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THE CORRELATION OF DEPRESSION LEVELS WITH *CHEMOTHERAPY CYCLES* IN PATIENTS WITH BREAST CANCER

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ABSTRACT

Breast cancer is the most common cancer among women in worldwide, including Indonesia. Women with breast cancer are more vulnerable to psychological symptoms compared to the general population before or after treatment. Psychological symptoms such as depression, anxiety, and fatigue correlate with increasing pro-inflammatory mediators as the response to the malignancy process and also anti-cancer treatment. The psychological symptoms have an impaired on cognitive functions and the quality of life for cancer patients. The research aims to determine the depression prevalence and chemotherapy cycle correlation with the severity of depression in breast cancer patients. This cross-sectional study was conducted in patients at the Cut Meutia General Hospital, North Aceh. We chose 66 breast cancer patients undergoing chemotherapy using consecutive sampling. Data on patient characteristics including age, stage, chemotherapy cycles and drug regimen were obtained. The Depression Anxiety Stress Scales (DASS 42) was used to detect depression in each participant. Analysis of the data used Spearman Correlation test. The results showed that the characteristics of the sample were mostly aged 46–55 years, already in stage IV, undergoing cycle 2 or 3 chemotherapy, using an anthracycline-based regimen, and not yet depressed (normal). Correlation analysis showed a positive correlation (p 0.001) of moderate degree (r = 0.42) between chemotherapy cycles and degrees of depression. It can be concluded that increasing chemotherapy cycles tends to increase the severity of depression.

Keywords: Chemotherapy, psychological symptoms, cognitive functions, inflammatory responses, DASS 42

INTRODUCTION

Breast cancer is a malignancy in breast tissue that can originate from the ductal or lobular epithelium. Breast cancer mostly occurs in women, although in a small percentage of cases it can also occur in men. Breast cancer is the most common cancer in women worldwide.[1] Based on data from the Global Cancer Observatory (GCO) in 2020, breast cancer is the first cancer with 2.2 million new cases of breast cancer worldwide.[2] Breast cancer is the most common cancer in Indonesia until 2020, reaching 68,858 cases (16.6%) out of a total of 396,914 new cases of cancer in Indonesia. Meanwhile, mortality reached more than 22 thousand cases.[3]

Breast cancer therapy includes surgery, radiotherapy, chemotherapy, immunotherapy. One of the treatments for breast cancer is chemotherapy. Chemotherapy is a systemic therapy by administering cytostatic drugs to eliminate cancer cells. Chemotherapy aims to treat and reduce the mass of cancer cells, improve quality of life, and reduce cancer complications due to metastasis.[4,5]

The target of chemotherapy is not only limited to malignant tissue, but can also affect normal cells in the body so that it can cause various side effects.[6] The side effects of chemotherapy will appear differently depending on the type of drug used. Side effects experienced include gastrointestinal disorders in the form of nausea and vomiting, diarrhea, constipation, loss of appetite, alopecia, stomatitis, anemia, thrombocytopenia, neutropenia, as well as psychological side effects or emotional disorders.[7]

Changes in cognitive function are one of the side effects of systemic anticancer therapy. This effect is known as chemo brain-related cognitive impairment, chemofog, or chemotherapy. This disorder is characterized by decreased verbal and visual memory, working memory, concentration, language abilities, response time and motor skills. These chemo brain symptoms affect 17%-75% of cancer patients undergoing therapy. It is usually mild and temporary and improves with treatment. Increased cytokines such as interleukin 1 (IL-1), interleukin 2 (IL-2), or tumor necrosis factor alpha (TNF-α) are thought to be one of the etiological factors of depressive disorders.[8]

Generally, chemotherapy takes a long time, which is called a cycle. One cycle consists of a period of drug administration that varies between one and five days, followed by a rest period of three weeks. Chemotherapy can

be given for four to eight cycles.[9] There are differences in side effects that appear as the chemotherapy cycle increases. The higher the chemotherapy cycle, the more symptoms and side effects the patient will experience.[10]

Depression is a medical condition in the form of feelings of sadness that have a negative impact on a person's thoughts, actions, feelings and mental health. As many as 16% - 25% of cancer patients suffer from depression.[11] Women with breast cancer experience high levels of stress from the time they are diagnosed with cancer and throughout treatment. Stress experienced mentally and physically due to increased inflammatory responses both related to the malignant process and systemic anticancer treatment. [12] Patients who cannot adjust to their illness will experience anxiety and depression which will cause a decrease in their immune system and make their illness worse.[13] Depression in cancer patients is still not a concern so therapy only focuses on physical aspects. Many cases of depression are not identified because depression in cancer patients is considered a normal process.

