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Profil Respon Kemoterapi Berbasis Platinum dan Antrasiklin pada Pasien Kanker Payudara

Profile of Chemotherapy Response with Platinum Based and Anthracycline Based on Breast Cancer Patients

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ABSTRACT

Breast cancer is the abnormal growth and development of cells in breast tissue. Chemotherapy is one of choice for treatment of breast cancer. Chemotherapy response was performed to predict survival rates in patients and can be a guideline for the next chemotherapy. The selection of chemotherapy regimen that is suitable for the patient's condition must be considered so that the body can respond properly. Reduction in tumor size (objective response) is an important target evaluation of chemotherapy response. The purpose of this research is to determine the chemotherapy response profile in breast cancer patients undergoing chemotherapy at Cut Meutia Regional General Hospital. This study method used cross sectional method which was carried out in November 2022. Number of samples is 45 respondents which using purposive sampling technique who met the inclusion and exclusion criteria. The results of this study showed that the most age was >50 years old as many as 24 patients (53,3%), and The most gender was obtained, namely women as many as 45 patients (100%). Based on stage obtained for stage I amounted to 3 patients (6.7%), stage II amounted to 7 patients (15,6%), stage III amounted to 14 patients (31,1%), and for stage IV amounted to 21 patients (37,8%). Based on the type of chemotherapy that used platinum based in 17 patients (37.8%) and anthracycline based in 28 patients (62.2%). This study showed that there were 45 breast cancer patients at cut meutia general hospital with the majority reaching stage IV of 21 patients and the most used type of chemotherapy drug was anthracycline based as many as 28 patients.

Keywords : Breast cancer; chemotherapy; response to chemotherapy; types of drug

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INTRODUCTION

Breast cancer is the abnormal growth and development of cells in breast tissue. These malignant tumors can grow in the mammary glands, gland ducts, and breast supporting tissue (1,2). This cancer is often found in women worldwide and it is the first cause of death in women. Based on data from the World Health Organization (WHO) adapted from the Global Cancer Observatory (GLOBOCAN 2020) breast cancer ranks first in terms of cancer incidence in the world, namely 65,858 (16.6%) and causes the second mortality rate after lung cancer, namely of 22,430 (9.6%). Most of the new cases, namely 70% of breast cancer, are in an advanced stage (3). In Aceh in 2020, after an early examination for breast cancer, 7,288 cases were found, 1,285 lumps were found and 675 were suspected of having breast cancer (4). The incidence of breast cancer based on medical record data on outpatient visits at Cut Meutia General Hospital for the period June 2021-May 2022 there were 319 cases of breast cancer.

Chemotherapy is one of the therapies used in the treatment of breast cancer patients. Giving drugs in chemotherapy can be in the form of pills, fluids, and injections through an infusion where all of that aims to kill cancer cells in the breast so that abnormal cell growth can be controlled. Chemotherapy can be given gradually at intervals of 21 days for 5-6 cycles (5). After chemotherapy, an assessment of chemotherapy response was carried out. The response to chemotherapy can be assessed subjectively based on patient complaints and an objective assessment is carried out by measuring the mass of the tumor after chemotherapy. Evaluation of chemotherapy response was carried out by measuring the tumor mass using two criteria. The first is the criteria according to WHO, and the second is according to RECIST (response evaluation criteria in solid tumor). The classification consists of Complete Response, Partial Response, Stable Disease and Progressive Disease (6).

The types of drugs commonly used for chemotherapy are platinum based and anthracycline based. In hypertensive patients, the anthracycline group is avoided because it can cause an increase in blood pressure. However, the administration of chemotherapy drugs must still be given in order to get the expected effect with acceptable side effects. Based on previous research, there were various responses using anthracycline and platinum groups in breast cancer patients (7).

Based on the description above, there are several variations of drugs used in breast cancer patients, so that the response to chemotherapy is to be known based on the type of drug given during chemotherapy. Researchers will evaluate the response to chemotherapy using WHO criteria. By using this criterion, the researchers directly measured the tumor without using other supporting examinations. The response to chemotherapy in breast cancer patients at Cut Meutia General Hospital is still unknown and previous studies have been limited with mixed results regarding the response to chemotherapy in breast cancer patients.

