Jurnal Ilmiah Farmasi (Scientific Journal of Pharmacy) 18(2) August-December 2022, 145-152
ISSN: 1693-8666
available at http://journal.uii.ac.id/index.php/JIF

Evaluation of single and combination chemotherapy agents in patients with metastatic breast cancer

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Abstract

Background: There are several ways to treat breast cancer, one of which is administering chemotherapy agents. Chemotherapy agents have activity in inhibiting the cell cycle. That will affect the effectiveness of therapy and the side effects of chemotherapy agents.
Objective: This study aimed to evaluate single and combination chemotherapy agent therapeutic efficacy and side effects
Method: The design of this study used an observational cohort study with retrospective data collection from January to December 2019. Patients obtained from medical records were diagnosed with metastatic stage of breast cancer at Panti Nirmala Hospital, Malang. The effectiveness of the chemotherapy agent was seen from the carcinoembryonic antigen (CEA) and cancer antigen 15-3 (CA15-3), which were carried out in the first and third cycles, then analyzed using the Wilcoxon and U-Mann Whitney tests. Side effects of chemotherapy agents were analyzed descriptively.
Results: Analysis of the Wilcoxon test showed differences between the two groups of chemotherapeutic agents in CEA and CA15-3 ($p<0.05$). U-Mann Whitney test analysis showed no difference after administration of the two groups of chemotherapy agents at CEA ($p>0.05$). However, there was a difference in CA15-3 ($p<0.05$). Both chemotherapy agents showed most common side effects such as pain, nausea, vomiting, and alopecia.
Conclusion: Patients who received a combination of chemotherapy agents had lower CA15-3 levels than single chemotherapy agents.
Keywords: Metastatic breast cancer, CEA, CA15-3, side effects of chemotherapy agents

1. Introduction

Metastatic stage breast cancer is one of the highest malignancies among other types of cancer in Indonesia and globally, with an increasing incidence (Kemenkes, 2019; Yang *et al.*, 2017). As the implementation, metastatic breast cancer patients need to be monitored continuously to increase the survival rate. One way to assess the therapeutic effect is by measuring tumor biomarkers (McDonald *et al.*, 2016; Yang *et al.*, 2017). Reference tumor biomarkers are widely used to measure response to treatment, early recurrence, and predict prognosis. The biomarkers that are widely referenced to assess the effectiveness of therapy are carcinoembryonic antigen (CEA) which is a protein involved in cell adhesion, and cancer antigen 15-3 (CA15-3) or MUC-1, which represents the mucin sequence in cells undergoing malignancy (Hosseini *et al.*, 2015; Yang *et al.*, 2017). CEA and CA15-3 are less sensitive for early detection but can predict positive treatment responses (Yang *et al.*, 2017). Serum levels of CEA and CA15-3 are also widely used to expect a response to therapy in metastatic breast cancer (Geng *et al.*, 2015).

In addition to the effectiveness of therapy, the side effects of chemotherapy agents also need to be monitored, which is important to improve the patient's quality of life. Many reports have stated the side effects induced by chemotherapeutic agents, including spinal cord suppression, neuropathy, gastrointestinal disorders, hair loss, weakness, and skin disorders (Chan & Ismail, 2014). In Indonesia, there have not been many studies that have looked at the differences in biomarkers and the frequency of possible side effects that occur with a single chemotherapy agent compared to combinations. This background underlies the need for a study to determine the differences in biomarkers of CEA and CA15-3 and the side effects of using a single agent compared to a combination that may occur.

2. Methodology

2.1. *Study design and setting*

The study design used an observational cohort study with retrospective data collection. Data was collected through medical records and laboratory results from January to December 2019. This research has passed ethical test No.E.5.a/209/KEPK-UMM/VIII/2020. The study location was at Panti Nirmala Hospital Malang and carried out in the Medical Record Unit and inpatient ward.

2.2. *Sample size and sampling technique*

The population of this study were inpatients diagnosed with breast cancer in the metastatic stage at Panti Nirmala Hospital and received chemotherapy agents. The study sample was breast cancer patients with metastases who entered the inclusion criteria. The sampling technique used in this study was the total sampling technique, where all population members were sampled. There were 45 samples from the medical record unit. 19 patients received single chemotherapy agents and 26 received combination chemotherapy agents.

