SRIWIJAYA JOURNAL OF MEDICINE

NEOADJUVAN CHEMOTHERAPY RESPONSE TO LOCAL ADVANCED BREAST CANCER PATIENTS AT DR MOHAMMAD HOESIN HOSPITAL PALEMBANG

Aldo Giovanno[1], Mgs. Irsan Saleh[2]. Nur Qodir[3], Mulawan Umar[4]

[1]General Doctor Education Study Program, Faculty of Medicine, Sriwijaya University, Palembang, Indonesia
[2]Department of Pharmacology, Faculty of Medicine, Sriwijaya University, Palembang, 30126, Indonesia
[3]Department of Surgical Oncology, Mohammad Hoesin Hospital, Palembang, 30126, Indonesia
[3]Department of Surgical Oncology, Mohammad Hoesin Hospital, Palembang, 30126, Indonesia

Email: giovansalv@gmail.com

Abstract

Breast cancer is a malignancy which invaded breast tissue in the form of ductal or lobular. One most therapy which is given is neoadjuvant chemotherapy. Neoadjuvant Chemotherapy can reduce tumor size so that surgery can be performed with good breast removal with Modification of Radical Mastectomy (MRM) and Breast Conservative Therapy (BCT). This purpose from this research is to find out neoadjuvant chemotherapy response in Locally Advanced Breast Cancer Patients which has received chemotherapy treatment in RSUP dr Mohammad Hoesin Palembang. This observational descriptive study was conducted at RSUP Mohammad Hoesin Palembang in the period between October until November 2019. The sample of this study was locally advanced breast Cancer patients who underwent chemotherapy that met the inclusion and exclusion criteria. The data were obtained by interviews and observed medical records from the patients which were then analyzed by univariate analysis using SPSS version 25. In this study there were 34 locally advanced breast cancer patients who fulfilled the inclusion and exclusion criteria. 24 of 34 patients (70,6%) received positive response and 10 of 34 patients (29,4%) received negative response.

Keyword: Breast Cancer, Chemotherapy Response, Neoadjuvant Chemotherapy.

1. Introduction

Breast cancer is a malignancy that attacks the ductal and lobular breast tissue, breast cancer accounts for the highest incidence of cancer of all types of cancer (2.089.000 cases in 2018) and with a death rate of 627.000 people in 2018, based on data from the Indonesian Ministry of Health In 2018, the incidence of breast cancer in Indonesia ranks first of all cancer incidence in women, with an incidence of 42 / 100.000 women with a mortality rate of 17 / 100.000 / year, 50% of whom are in an advanced stage[15].

One of the treatments given to breast cancer patients is chemotherapy. Chemotherapy based on its function is divided into several types such as adjuvant, neoadjuvant and palliative[31].

Neoadjuvant chemotherapy is a therapy that is given before surgery that aims to reduce the size of a tumor that is initially non-operable to operable so that breast removal surgery can be performed using both *Modified Radical Mastectomy (MRM) and Breast Conservative Surgery (BCS).*

Neoadjuvant chemotherapy is given mainly to patients with locally advanced breast cancer who have the following characteristics: (1) the presence of cancer cell infiltration into lymph nodes and blood vessels, (2) tumor size that exceeds 4 cm, therefore it is necessary given neoadjuvant chemotherapy which aims to reduce the size of the tumor and stop the process of infiltration of cancer cells to the nearest lymph nodes so that the surgical removal of the breast can be done optimally[31]

Based on the research of Salem (2017), it was found that of the 49 patients who received neoadjuvant chemotherapy, about 87.5% of the total patients gave responses that were assessed based on RECIST criteria: 5 patients (9%) received complete responses, 44 patients (78.5%) received partial response, 6 patients (10.7%) got stabled disease and 1 patient (1.8%) got progressive disease28 and whereas based on Khotimah's research (2011) that of 37 patients treated with neoadjuvant chemotherapy who initially had an inoperable status after being given chemotherapy neoadjuvant about 28 of 37 patients (75.6%) changed to operable[14].