METHOD

This research is an observational descriptive study. The research was conducted from November 2022 to January 2023 at the Cut Meutia General Hospital, North Aceh. In taking the sample, the

technique used the cross sectional method with a sample of 45 patients taken by purposive sampling and it is necessary to determine inclusion and exclusion criteria in sampling so that the sample criteria do not deviate from the population. Inclusion criteria in this study included: Patients diagnosed with breast cancer as confirmed by anatomical pathology results and breast cancer patients who undergo chemotherapy after three cycles, regularly and according to schedule.

The instruments used in this study used medical records, conducted interviews regarding patient complaints and direct observation to assess chemotherapy response by measuring tumors using calipers in breast cancer patients undergoing chemotherapy. Data analysis used is univariate data analysis to describe the frequency distribution of the variables studied.

Health Research Ethics Commission, Faculty of Medicine, Malikussaleh University has granted this study ethical feasibility, with number: 029/KEPK/FKUNIMAL-RSUCM/2022. While the exclusion criteria who are non-compliant with chemotherapy as scheduled, or who are unable to tolerate chemotherapy side effects, resulting in changes to the schedule and regimen.

RESULT

Table 1. Distribution of characteristics of breast cancer patients

Characteristics	Frequency (n)	Percentage (%)
Age (years)		
31-40 years	2	4,4
41-50 years	19	42,2
>50 years	24	53,3
Total	**45**	**100**
Sex		
Male	0	0
Female	45	100
Total	**45**	**100**

Table 1 shows that the highest incidence of breast cancer was the age group >50 years with 24 patients (53.3%) and the least was the age group 31-40 years with 2 patients (4.4%). Data on the incidence of breast cancer by sex were 45 female patients and not found in males.

Table 2. Frequency of breast cancer stages

Breast Cancer stages	Frequency (n)	Percentage (%)
Stage I	3	6,7
Stage II	7	15,6
Stage III	14	31,1
Stage IV	21	46,7
Total	**45**	**100,0**

Table 2 shows that most of the 45 patients with breast cancer were patients with stage 4, with a percentage of 46.7% (21 patients). Cancer patients with the least stage level are stage 1 with a percentage of 6.7% (3 patients) of 45 patients.

Table 3. Description of breast cancer based on histopathological type

Histopathological Type	Frequency (n)	Percentage (%)
Invasive ductal carcinoma	36	80,0
Invasive lobular carcinoma	6	13,3
Mucinous carcinoma	2	4,4
Metastatic lobular carcinoma	1	2,2
Total	**45**	**100,0**

Table 3 shows that the most common histopathological type of breast cancer patients at North Aceh General Hospital in 2023 is the type of invasive ductal carcinoma in 36 patients (80.0%) and the least is the type of mucinous carcinoma and metastatic lobular carcinoma, each of which is 2 patients (4.4%) and 1 patient (2.2%).

Table 4. Frequency of chemotherapy response

Chemotherapy Response	Frequency (n)	Percentage (%)
Complete response	11	24,4
Partial response	20	44,4
Stable disease	8	17,8
Progressive disease	6	13,3
Total	**45**	**100,0**

Table 4 shows that the frequency of chemotherapy responses in breast cancer chemotherapy patients, it was found that the majority of patients had the most chemotherapy response, partial response with a percentage of 44.4% (20 patients) and for the lowest chemotherapy response was progressive disease with a percentage of 13.3% (6 patients).

Table 5. Frequency of types of chemotherapy drugs

Chemotherapy Drugs	Frequency (n)	Percentage (%)
Platinum based	17	37,8
Anthracycline based	28	62,2
Total	**45**	**100,0**

Table 5 shows that the most used type of chemotherapy drug was the anthracycline type, amounting to 28 patients or (62.2%), while for the Platinum chemotherapy type there were 17 patients or as many as (37.8%).

