

# Neuropathic and Activity Disorders in Breast Cancer Patients Receiving Chemotherapy

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# NEUROPATHIC PAIN AND ACTIVITY DISORDERS IN BREAST CANCER PATIENTS RECEIVING CHEMOTHERAPY

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**ABSTRACT Introduction:** Pain is one of the complaints from breast cancer patients who received chemotherapy. One of the side effects of chemotherapy to breast cancer patients is neuronal damage resulting in neuropathic pain. The increased incidence of neuropathic pain in chemotherapy patients often results in impaired activity. This study was conducted to determine the correlation between neuropathic pain and impaired daily activity before the first injection and after the third injection in breast cancer patients receiving chemotherapy. **Methods:** This was an observational analytic study with a prospective cohort design. The subjects were postoperative breast cancer patients who received chemotherapy at the Kasuari Ward, Dr. Kariadi Hospital, Semarang, who fulfilled the inclusion and exclusion criteria. It was conducted from September 2019 to February 2020. Examination of neuropathic pain and pain scoring was assessed using the LANSS questionnaire and Brief Pain Inventory (BPI). Data were analyzed using Spearman's bivariate correlation test. The results were significant if the p-value <0.05. **Results:** 23 breast cancer patients who received chemotherapy at the Kasuari Ward, Dr. Kariadi Hospital, Semarang participated in this study. The incidence of neuropathic pain increased after the third injection of chemotherapy. The correlation between pain score and activity disorder score before the first chemotherapy was significant ( $p = 0,000$ ;  $\rho = 0.697$ ) and after the third chemotherapy was also significant ( $p = 0.045$ ;  $\rho = 0.421$ ). In addition, there was a strong correlation between pain score and activity disorder score after third chemotherapy being controlled with age ( $p = 0.003$ ;  $\rho = 0.589$ ). **Conclusion:** There was an increased of neuropathic pain and activity disorder after the third injection of chemotherapy. There was a correlation between pain scores and activity disorder in breast cancer patients receiving chemotherapy.

**KEYWORDS** Breast cancer, neuropathic pain, chemotherapy, activity disorders

## Introduction

Breast cancer is a disease caused by the process of oncogenes from normal cells to cancer in the breast tissue. Breast cancer was estimated to cause 232,340 new cases and 39,620 deaths in 2013. Riset Kesehatan Dasar (Riskesdas) in 2013 placed breast cancer in second place in women in Indonesia [1,2]. According to The International Association for The Study of Pain (IASP 2011), neuropathic pain was a pain due to lesions or primary disorders of the nervous system. Previous studies estimated that the prevalence of neuropathic pain in cancer patients was

approximately 20%, increasing to 40% in patients with both nociceptive and neuropathic pain [3,4].

Pain in breast cancer can be caused by tumor invasion to the peripheral nerves or side effects of chemotherapy, radiotherapy, and / or surgery. Persistent Pain after Breast Cancer Surgery (PPBCS) present with symptoms of sharp pain, burning pain, paresthesia, hyperesthesia and numbness in patients after undergoing breast cancer surgery. About 20% - 50% of breast cancer patients had pain, increasing to 90% at the terminal stage. Pain in breast cancer patient was found in 39.3% of cases after curative treatment, 55.0% during cancer treatment, and 66.4% at an advanced stage [5,6].

Chemotherapy treatment is used as the modality for most cancers and associated with neuropathy and pain. They are persistent and difficult to treat even long after the cancer is in remission or recovery. This problem is exacerbated by increasing cancer survival rates. It is estimated that 40% of patients receiving chemotherapy experienced neuropathic pain. Signs and symptoms that describe neuropathic pain in patients receiving chemotherapy are burning (71%), tingling (66%), pins and

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needles feeling (63%), squeezing (63%), pressure (61%), electric shock (61%), stabbing (60%), and hypersensitive to touch sensations [6]. Therefore, the main objective of this study was to determine the presence of neuropathic pain and activity disorders in breast cancer patients receiving chemotherapy [5,7].