Given the importance of giving neoadjuvant chemotherapy so that the operation can run optimally, data is needed on the response of giving neoadjuvant chemotherapy to local advanced breast cancer patients, especially at Dr. Mohammad Hoesin General Hospital, which is currently unknown, therefore it is necessary to assess the response of neoadjuvant chemotherapy in locally advanced breast cancer patients in RSUP Dr. Mohammad Hoesin Palembang. Based on the above considerations, the researcher is interested in conducting this research

2. Method

The research was conducted by using an observational descriptive method. The research was conducted for three months, from September to November 2019.

The research was conducted at the dr. Mohammad Hoesin Palembang. The study sample was local advanced breast cancer patients undergoing neoadjuvant chemotherapy. Samples were taken using *consecutive sampling techniques*, where samples were selected sequentially, the order of collection was in accordance with the accessibility of the sample data to reach the total number of samples. The sample required is as much as 31 data and to prevent *drop-out* is added by 10% to 34 data

The data collected by interview and filling out a questionnaire. Then analyzed using the IBM SPSS® (Statistical Package for Social Science) application. Univariate analysis is an analysis carried out by analyzing each variable from the research results. Univariate analysis was performed to summarize the measurement data and obtain the distribution and percentage of each variable under study.

3. Results

Data were collected from October to November 2019 on breast cancer patients undergoing neoadjuvant chemotherapy treatment at the Surgical Section of dr.

Mohammad Hoesin Palembang used primary data in the form of a questionnaire conducted with interviews and patient medical records.

From the data collected, it was found that breast cancer patients undergoing chemotherapy treatment at dr. Mohammad Hoesin Palembang who met the inclusion criteria and those who did not belong to the exclusion criteria totaled 34 people.

3.1. Characteristics of Breast Cancer Patients by Age

Of 34 breast cancer patients who came to undergo neoadjuvant chemotherapy at RSUP Dr. Mohammad Hoesin Palembang, it was found that the age group of patients aged ≥ 40 was more than those aged <40 years, namely 26 people (73.5%).

3.2. Characteristics of Clinical Stage of Breast Cancer Patients

The results of data processing showed that out of 34 breast cancer patients undergoing neoadjuvant chemotherapy, the majority of patients who came were patients with stage IIIB cancer, namely 27 people (79.4%), followed by stage IIIC as many as 5 people (14.7%), and the least number found was stage IIIA, namely 2 people (5.9%).

3.3. Characteristics of the type of chemotherapy regimen

Based on the type of neoadjuvant chemotherapy regimen given to 34 breast cancer patients undergoing treatment, the most widely used regimen was tax-based, namely 21 people (61.8%), followed by a combination of taxane and anthracycline-based chemotherapy regimens of 12 people (35 , 3%), and the lowest was an anthracycline-based regimen, that was 1 person (2.9%).

3.4. Characteristics of types of molecular subtypes

Based on the types of molecular subtypes found in 34 breast cancer patients who underwent treatment, the most frequently found subtypes were Luminal B subtypes with 18 people (52.9%), followed by Luminal A subtypes as many as 10 people (29.4%) and rare subtypes. which was found was a Triple Negative of 1 person (2.9%)

3.5 Characteristics of patient status before and after administration of neoadjuvant chemotherapy

Based on the patient status, there were 34 patients who underwent neoadjuvant chemotherapy who initially had non-operable status after undergoing neoadjuvant chemotherapy, 24 respondents (70.6%) became operable, and 10 respondents (29.4%) were still non-operable

3.6 Response Characteristics of Neoadjuvant Chemotherapy

Based on the response to neoadjuvant chemotherapy, 24 patients (70.6%) received a positive response, namely a condition where the patient underwent neoadjuvant chemotherapy no more than 4 times and underwent breast removal surgery and 10 patients (29.4%) received a negative response, namely a condition where Patients who underwent neoadjuvant chemotherapy more than 4 times and had not undergone surgery, based on the percentage of success of the neoadjuvant chemotherapy regimen, the combination-based regimen (Taxane and Anthracycline) produced the highest success rate with a value of 75%