The aim of this study is to determine the prevalence of depression and the correlation between chemotherapy cycles and the level of depression in breast cancer patients at the Cut Meutia General Hospital, North Aceh.

METHOD

A cross-sectional study was conducted at the Cut Meutia General Hospital, North Aceh. The approval and ethical clearance was obtained from the Faculty of Medicine of Universitas Malikussaleh (No:17/KEPK/FK/UNIMAL_RSUCM/2023). Sixty-six patients were enrolled in this study.We used a consecutive sampling method to select patients diagnosed with breast cancer patients. The inclusion criteria were breast cancer patients undergoing chemotherapy. Patients had medical records incomplete, who denied participation, those who were undergoing targeted therapy, and patients with metastatic cancer to the brain were excluded. Data patient characteristics (age, stage, chemotherapy cycles and drug regimen) were collected from medical records. Subject information remained completely confidential. The Depression Anxiety Stress Scales (DASS 42) was used to assess the depression levels of each participant. Scores 0-9, 10-13, 14-20, 21-27 and ≥ 28 represent normal, mild, moderate, severe and very severe anxiety, respectively

The data obtained were analyzed using computer statistical software. Each variable was calculated and represented as a number (percentages) in the table. Spearman Correlation test analysis was performed to determine if there was a significant correlation between chemotherapy cycles and depression level. The significance (p-value) was set at 0.05.

RESULT

Sixty-six patients were enrolled in this study. Of the total, 33 (50%) were women, with most of the age of the entire patients being 46-55 years. Among stage status, most of the patients had stage IV breast cancer (n = 23, 34.8%), had 2 and 3 Chemotherapy cycles about 22.7% (15), respectively.

The data showed that 62.1% (35) of the patients had anthracycline based regimen. About 42.2% (28) of the study participants had normal, 21.2% (14) mild anxiety, 22.7% (15) moderate anxiety, 9.1% (6) severe anxiety while only 4.5% (3) had very severe anxiety (Table 1).

Table 1. Characteristics of the study participants (n = 66)

Characteristics	N	Percentage
Age (year)		
26-35	1	1.5
36-45	13	19.7
46-55	33	50.0
56-65	19	28.8
Stage		
I	7	10.6
II	14	21.2
III	22	33.3
IV	23	34.8
Chemotherapy cycles		
1	6	9.1
2	15	22.7
3	15	22.7
4	10	15.2
5	10	15.2
6	10	15.2
Regimen		
Platinum-Based	25	37.9
Anthracycline-Based	41	62.1
Depression		
Normal	28	42.2
Mild	14	21.2
Moderate	15	22.7
Severe	6	9.1
Very severe	3	4.5

Table 2 summarized that there was a significant correlation between chemotherapy cycles and the level of depression in breast cancer patients (P =0.001; r=0.42)

Table 2. Correlation between chemotherapy cycles and depression

Variables	Mean±SD	r	*p*-value
chemotherapy cycles	3.4±1.56	0.42	0.001*
depression	12.7±7.32		

**Spearman Correlation test* (*P value* ≤ 0.05)

The results of the analysis showed that the correlation coefficient (r) value was 0.42, indicating a moderate strength of correlation between chemotherapy cycles and depression levels, with a positive correlation direction. This can be interpreted that the level of depression increases with increasing chemotherapy cycles.

DISCUSSION

This study showed that the age distribution of breast cancer patients increases with age. The highest prevalence is in the age range 46-55 years, but decreases at ages > 55 years.