## 2 Methods

This was an observational analytic study using a prospective cohort study conducted at the Kasuari ward, dr. Kariadi Hospital, Semarang in September 2019. The samples were postoperative breast cancer patients who received three chemotherapy injections with an interval of 3 weeks and 9 weeks. The inclusion criteria were stage I or II breast cancer patients, postoperative partial mastectomy patients who will receive Taxane chemotherapy (Paclitaxel, Docetaxel) alone or in combination who sign the informed consent. Subjects with a history of malignancies other than breast cancer, diabetes mellitus, diabetic neuropathy, metastases, and history of neuropathy were excluded from this study. This research had received ethical clearance from the FK UNDIP / RSDK Research Ethics commission with number 302 / EC / KEPK-RSDK / 2019.

Subjects included in the inclusion criteria were asked for proof of consent in writing by putting a signature on the informed consent sheet. Before the patient received the injection, the subjects were interviewed and examined the pain scale using the LANSS questionnaire and the Brief Pain Inventory (BPI). The pain scale was examined using LANSS to assess neuropathic pain, and the Brief Pain Inventory (BPI) assessed the severity of pain felt by subjects with a pain score of 1-10 and activity disturbances with a score of 1-10. The study was conducted for nine weeks per patient with an evaluation every three weeks after injection. The injections consisted of the first to the third injection.

Spearman's bivariate correlation analysis was used to determine the relationship between pain scores and activity disorder in breast cancer patients receiving chemotherapy. The p-value was considered significant if less than 0.05. A partial correlation test was carried out to see the effect of the age factor on the pain score and activity disorder.

## 2 Results

At the end of the study, 23 subjects met the inclusion and exclusion criteria. The mean age of subjects was  $48.91 \pm 11.41$  years (Table 1). The oldest age was 70 years while the youngest was 25 years. There was an increase in the mean score of pain and activity disorder from pre-chemotherapy to the third chemotherapy. The enhancement of pain score and activity disorder was relatively high in the first chemotherapy and relatively low in the second chemotherapy.

Before getting chemotherapy, there was only 1 (4.4%) subject who experienced neuropathic pain, but after chemotherapy, there were 21 (91.3%) subjects (Table 2). It indicates that chemotherapy increased subjects who experienced neuropathic pain.

In this study, there was an increase in the number of neuropathic pain in subjects who had undergone the third chemotherapy, namely an increase in the number of subjects experiencing neuropathic pain after the third chemotherapy by 21 cases compared to 1 case before chemotherapy (Table 2).

Figure 1 illustrated the pain score (blue line) and activity disorder (red line) of the subjects using the BPI questionnaire,

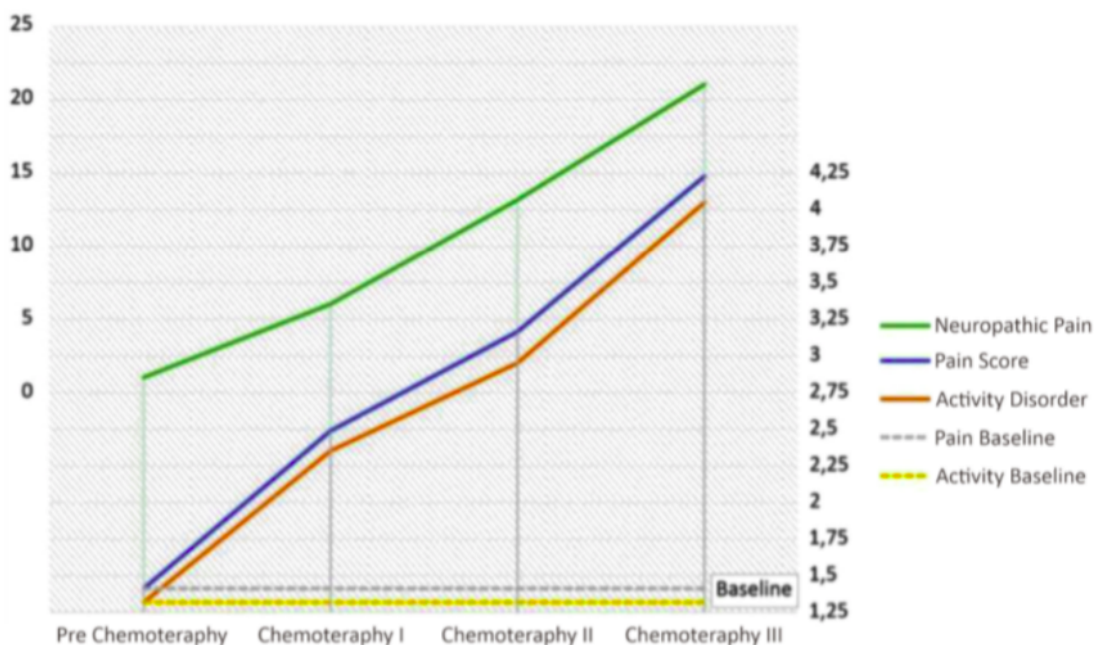
**Table 1** The characteristics of subjects