Table 1. Distribution of breast cancer patients by age

Age	N	%
≥ 40 years	25	73.5 %
< 40 years	9	26.5 %
Total	34	100 %

Table 2. Patient Frequency Distribution by Clinical Stage

Clinical Stage	N	%
III A	2	5.9 %
III B	27	79.4 %
III C	5	14.7 %
Total	34	100 %

Table 3. Patient Frequency Distribution by Type of Chemotherapy Regimen

Type of Chemotherapy Regimen	N	%
Anthracyclines (FAC)	1	2.9 %
Taxan (TC)	21	61.8 %
The combination of the two (TAC)	12	35.3 %
Total	34	100 %

Table 4. Patient Frequency Distribution by Molecular Subtype

Type of Chemotherapy Regimen	N	%
HER2	1	2.9 %
Luminal A.	21	61.8 %
Luminal B	12	35.3 %
Triple Negative		
Total	34	100 %

.Table 5. Distribution of Patients by Clinical Status

Change in Patient Status	Before Neoadj		After Neoadj	
	N	%	N	%
Operable.	0	0	24	70.6 %
Non Operable	34	100%	10	29.4 %
Total	34	100%	34	100 %

Table 6. Distribution of Patients Based on Response to Neoadjuvant Chemotherapy

Types of Chemotherapy Regimens	Positive Response		Negative Response	
	N	%	N	%
Anthracyclines (FAC).	0	0	1	100 %
Taxan (TC)	15	71.4 %	6	28.6 %
The combination of the two (TAC)	9	75%	3	25 %

4. Discussion

The results showed that there were sociodemographic variations based on age groups, with 25 respondents (73.5%) over 40 years old, and 9 respondents (26.5%) under 40 years old. This is in line with the research by Shah (2014) that the incidence of breast cancer increases with age, patients over 40 years of age are at risk of developing breast cancer 9 times (1 in 26 women) compared to those under 40 years (1 in 202 women)[28], Diahprad's research (2018) also found that the incidence of breast cancer was most often found in women over 40 years of age by 86% (442 of 514 people), while those under 40 years of age were 14% (72 of 514 people)[7]. This shows that breast cancer is more often found in respondents aged 40 years and over in this study according to this study, this is due to hormonal involvement where women aged 40 years and over will mostly use family planning so that it will produce the hormone estrogen, this estrogen hormone later it will cause the proliferation of breast cells which will later become cancer cells.

The results regarding the most clinical stage found in dr Mohammad Hoesin General Hospital in this study were stage IIIB of 79.4% (27 respondents), followed by stage IIIC of 14.7% (5 respondents), this is in line with Purnamasari (2015) research who also found the highest prevalence of the clinical stage in Dr. Wahidin Sudirohusodo General Hospital, stage IIIB, amounting to 55.24%[25] this is due to

the low concern of patients to screen or early detection of breast cancer, which causes new breast cancer to be detected at an advanced stage which will worsen patient prognosis. Puspandari's research (2014) explains that the high incidence of breast cancer detected at an advanced stage is due to the patient's lack of education and knowledge about the early signs and symptoms of breast cancer and also the patient's low educational history26. This is in accordance with this study which found that the prevalence of the most frequent clinical stage in RSUP Dr. Mohammad Hoesin Palembang is stage IIIB, the number of incidents of stage IIIB found at RSUP Dr. early symptoms of breast cancer, so most of them come for treatment at an advanced stage. The level of knowledge of respondents is very important in detecting breast cancer as early as possible through self-examination such as BSE so that cancer can be treated early so that the prognosis will be better.