Table 6. Description of chemotherapy response based on the type of chemotherapy drug

Type of Chemotherapy Drug	Chemotherapy Response									
	Complete Response		Partial Response		Stable Disease		Progressive Disease		Total	
	N	%	N	%	N	%	N	%	N	%
Platinum based	5	29,4	11	64,7	0	0,0	1	5,9	17	100,0
Anthracycline based	6	21,4	9	32,1	8	28,6	5	17,9	28	100,0

Based on the results of the research that has been obtained, it shows that the response to chemotherapy with a type of platinum-based drug was 17 patients, 5 patients (29.4%) experienced a complete response, 11 patients (64.7%) experienced a partial response, 1 patient (5 .9%) had progressive disease, and no patients were found to have a stable response or stable disease. While the type of anthracycline-based drugs were obtained by 28 patients at the time of the study, it was found that 6 patients (21.4%) had a complete response, 9 patients (32.1%) experienced a partial response, 8 patients (28.6%) experienced stable disease, and 5 patients (17.9%) had progressive disease.

DISCUSSION

Description of Characteristics of Breast Cancer Patients

The results showed that breast cancer patients with the highest distribution were in the age group >50 years with 24 patients (53.3%) and the least in the 31-40 year age group with 2 patients (4.4%). The case with the youngest age was found at the age of 34 years, and the case with the oldest age was found at the age of 63 years.

Breast cancer is a cancer that is often found in women worldwide and is the first cause of death in women. The risk of getting breast cancer increases with age. This condition is most common in women over the age of 50 who have gone through menopause. Menopause is a condition in which there is a natural decrease in the hormone estrogen and the ovaries run out of eggs in the ovaries. Lack of estrogen causes women to go through menopause and lose natural protection against breast cancer (8).

In this study all breast cancer patients were women. This is because women experience more exposure to the hormone estrogen such as menstruation, pregnancy, breastfeeding and is also an important female hormone, while in men the hormone estrogen is not too much as in women it is relatively small. This causes men to rarely get breast cancer. Women have more estrogen receptors than men, so men rarely get breast cancer because estrogen receptors are very low (9).

Frequency of Breast Cancer Stage

From the results of the study it was found that breast cancer patients who are undergoing chemotherapy at Cut Meutia General Hospital that what is often found is breast cancer patients with stage 3 and stage 4 who are undergoing chemotherapy, this happens because most breast cancer patients coming to the hospital for examination when in stage 3, due to the symptoms that are starting to occur, sufferers are already feeling more, compared to when they were still in the early stages.

The results of this study are also in line with research conducted by Lola Depitasari and Dila Nofrianti (2017), that breast cancer patients in the Surgery Clinic of Dr.M. Djamil Padang experienced a delay in carrying out the examination (65.1%) and was already in an advanced or severe stage so that action could not be taken. Patients with breast cancer are said to be late for treatment if they come for treatment at stages III and IV (10). Breast cancer patients at stage III, which is 49%, were also found in H Sahudin hospital Kutacane Southeast Aceh (11).

Description of breast cancer patients based on histopathological type

Cancer has various characteristics with abnormal and uncontrolled growth of cells. These cancer cells can spread to other parts of the body, this spread is known as metastasis. There are several examinations that can be used to diagnose breast cancer, one of which is an anatomic pathological examination in the form of histopathology and biopsy. Biopsy is the gold standard for breast cancer screening to confirm whether there is malignancy or not (2).

Histopathologically, breast cancer is divided into invasive and non-invasive carcinomas. For invasive carcinoma consists of invasive ductal carcinoma, invasive lobular carcinoma and other types. While non-invasive carcinoma is divided into ductal carcinoma in situ (DCIS) and lobular carcinoma in situ (LCIS). Knowledge of the staging and histopathological type is also an important indicator in determining the prognosis of breast cancer. The histopathological picture obtained is in the form of morphology of cancer tissue microscopically from anatomical pathology which is an important parameter and is a gold standard followed by physical examination and other supporting examinations in the diagnosis of breast cancer. The most common histological type of breast cancer is invasive ductal carcinoma, which accounts for 75% of all types of breast cancer, followed by invasive lobular carcinoma, which accounts for 5-15%, and for mucinous carcinoma, which accounts for 3% of breast cancer. Ductal carcinoma usually spreads to the bone, lung, liver or brain, while lobular carcinoma usually metastasizes to the meningeal surface or other unusual sites (9).