Breast cancer case			
	Mean	Neuropathic pain frequency (n)	Not neuropathic pain frequency (n)
Age	48.91 ± 11.41		
Pre Chemotherapy			
Pain score	1.4126	1	22
Activity disorder score	1.3184	1	22
Chemotherapy I			
Pain score	2.4891	6	17
Activity disorder score	2.3526	6	17
Chemotherapy II			
Pain score	3.1659	13	10
Activity disorder score	2.9521	13	10
Chemotherapy III			
Pain score	4.2282	21	2
Activity disorder score	4.05	21	2

**Table 2** Incidence of neuropathic pain pre-chemotherapy and after the third chemotherapy

Chemotherapy	Neuropathic pain (%)	Not neuropathic pain (%)
Pre Chemotherapy	1 (4.4%)	22 (95.6%)
Chemotherapy I	6 (26.1%)	17 (73.9%)
Chemotherapy II	13 (56.5%)	10 (43.5%)
Chemotherapy III	21 (91.3%)	2 (8.7%)

**Figure 1. Graph of changes in neuropathic pain and activity disorder pre-chemotherapy and after the third chemotherapy**



which showed an increasing trend from pre-chemotherapy to the third chemotherapy. Neuropathic pain (green line) using the LANSS questionnaire showed the same growing trend for pain score and activity disorder from pre-chemotherapy to the third chemotherapy.

Table 3 showed a significant relationship between pain score and activity disorder from pre-chemotherapy to the third chemotherapy. A very strong relationship was found in the first chemotherapy and reduced to sufficient on the third chemotherapy, which was influenced by anxiety and depression of the subjects. Table 4 showed that the relationship between pain and activity disorder became significantly stronger ( $\rho: 0.421$  to  $\rho: 0.598$ ) after the third chemotherapy after controlling the age.

### Discussion

Our study found an increase in the mean score of pain and activity disorder from pre-chemotherapy to the third chemotherapy. The enhancement of pain score and activity disorder was relatively high for the first chemotherapy and relatively low at the second chemotherapy. Study of Ventzel, et al. which evaluated 100 subjects who received taxane as chemotherapy, found 76 subjects experienced anxiety and depression on the first chemotherapy and 66 subjects on the second chemotherapy which effected the high pain scores and activity disorder. Neuropathic pain also increased from pre-chemotherapy to the third chemotherapy [8].

The increasing number of subjects who experienced neuropathic pain on chemotherapy was appropriate with the study of Velasco et al on 60 subjects who received chemotherapy. The sub-

**Table 3** Relationship between pain score and activity disorder

Pain score – Activity disorder	p	rho	Note
Pre-chemotherapy	0.000	0.697	Significant, strong
Chemotherapy I	0.000	0.841	Significant, very strong
Chemotherapy II	0.000	0.679	Significant, strong
Chemotherapy III	0.045	0.421	Significant, sufficient

**Table 4** The relationship between pain score and activity disorder with controlling the age after the third chemotherapy

Control	Variable	p	rho	Note
Before controlling	Pain score – activity disorder of the third chemotherapy	0.045	0.421	Significant, sufficient
After controlling the age	Pain score – activity disorder of the third chemotherapy	0.003	0.598	Significant, strong

jects who experienced neuropathic pain from the results of high serum levels of Nerve Growth Factor in the third and fourth chemotherapy increased due to the effects of drug buildup chemotherapy, causing nerve damage [9].