Based on the selection of drug regimens used in neoadjuvant chemotherapy in breast cancer patients at RSUP Dr. Mohammad Hoesin Palembang, 61.8% (21 respondents) used a taxane-based regimen (*Docetaxel + Cyclophosphamide*), followed by the use of the TAC regimen (*Docetaxel + Doxorubicin + Cyclophosphamide*) by 35.3% (12 respondents). The same thing was also found in Chakravarthy's (2014) study where the Taksan-based regimen was most widely used. Taksan is a drug derived from brevifolia which is proven to have antitumor activity in the rodent cell line, this drug stabilizes microtubules through tubulin heterodimer bonds. The use of the Taxan class can reduce the tumor size of inoperable patients to operable by 89% so that patients can undergo surgery properly with MRM Modified Radical Mastectomy) or BCS (Breast Conservative Surgery), this makes the Taksan group very often used in neoadjuvant therapy carried out before surgery considering the good pathological response rate, while the Anthracycline group is a class of antibiotics that have cytotoxic properties, the way Anthracyclines work, namely by inhibiting the Topoisomerase II enzyme so that the transcription and DNA replication processes are disrupted, however, the use of the Anthracycline group needs to be considered because of its high level of toxicity, the long-term use of the Anthracycline group will decrease. Increase the risk of cardiomyopathy[14]. The prevalence of using the most common Taxan-based regimen (*Docetaxel + Cyclophosphamide*) in Dr. Mohammad Hoesin's General Hospital is because the Taksan group produces high pathological response rates and has become the Drugs of Choice for neoadjuvant chemotherapy worldwide and the gold standard of neoadjuvant chemotherapy[14]

Based on the molecular subtype, it was found that the most subtypes were *Luminal B* at 52.9% (18 respondents) followed by *Luminal* A at 29.4% (10 respondents). This is in line with Diahprad's research (2018) which states that the prevalence of the most molecular subtypes of breast cancer patients in Sanglah Hospital Bali is Luminal B, amounting to 43.1% 7, Hasmi (2018) also found that the prevalence of Luminal B subtype contributed 69% (845 out of 1224 respondents) of the total breast cancer cases recorded in Karachi Pakistan followed by *Luminal A* by 31% (379 out of 1224 respondents). The highest prevalence of Luminal B was also found in Italy with a frequency of 36% and followed by Luminal A at 34% of the total incidence of breast cancer found in Italy[11]. The prevalence of *Luminal B* subtype is the most common found in breast cancer patients at RSUP Dr. Mohammad Hoesin Palembang because Indonesia is located in Asia, the prevalence of *Luminal A and Luminal B* subtypes is still the highest found in Asia and Africa. The Luminal B subtype has hormonal characteristics such as the expression of Estrogen Receptor (ER) with or without Progesterone Receptor (PR) expression with positive Human Epidermal Receptor (HER2-neu) involvement and the presence of high grade KI-67 gene expression (Rachmawati, 2018)[2]

Based on the status of patients who received neoadjuvant therapy, out of 34

respondents who initially had a non-operable status after being given neoadjuvant therapy, it was found that 70.6% (24 respondents) became operable and about 29.4% (10 respondents) were still non-operable. This is in accordance with the research of Salem (2017) which states that giving neoadjuvant chemotherapy will reduce tumor size from non-operable to operable. Of the 56 patients treated with neoadjuvant chemotherapy, 49 respondents (87.5%) became operable[28]. Giving neoadjuvant chemotherapy can reduce tumor staging so that patients can undergo primary therapy in the form of surgery both MRM (Modified Radical Mastectomy) and BCS (Breast Conservative Surgery), Giving neoadjuvant chemotherapy can also control tumor metastasis microscopically in local advanced breast cancer where this metastasis It is very difficult to detect, and makes tumors that can be palpable initially become non-palpable which indicates a reduction in tumor size, but many factors can cause breast cancer recurrence such as the involvement of HER2 (Human Epidermal Growth Factor Receptor 2)