Frequency of chemotherapy response

The results of this study indicate that the frequency of chemotherapy responses in breast cancer patients at Cut Meutia General Hospital found a partial response with a percentage of 44.4% (20 patients), a complete response with a percentage of 24.4% (11 patients), stable disease 17.8 % (8 patients) and the least was progressive disease 13.3% (6 patients). Neoadjuvant chemotherapy is the administration of chemotherapy to cancer patients with high-grade malignancy and have never received local-regional surgery or radiation. Neoadjuvant chemotherapy aims to reduce tumor size and control micrometastases, besides that neoadjuvant chemotherapy can provide information about chemotherapy response (12). After neoadjuvant chemotherapy for more than 3 cycles, the response to chemotherapy was assessed by measuring the tumor.

Assessment of chemotherapy response is used to predict patient survival rates and can be used as a guideline for further chemotherapy. Shrinkage of tumor size (objective response) is an important target in the evaluation of chemotherapy response (3). Evaluation of chemotherapy response was carried out in this study using WHO criteria by means of direct measurements on patients using calipers without carrying out additional examinations. Before taking measurements, a subjective assessment is carried out by asking complaints to patients including complaints of pain, lump size and whether there are wounds in the breast.

Frequency of use of chemotherapy drugs

Based on the table in this study, the most used type of chemotherapy drug was the anthracycline group with a percentage of 62.2% (28 patients), while the platinum type was less, namely with a percentage of 37.8% (17 patients). This is done because anthracyclines are a class of antibiotics that have high effectiveness in treating cancer cells, both hematological cancers and solid cancers, including breast cancer. Drugs that belong to the anthracycline class include doxorubicin, daunorubicin, epirubicin, and idarubicin. Doxorubicin is one of the drugs from the anthracycline class which is most often used in combination chemotherapy for breast cancer (13). The use of platinum-based drugs such as cisplatin and carboplatin is considered effective for the treatment of sarcoma and carcinoma, but has the main side effect, namely nephrotoxicity, so that kidney function assessment is required using the creatinine level parameter before starting chemotherapy (14). Therefore, platinum based is the second choice for use in treatment.

Examination that is a reference and helps determine the diagnosis and management of breast cancer cases is Immunohistochemistry (IHK) to see Human Epidermal Receptors-2 (HER2), Estrogen Receptors (ER), Progesterone Receptors (PR) and Ki-67 protein. Immunohistochemistry is a process of identifying specific proteins in tissues or cells using antibodies. Expression of ER, PR and HER-2 hormone receptors found on immunohistochemical examination is useful for determining therapeutic options so that the selection of the type of drug used is according to patient needs (15).

Description of chemotherapy response based on the type of chemotherapy drug

Based on the results of the research that has been obtained, it shows that the response to chemotherapy with a type of platinum-based drug was 17 patients, 5 patients (29.4%) experienced a complete response, 11 patients (64.7%) experienced a partial response, 1 patient (5 .9%) had progressive disease, and there were no patients who experienced a stable response or stable disease. While the type of anthracycline-based drugs were obtained by 28 patients at the time of the study, it was found that 6 patients (21.4%) experienced a complete response, 9 patients (32.1%) experienced a partial response, 8 patients (28.6%) experienced stable disease, and 5 patients (17.9) had progressive disease.

Chemotherapy is a series of therapies that are carried out continuously and programmed, the quantity of chemotherapy given to each patient is different according to the patient's condition and the type of anticancer drug used. The frequency of chemotherapy for each patient is different depending on the type of cancer, the goals of treatment, the type of chemotherapy used and how the body responds to chemotherapy (16). From the results of this study it was found that there were varied chemotherapy responses in breast cancer patients who had done chemotherapy for more than 3 cycles. Evaluation of chemotherapy response is used to predict survival rates and can be used as a guideline for further chemotherapy, while guidelines for administering chemotherapy drugs must be considered according to the patient's condition prior to chemotherapy.