The increasing rate of neuropathic pain in subjects who had undergone the third chemotherapy was appropriate with a study by Perez et al. in cross-sectional design on 352 subjects who received chemotherapy using LANSS. Subjects with neuropathic pain were 29.5% [10]. Whereas, the study of Cielito, et al. which assessed neuropathic pain using the National Cancer Institute Common Toxicity Criteria, as much as 240 (27%) subjects experienced neuropathic pain after chemotherapy [11]. The study of Ulas, et al. on 156 subjects using the Dolour neuropathic 4 test reported that the percentage of subjects with neuropathic pain after undergoing chemotherapy was 79% [12]. Our study was also supported by the study of Ian et al. on 295 subjects who experienced neuropathic pain. The increasing of activity disorder, evaluated using the Brief Pain Inventory, was found in all subjects [13]. Another study by Neris, et al. using the Brief Pain Inventory to assess 17 women with breast cancer who underwent chemotherapy found an increase in pain scores with a pre-chemotherapy mean score was 1.88 and the third chemotherapy was 3.59 [14]. Study of Tegegn, et al. in Ethiopia on 83 subjects of breast cancer patients also found disruption of activity in 68 (89.2%) subjects, of which 61 (73.5%) subjects received chemotherapy [15]. A study by Ganesh, et al. on breast cancer patients who received taxane chemotherapy using the Brief Pain Inventory, showed an increase in the mean score of activity disorders. The mean score before chemotherapy was 0.53, and after the third chemotherapy was 1.74 [16].

The relationship between pain scores and activity disorder of this study was in accordance with the previous research by Neris et al. which evaluated each stage of chemotherapy with taxane and found a significant relationship between the level of pain and activity disorders in the first, second, and third chemotherapy ( $p < 0, 05$ ) [14]. Study of Ventzel, et al. which evaluated chemotherapy subjects using taxane found that anxiety and depression were high after the first chemotherapy and decreased after the next chemotherapy, affecting changes in pain scores and activity disturbances ( $p < 0.05$ ) [8].

Pain and activity disorder were influenced by chemotherapy

but not by age. Our results were in accordance with Watters et al., who conducted a study on breast cancer patients who received chemotherapy by evaluating the disturbance of daily activities. The activities were disturbed, but there was no difference between young and old subjects ( $p < 0.01$ ) [17]. Wong et al., who studied breast cancer patients who received chemotherapy, stated that there was no difference in the incidence of pain between old and young age ( $p > 0.05$ ) [18].

This study has several limitations. First, it did not analyze the depression and anxiety scales. Second, it used taxane for chemotherapy, which was still combined with other drug classes, even though they had almost the same combination. In addition, we also did not analyze the drugs given to subjects due to the national healthcare system restrictions. Our study has not yet classified other comorbid factors apart from diabetes, as well as other predictors that can influence the improvement of pain scores such as education and performance status as suggested in previous studies.

## Conclusion

There was an increase in neuropathic pain score and activity disorder before the first injection and after the third injection of chemotherapy. There was an association between pain scores and activity disorder before the first injection and after the third injection in breast cancer patients who received chemotherapy. There was no effect of age on pain scores and activity disorder in them.

Further studies are needed to analyze anxiety and depression scales in subjects receiving chemotherapy. In addition, studies need to be carried out by considering several predictor factors and other comorbidities that can affect the increase in the degree of pain such as education, performance status, and history of comorbidities besides diabetes. We recommend providing additional painkillers to reduce pain felt by breast cancer patients receiving chemotherapy.

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## Conflict of interest

The authors declared that this project was done independently without any conflict of interest.