2.3. Inclusion and exclusion criteria

The inclusion criteria were metastatic breast cancer patients who received single and combination chemotherapy agents; patient data was taken from the patient medical record according to biomarkers Carcinoembryonic Antigen (CEA) and Cancer Antigen 15-3 (CA15-3). Exclusion criteria were patients who passed away and patients who did not have complete laboratory data when administering chemotherapy agents.

2.4. Data collection

The data collected in this study were patient characteristics which included: age, education, employment status, marital status, comorbidities, and history of hormonal contraceptive use. The data on the effectiveness of therapy was seen from the biomarkers of CEA and CA15-3. Data of the side effects were taken from using single and combination chemotherapy agents. The single chemotherapy agents used were Carboplatin, Navelbin, and Zometa/Zolenic. Combination chemotherapy agents consist of two or three chemotherapeutic agents. Two chemotherapeutic agents include Carboplatin+Docetaxel, Cisplatin+Docetaxel, and Cisplatin+Paclitaxel. The three chemotherapy agents were Carboplatin+Docetaxel+Fluorouracil and Cyclophosphamide+Epirubicin+Fluorouracil.

2.5. Data analysis

The data of this study were analyzed using the open-source R software. The relationship between chemotherapy agents and the characteristics of the respondents were analyzed using the Chi-Square test. The U-Mann Whitney test was used to compare therapeutic efficacy as measured by biomarkers CEA and CA15-3. Side effect data were analyzed descriptively as a percentage of events.

3. Result and discussion

Patient characteristics data are briefly presented in Table 1. Characteristics of metastatic breast cancer patients in the group receiving single or combination chemotherapy agents showed no relationship ($p>0.05$).

Table 1. Patient characteristics data

Characteristic	Number of patient with single chemotherapy* (%)	Number of patient with combination chemotherapy** (%)	p-value
Age (year)			
26-45	3 (15.8)	5 (19.23)	0.917
46-65	14 (73.68)	19 (73.07)	
66-85	2 (10.53)	2 (7.69)	
Mean: 52			
Education			
Elementary	5 (26.31)	9 (34.61)	0.844
Junior High School	0	1 (3.85)	
Senior High School	6 (31.58)	7 (26.92)	
Associate Degree	3 (15.79)	3 (11.54)	
Bachelor Degree	2 (10.53)	6 (23.08)	
Master Degree	3 (15.79)	0	
Comorbidities			
Yes	6 (31.58)	6 (23.08)	0.767
No	13 (68.42)	20 (76.92)	

Characteristic	Number of patient with single chemotherapy* (%)	Number of patient with combination chemotherapy** (%)	p-value
Occupation			
Yes	6 (31.58)	12 (46.15)	0.498
No	13 (68.42)	14 (53.85)	
Married Status			
Married	15 (78.95)	18 (69.23)	0.308
Single	0	3 (11.54)	
Divorce	4 (21.05)	5 (19.23)	
Hormonal History			
Contraception	16 (84.21)	17 (65.38)	0.171
Hormonal Contraception	1 (5.26)	7 (26.92)	
Non-Hormonal No ontraception	2 (10.53)	2 (7.69)	
Biomarker CEA			
Normal	1 (5)	1 (3.85)	1.000
Abnormal	18 (95)	25 (96.15)	
Biomarker CA 15-3			
Normal	1 (5)	1 (3.85)	1.000
Abnormal	18 (95)	25 (96.15)	

Information:
*Carboplatin, Navelbin, Zometa/Zolenic
**Combination of two therapy agents: carboplatin+docetaxel, cisplatin+docetaxel, cisplatin+paclitaxel; combination of three therapy agent: carboplatin+docetaxel+fluorouracil, cychlophosphamide+epirubicin+fluorouracil

Patients were dominated by 46-65 years, without comorbidities, married status, and previously used hormonal family planning. Furthermore, the analysis of differences in CEA and CA15-3 biomarkers between those receiving single and combined chemotherapy agents can be seen in Table 2. There are differences in CA15-3 biomarkers after administration of single and combination chemotherapy agents. However, there was no difference in the CEA biomarker after administering single chemotherapy agents (mean CEA = 9.42 ng/mL) and combination chemotherapy agents (mean CEA = 9.70 ng/mL). CA15-3 levels of chemotherapeutic agents combinations had lower concentrations (mean CA15-3 = 105.60 U/mL) than single chemotherapy agents (mean CA15-3 = 129.48 U/mL).