Platinum regimen chemotherapy is still a systemic combination therapy for various solid tumors because of its ability to reduce the risk of recurrence or extend survival in advanced disease. There are three platinum-based drugs used worldwide for the treatment of cancer namely cisplatin, carboplatin, and oxaliplatin. Carboplatin is mainly used in the treatment of breast cancer, endometrial cancer, ovarian cancer, brain tumors, and germ cell tumors. The main targets of carboplatin are the interstrand and intrastrand DNA of tumor cells, which bind efficiently thereby inhibiting replication and transcription and promoting cell death. The amount of chemotherapy given to the patient depends on the type of tumor or cancer. The average administration of chemotherapy is 3-6 cycles. However, for high-grade tumors, 6 cycles of chemotherapy are recommended. Carboplatin is analogous to cisplatin. The difference is that carboplatin is more stable and has less nephrotoxicity, neurotoxicity, ototoxicity, and emeto-genesis. However, long-term administration of carboplatin can increase its accumulation in the body, thereby increasing side effects and producing toxicity in various organs, one of which is the kidney (17). At the time of the research, the most common type of cancer cells found was epidermoid, so using platinum based gave a better response.

The main choice of chemotherapy drug regimen for chemotherapy is anthracycline based. Anthracyclines interact with the TOP2A enzyme in cancer cells. A meta-analysis study revealed a significant increase in survival rate in a group of breast invasive ductal carcinoma patients who received anthracycline-based neoadjuvant chemotherapy, compared to other regimens. But not all patients will benefit from anthracycline therapy. For the anthracycline group it is avoided in comorbid patients because it can cause an increase in blood pressure (18).

The response to chemotherapy from platinum-based and anthracycline-based drugs provides a varied response. This is because the response from each patient differs depending on the type of cancer and how the body responds to the chemotherapy. Based on previous studies, for platinum based on neoadjuvant chemotherapy more than 3 cycles had a positive response in lymph nodes and primary tumors which were larger than 3 cycles, then obtained an objective response of 80% (CR 19%, PR 61%) and a negative response by 20% (SD 14% and PD 6%) after 3 cycles of NAC with cisplatin-paclitaxel. Whereas anthracycline-based neoadjuvant can increase PR from 40% to 65% and CR from 13.7% to 26.1% (19).

Regarding the safety of platinum-based regimens, the most common side effects are hematological and gastrointestinal. In a meta-analysis of platinum-containing regimens in metastatic breast cancer, the majority of patients experienced neutropenia (38.6%), hair loss (33.7%), leukopenia (24.3%) and nausea/vomiting (14.3%) . Therefore, it is recommended to ensure that the patient is in optimal condition, proper counseling is carried out about the pros and cons of platinum-based chemotherapy and careful clinical follow-up during treatment is very important in chemotherapy so that all side effects can be tolerated and managed appropriately (20). Chemotherapy with a combination of paclitaxel + anthracycline + carboplatin can be tolerated by breast cancer patients with a complete pathological response rate of 60% (21).

If post-chemotherapy a positive clinical response (PR/CR) is obtained, then surgery is performed and continued with 4-6 cycles of adjuvant chemotherapy (the regimen chosen will be adjusted to the pathological response that occurs) and adjuvant radiation (the schedule should not exceed 16 weeks from the schedule operation). Meanwhile, if it is clinically unresponsive and even progressive, chemotherapy is continued plus radiation (on cycle after cycle the response is still evaluated). If it shows progressive spread to organs or bones, a palliative therapeutic approach is decided (1).

CONCLUSION AND SUGGESTION

The results of the study found that the highest incidence of breast cancer was the age group >50 years of 24 patients (53.3%) and the least was the age group of 31-40 years of 2 patients (4.4%). The incidence of breast cancer by sex, namely women as many as 45 patients and not found in men. The most common histopathological type of breast cancer was invasive ductal carcinoma in 36 patients (80.0%). There were 17 patients who responded to chemotherapy with platinum-based drugs, 5 patients (29.4%) had a complete response, 11 patients (64.7%) had a partial response, 1 patient (5.9%) had progressive disease, and There were no patients who experienced a stable response or stable disease. Response to chemotherapy with anthracycline-based drugs was found in 28 patients, 6 patients (21.4%) experienced a complete response, 9 patients (32.1%) experienced a partial response, 8 patients (28.6%) experienced stable disease, and 5 patients (17.9%) had progressive disease.

This research hopes that breast cancer patients undergoing chemotherapy will also increase their promotional and preventive efforts related to breast cancer and early detection behavior using the BSE method, so that the public will be more responsive and vigilant from an early stage. Patients are also expected to have knowledge about the response to chemotherapy with platinum-based drugs and anthracyclines after chemotherapy, so they can assess post-chemotherapy improvements.

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