Based on the response of giving neoadjuvant chemotherapy to breast cancer patients at Dr Mohammad Hoesin General Hospital, Palembang, 70.6% (24 respondents) received a positive response and a negative response of 29.4% (10 of 34 respondents) with the largest percentage of success who received a positive response 75% (9 of 12 respondents) used a combination-based regimen (TAC) followed by a Taxane-based regimen (TC) of 71.4% (15 of 21 respondents). Research conducted by (Salem, 2017) that out of 49 out of 56 received responses in the form of a complete response *(Complete Response)* and partial response (*Partial Response*), this shows that most patients treated with neoadjuvant chemotherapy received a response, which means that there was a reduction the size of a tumor after receiving neoadjuvant chemotherapy so that surgery can be performed. According to Costa (2016), there are 791 out of 907 patients who received a very effective combination-based regimen (TAC), 791 patients who were treated became operable after being given a combination-based regimen[2]. According to Gradishar (1997) that the use of a Taxane-based regimen will provide a clinical response value of 78% of a total of 43 patients who receive Taxane[2]-based therapy, whereas according to Minckwitz (1999) states that the use of a taxane-based regimen combined with the Anthracycline group will produce a clinical response value that is very satisfying, which is 93% 2, and also the use of taxa combined by anthracyclines will produce benefits such as (1) Increasing the *Free Disease Survival rate* (2) Reducing the locoregional recurrence rate and (3) Increasing the likelihood of obtaining a complete response (Pathak) M, 2018)[23].

According to (Johanna, 2003) another factor that influences the success of neoadjuvant chemotherapy response is the involvement of hormonal status expressions such as the involvement of *Estrogen Receptor (ER) and Progesterone Receptor (PR)* gene expression which affects the recurrence rate of a tumor, the involvement of Ki-67 expression which affects on the rate of tumor proliferation, the expression of the protein Human Epidermal Growth Factor Receptor-2 (HER2-neu)[12], Therefore, the involvement of the expression of hormonal status is very influential in determining the response to the success of giving neoadjuvant chemotherapy, so it must be specifically managed by giving hormonal therapy such as Tamoxifen. Neoadjuvant chemotherapy combined with hormonal therapy will result in a better pathological response rate than without hormonal therapy. In addition, the correct regimen is very important in determining the successful response of neoadjuvant chemotherapy. Other determining factors such as patient age and clinical history of the patient will play a role in determining the patient's prognosis in undergoing neoadjuvant therapy.

5. Conclusion

Based on the response to neoadjuvant chemotherapy, there was a positive response (70.6%) and a negative response (29.4%).

Based on the use of the most common regimen was the taxa based regimen (TC) (61.8%)

Based on the most clinical stage is stage IIIB (79.4%)

Based on the most subtypes is Luminal B (52.9%)

Based on patient status, approximately (70.6%) patients became operable after receiving neoadjuvant chemotherapy

Based on socio demographic, most people are over 40 years old (73.5%).

Based on clinical status, the largest stage was stage IIIB (79.4%).

Based on the percentage of success rate of the regimen, the regimen that gave a lot of positive responses was combination-based (TAC) of 75%.

