to disclose.

Funding

This study received no fund.

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