## References

- De Jong W, Sjamsuhidajat R. Buku Ajar Ilmu Bedah. Edisi 4. Jakarta : EGC. 2017.p.211-237
- Kementrian Kesehatan Republik Indonesia . Laporan Hasil Riset Kesehatan Dasar (Riskesdas) Indonesia. 2013
- Reyes G, Morrow P, Bennet M, Jansen M, Sette S. Neuropathic Pain in Breast Cancer Survivors: Using the ID Pain as a Screening Tool. Washington:J Pain Symptom Manage. 2010; 39(5):882–889
- Raffa R, Langford R, Pergolizzi J, Porreca F, Tallarida R. Chemotherapy-Induced Neuropathic Pain. CRC Press. Taylor & Francis Group. 2013.p.113-135

5. Costa W, Monteiro M. Pain and quality of life in breast cancer patients. *Universidade Federal do Rio Grande do Norte. Clinics.* 2017; 72(12):758-76
6. Stark A, Carter SM, Kesmann J, Rea W. A Potential Role Of Chronic Exposure To Extremely Low-Frequency Electromagnetic Fields In Triggering Persistent Pain Post Breast Cancer Surgery: A Review. *International Journal of Surgery and Medicine.*
7. Cindy T. Patient Perceptions Associated With Chemotherapy-Induced Peripheral Neuropathy. *Clinical Journal of Oncology Nursing.* 2010; 4(3):22-8
8. Ventzel L, Anders B J, Anni R J, Troels S J, Nanna B. Chemotherapy-induced pain and neuropathy: a prospective study in patients treated with adjuvant oxaliplatin or docetaxel. *PAIN.* 2016;157(3):560-568
9. Velasco R, Xavier N, Miguel G, Mireia H, Aina C, Jordi B. Neuropathic Pain and Nerve Growth Factor in Chemotherapy-Induced Peripheral Neuropathy: Prospective Clinical-Pathological Study. *Journal of Pain and Symptom Management.* Elsevier Inc
10. Pérez C, Sánchez-Martínez N, Ballesteros A, Blanco T, Colazo A, González F, et al. Prevalence of pain and relative diagnostic performance of screening tools for neuropathic pain in cancer patients: A cross-sectional study. *United Kingdom : Eur J Pain.* 2015;19(6):752-61.
11. Cielito C, Phuong K, Aman B, Sanjay S. Chemotherapy-induced peripheral neuropathy as a predictor of neuropathic pain in breast cancer patients previously treated with paclitaxel. *J Pain.* 2009; 10(11): 1146-1150
12. Ulas S, Eyigor S, Caramat I. Quality of life and neuropathic pain in hospitalized cancer patients: A comparative analysis of patients in palliative care wards versus those in general wards. *Indian J Palliat Care.* 2018; 24(3): 325-333
13. Ian K, Markay H, Cappeleri J, Alesia S, King K, Liebert L et al. characteristics of patients with neuropathic pain syndromes screened by the painDeTecT questionnaire and diagnosed by physician exam. *New York: Journal of Pain Research.* 2019;12:255-268
14. Neris RR, Magnabosco P, Do Amaral PA, Ribeiro MÁ, Dos Anjos ACY. Pain induction by chemotherapy medication docetaxel in women with breast cancer. *ACTA Paul Enferm.* 2016;29(4):397-404.
15. Tegegn HG, Gebreyohannes EA. Cancer Pain Management and Pain Interference with Daily Functioning among Cancer Patients in Gondar University Hospital. *Pain Res Manag.* 2017; 5698640
16. Ganesh V, Drost L, Chiu N, Zhang L, Chiu L, Chow R, et al. Symptom clusters using the brief pain inventory in patients with breast cancer. *Ann Palliat Med.* 2017;6(2):170-172
17. Watters JM, Yau JC, O'Rourke K, Tomiak E, Gertler S. Functional status is well maintained in older women during adjuvant chemotherapy for breast cancer. *Annals of Oncology.* 2003; 14(2): 1744-1750
18. Wong ML, Bruce AC, Steven MP, Gary A, Kimberly T, Kord MK, Margaret AC, et al. Age-related differences in patient-reported and objective measures of chemotherapy-induced peripheral neuropathy among cancer survivors. *Supportive Care in Cancer.* 2019; 27(10):3905-3912

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