Table 2. The U-Mann Whitney test of single and combination chemotherapy agents

Biomarker	*U*	p-value
CEA	256	0.422
CA15-3	325.5	0.036

Administration of single and combined chemotherapeutic agents decreased CA15-3 biomarkers, but not CEA. This result showed a significant response to the effectiveness of therapy after chemotherapy. Parameters of response to chemotherapy agents evaluated through CEA's tumor markers while in metastatic breast cancer had continuously increasing CEA levels. Therefore, the result (Table 2) showed that cancer cells did not

respond to treatment/relapse after getting treatment (p>0.05). However, CEA is an insensitive biomarker in breast cancer, so it cannot be used as the only screening. This condition caused the need for supporting data in the form of a CA15-3 biomarker. The CA15-3 biomarker aims to determine the prognosis of metastatic breast cancer. Monitoring response to therapy on CA15-3 was seen from increased levels of CA15-3, which was associated with the high severity of breast cancer (Kabel, 2017).

In a retrospective study, serum CA15-3 correlated with the location of the number of metastases in breast cancer patients but not with CEA. CEA has a higher sensitivity in patients with metastases that spread to other organs. Hence, it can be concluded that in patients with metastatic breast cancer, the sensitivity of the CA15-3 biomarker is intended for serum tumor markers in the breast. In contrast, the CEA biomarker is designed for sensitivity/marker of metastases in breast cancer patients (Yang *et al.*, 2017). The limitation of the problem in this study was that the sampling of CEA and CA15-3 biomarker data was only in the first and third cycles.

Table 3. Descriptive data side effects of single chemotherapy agents

Single chemotherapy agent (n=19 patients)	Side effects	Number of patients (%)
Carboplatin 400 mg inj (n=1)	Nausea/vomiting and alopecia	1 (100)
Navelbine 40 mg inj (n=15)	Pain	8 (53.33)
	Extravasation	1 (6.67)
	Nauseous/vomiting	12 (80)
	Short of breath	1 (6.67)
	Alopecia	12 (80)
Zometa/Zolenic 4mg (n=3)	Pain	2 (66.67)
	Nauseous/vomiting	3 (100)
	Alopecia	1 (33.33)

The side effects data for single chemotherapy agents are represented in Table 3. The most common side effects were nausea/vomiting, alopecia, and pain. Nausea/ vomiting was caused by chemotherapy-induced nausea and vomiting (CINV). The risk of developing CINV was higher with the short-term IV infusion route than with long-term or oral preparations. Neurotransmitters that play a role in activating CINV are 5-hydroxytryptamine (5-HT2, 5-HT3, and 5-HT4), dopamine (D2), histamine (H1), and acetylcholine (Ach). Receptors of the neurotransmitter 5-HT and dopamine were abundant in the intestinal mucosa and activated when the neurotransmitter was released, causing nausea and vomiting. Chemotherapy agents given to patients will also quickly bind to the chemoreceptor trigger zone (CTZ) in the brain close to the vomiting center, resulting in nausea and vomiting (Antonarakis & Hain, 2004; Singh *et al.*, 2016).