REFERENCES

1. Anjasari, D., Sumarny, R., Uun, W., Kunci, K., Breast, K., & Soebroto, G. (2017). Evaluation of the Use of Chemotherapy Drugs in Breast Cancer Patients in Gatot Soebroto Hospital Period January-December 2015 Evaluation of Use of Chemotherapy Drug on Breast Cancer Patients in Hospital Gatot Soebroto January Period-December 2015. Social Clinical Pharmacy Indonesia Journal, 2 (2), 2502–8413. (http://journal.uta45jakarta.ac.id/index.php/SCPIJ/article/view/987 accessed on 10 June 2019)
2. Amat, S., P Bougnox., F Penault-Llorca. (2003). Neoadjuvant Docetaxel For Operable Breast Cancer Induces a High Pathological Response and Breast Conservation Rate. British Journal of Cancer 88, 1339-1345. (Https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2741049 , accessed on 21 November 2019)
3. Arnaout, A., Lee, J., Gelmon, K., Poirier, B., Lu, F. I., Akra, M.,… Grenier, D. (2018). Neoadjuvant therapy for breast cancer: Updates and proceedings from the seventh annual meeting of the canadian consortium for locally advanced breast cancer. Current Oncology, 25 (5), 1–9. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6209552/ , accessed on 14 June 2019)
4. Badve, S. S., Beitsch, P. D., Bose, S., Byrd, D. R., Chen, V. W., Mayer, I. A.,… Winchester, D. J. (2017). 8th AJCC breast cancer staging. (https://cancerstaging.org/references-tools/deskreferences/Documents/AJCC%20Breast%20Cancer%20Staging%20System.pdf , accessed June 20, 2019)
5. Clarke, M., Collins, R., Davies, C., Godwin, J., Gray, R., & Peto, R. (1998). Polychemotherapy for early breast cancer: An overview of the randomized trials. Lancet, 352 (9132), 930–942 (https://www.ncbi.nlm.nih.gov/pubmed/9752815, accessed June 13, 2019)
6. Del Mastro, L. (2003). M.H. Torosian (ed). Breast Cancer: a Guide to Detection and Multidisciplinary Therapy. Annals of Oncology.
7. Diahpradnya, Putu, Wayan Niryana, Putu Anda T.A. (2018) Characteristics of Young Breast Cancer in the Subdivision of Surgical Oncology at Sanglah Central General Hospital, 2014-2016. Digest of Medical Science 2018. Vol 9 Number 1: 76-79 (https://isainsmedis.id/index.php/ism/article/view/163, accessed on 12 November 2019)
8. Fujii, T., Le Du, F., Xiao, L., Kogawa, T., Barcenas, C. H., Alvarez, R. H.,… Ueno, N. T. (2015). Effectiveness of an adjuvant chemotherapy regimen for early-stage breast cancer. JAMA Oncology, 1 (9), 1311–1318. (https://www.ncbi.nlm.nih.gov/pubmed/26402167, accessed on 12 June 2019)
9. Golan, D. E., Armstrong, E. J., & Armstrong, A. W. (2012). Principles of Pharmacology: The Pathophysiologic Basis of Drug Therapy. In Climate Change 2013 - The Physical Science Basis. https://doi.org/10.1017/CBO9781107415324.004
10. Global Cancer Observatory. (2018). New Global Cancer Data 2018. https://www.uicc.org/news/new-global-cancer-data-globocan-2018, accessed on 11 November 2019)
11. Hashmi, Atif Ali., Saher Aijaz., Saadia Mehmood Khan. (2018). Prognostic Parameters of Luminal A and Luminal B Intrinsic Breast Cancer Subtypes of Pakistani Patients. World Journal Surgical of Oncology 2018.16: 1. (Https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5749004/, accessed on 20 November 2019)
12. Johanna, David L Watcher, Peter A Fasching. Invasive Breast Cancer: Recognition of

Molecular Subtypes. Breast Care (Basel) 2011 Aug; 6 (4): 258–264. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3225209/, accessed on 20 November 2019

13. Kamińska, M., Ciszewski, T., Łopacka-szatan, K., Miotła, P., & Starosławska, E. (2015). Review paper Breast cancer risk factors. 14 (3), 196–202. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4612558/, accessed on 23 June 2019)
14. Khotimah, S., Gondhowiardjo, S. A., Poetiray, E. D. C., & Djoerban, Z. (2011). Neoajuvan chemoradiation in locally advanced breast cancer. (1), 1–4. (Https://www.researchgate.net/publication/321507484_Kemoradiasi_Neoajuvan_pada_Kanker_Payudara_L Contin_Lokal, accessed on 11 July 2019)
15. National Cancer Management Committee of the Indonesian Ministry of Health. (2015a). Guide to Breast Cancer Management. Ministry of Health of the Republic of Indonesia. National Cancer Management Committee, 1–56.
16. National Cancer Management Committee of the Indonesian Ministry of Health. (2015b). Guide to Breast Cancer Management. Ministry of Health of the Republic of Indonesia. National Cancer Management Committee.