This result was supported by Herawati (2021) that breast cancer patients were predominantly aged ≥40 years with an age range of 40-55 years. [14] The risk of breast cancer tends to increase with age. The prognosis for breast cancer patients between the ages of 50-59 is good, but it begins to decline after the age of 60 and is poor for those at the age of >70 and <40 years. Patients at age > 70 years have a poor prognosis. This can be related to comorbidities which increase with age. The poor prognosis is also found in women aged <40 years is associated with more aggressive types of breast cancer (such as triple negative) and higher recurrence rates.[15] The risk of breast cancer increases by 1.5% at age 40 years, 3% at age 50 years, and more than 4% at age 70 years. The accumulation of cellular changes results in a potential increase in cancer risk and accelerated carcinogenesis with age.[16]

In this study, most of the patients with breast cancer were in advanced stages (stages III and IV). Patients at similar stages are typically concentrated in low-income communities with limited access to healthcare services. The problem at hand can be due to several factors, including the absence of routine screening programs, insufficient information and awareness on early detection of breast cancer, and limited access to high-quality diagnostic and treatment facilities in health services.[17,18]

Our study revealed that about 42.2% (28) of the study participants had normal, 21.2% (14) mild anxiety, 22.7% (15) moderate anxiety, 9.1% (6) severe anxiety while only 4.5% (3) had very severe anxiety. This result is consistent with research on women undergoing cycles 2 and 3 of chemotherapy for breast cancer that reported that during cycle 2, 42.2% of women reported moderate to severe levels (severity 4–10) of depressed mood and 35.3% of women reported moderate to severe levels (severity 4–10) of depressed mood during cycle 3 at least one time.[19] Each patient experiences side effects to varying degrees during each cycle of chemotherapy. Symptoms and side effects usually worsen in patients as chemotherapy cycles progress.[10]

This study findings have shown a significant correlation between the level of depression increases with increasing chemotherapy cycles. These results show that the degree of depression increases as the patient undergoes more cycles of chemotherapy. The visual and spatial abilities, working memory, depressive symptoms, visual memory, verbal learning capacity, and language and memory function are significantly influenced in cancer survivors undergoing chemotherapy. In addition, 23% of women with breast cancer experienced cognitive decrease some time recently chemotherapy and expanded to 52% amid chemotherapy.[8]

Recent studies have found an important role for inflammatory processes activated by cancer or chemotherapy in cognitive impairment and behavioral changes. Cytokines influence the central nervous system, leading to cognitive changes. This effect arises from the interplay between neuroinflammation and neuroplasticity, particularly during neurogenesis, which is regulated by brain-derived neurotrophic factor (BDNF). Furthermore, neurotrophic factors have a significant impact on long-term potentiation, learning, and memory processes, and act as regulators of synaptic plasticity, neuronal survival, and neurogenesis. Brain-derived neurotrophic factor (BDNF) initiates numerous biological activities by interacting with the cell surface receptor tropomyosin kinase B (TrkB). The BDNF/TrkB signaling pathway serves as a regulator of carcinogenesis and metastasis. Additionally, overexpression of BDNF/TrkB is associated with poor clinical outcomes and prognosis in patients with breast cancer. Interestingly, changes in TrkB/BDNF levels exhibited an inverse relationship with depressive symptoms and sleep quality. Depressive symptoms and sleep quality are associated with typical levels of neuroplasticity and shifts in serum BDNF and TrkB caused by melatonin.[20]

Previous research has shown that the day after chemotherapy, cytokine levels increase significantly. Increased levels of cytokines such as interleukin 1 (IL-1), interleukin 2 (IL-2), and tumor necrosis factor alpha (TNF-α) accompany the development of mental impairment. This condition can be one of the causes of depression. These protein mediators can induce inflammation through oxidative and nitrosative mechanisms in the hippocampus and other areas rich in cytokine receptors.[8] In other research, Li et al reported that physiologically, levels of peripheral pro-inflammatory mediators are regulated through the hypothalamic–pituitary–adrenal (HPA) axis, which has a two-way and complex relationship with the immune system. The HPA axis can be suppressed by chemotherapy and radiotherapy during cancer treatment. This results in increased inflammation. Activation and disruption of the HPA axis (such as impaired cortisol activity, increased levels of cortisol and adrenocorticotropic hormone) during cancer treatment and modulation of levels of pro-inflammatory mediators result in individual differences in susceptibility to psychological symptoms. Regulation of peripheral inflammation by the HPA axis is influenced by both peripheral cortisol levels and the sensitivity of glucocorticoid receptors on immune cells.[12]

CONCLUSION

This study concluded a high prevalence of depression among breast cancer patients undergoing chemotherapy.in the Cut Meutia General Hospital, North Aceh, with a significant correlation of chemotherapy cycles with depression level. It is believed that the inflammatory pathway mechanism that becomes activated by chemotherapy and cancer influences behavioral changes and cognitive impairment. The screening for depression disorders among breast cancer patients undergoing chemotherapy should be considered for beginning the necessary referral or therapy.

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