Table 4. Descriptive data side effects of combination chemotherapy agents

Combination chemotherapy agent (n=26 patients)	Side effects	Number of patients (%)
Carboplatin 300 mg inj + docetaxel 110 mg inj (n=3)	Pain, Nausea/vomiting Alopecia	2 (66.67) 3 (100) 3 (100)
Carboplatin 300 mg inj + docetaxel 120 mg inj (n=1)	Pain, nausea/vomiting, and alopecia	1 (100)
Carboplatin 400 mg inj + docetaxel 120 mg inj (n=1)	Extravasation, pain, nausea/vomiting, and alopecia	1 (100)
Carboplatin 450 mg inj + docetaxel 110 mg inj (n=2)	Pain, nausea/vomiting, alopecia, and short of breath	2 (100)
Carboplatin 450 mg inj + docetaxel 120 mg inj (n=4)	Extravasation Pain	1 (25) 3 (75)
Cisplatin 50mg inj + docetaxel 100mg inj (n=4)	Extravasation Pain Nausea/vomiting Alopecia	1 (36.36) 2 (50) 4 (100) 1 (25)
Carboplatin 60 mg inj + docetaxel 120 mg inj (n=3)	Pain Nausea/vomiting Alopecia	3 (100) 3 (100) 1 (50)
Cisplatin 50 mg inj + paclitaxel 200 mg inj (n=1)	Extravasation and nausea/vomiting	1 (100)
Cisplatin 60 mg inj + paclitaxel 230 mg inj (n=1)	Extravasation, nausea/vomiting and alopecia	1 (100)
Carboplatin 450 mg inj, belotaxel 120 mg inj* + curacil 500 mg inj* (n=5)	Extravasation Pain Nausea/vomiting Short of breath Alopecia	1 (20) 5 (100) 5 (100) 1 (20) 4 (80)
Cyclovid 600 mg inj*, epirubicin 500 mg inj + curacil 500 mg inj* (n=1)	Extravasation, pain, nausea/vomiting, and alopecia	1 (100)

The side effects data for combination chemotherapy agents are represented in Table 4. The most common side effects are nausea/vomiting, alopecia, pain, extravasation, shortness of breath. The previous study also showed that the most common side effect was alopecia/chemotherapy-induced alopecia (CIA) (Rossi *et al.*, 2017). The incidence of alopecia was associated with the type of chemotherapeutic agent used in this study. The finding showed that 80% of the incidence occurred in the antimicrotubule group (vinorelbine, paclitaxel, docetaxel, epirubicin), 60% in alkylators (carboplatin and cisplatin), and 10-50% in antimetabolites (fluorouracil), 60-100% on topoisomerase. Alopecia results from the main target of chemotherapeutic agents, the keratinocyte matrix, which proliferates during the anagen/hair formation phase. The keratinocyte matrix is sensitive to chemotherapeutic agents and causes rapid apoptosis, which affects the anagen phase, namely hair follicle growth, and causes baldness (Haslam & Smart, 2019). However, this baldness is not permanent; within six months, the hair growth will occur again (Rossi *et al.*, 2017).

The subsequent most common side effect was a painful condition, often referred to as chemotherapy-induced peripheral neuropathy (CIPN). Peripheral neuropathy induced by platinum-based drugs (carboplatin and cisplatin) causes glial cell activation, increasing the inflammatory pro-cytokines that increase nociceptor sensitivity and hyperexcitability of peripheral neurons. The effects, together with ROS (reactive oxygen species), damage the blood-brain barrier and leads to the development of neuroinflammation, damage to mitochondria, and increases ROS, which causes damage to enzymes, proteins, and lipids in neurons as well as dysregulation of calcium homeostasis which induces apoptotic changes in peripheral nerves. Peripheral neuropathy in using antimicrotubule (vinorelbin, paclitaxel, docetaxel, epirubicin) interferes with axonal transport. It causes degeneration of distal nerve segments, alters ion channel activity and hyperexcitability of peripheral neurons, and modifies the expression and function of Na^+, K^+ ion channels. Activation of microglia leads to the release and increase of pro-inflammatory cytokines. This process leads to nociceptor sensitivity and the development of neuroinflammation (Zajączkowska *et al.*, 2019).

4. Conclusion

The achievement in this study was that the CA15-3 biomarker in combination chemotherapy agents has lower levels than single chemotherapy agents. However, CEA levels did not give a significant change in single and combined agents. Both chemotherapy agents cause side effects, especially nausea/vomiting, alopecia, and pain.

Acknowledgment

We would like to thank Panti Nirmala Hospital Malang for assisting the research administration process, Mrs. Suhul Raos, who helped complete the research data, and Mrs. Martanty Aditya, who assisted in preparing this article.

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