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Comparative Utility of Doxorubicin, Cyclophosphamide, and Docetaxel in Breast Cancer Treatment in West Sumatera.

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Abstract: The large number of breast cancer cases in Indonesia and the high cost of treatment cause the need for utility analysis. West Sumatra province ranks second with the highest prevalence of breast cancer in Indonesia. This study aimed to determine the quality of life of breast cancer patients at the national referral hospital Dr. M. Djamil, West Sumatra, who underwent chemotherapy. This study used a cross-sectional design from January to April 2024. Data collection was done prospectively by filling out questionnaires at the Chemotherapy Unit. Utility value was obtained from filling out a questionnaire with the EQ-5D-5L instrument. Data were analyzed using the Mann-Whitney and Kruskal-Wallis tests. The data obtained was 47 respondents who received Doxorubicin and Cyclophosphamide chemotherapy regimen (24 respondents) and a Docetaxel chemotherapy regimen (23 respondents), all of whom met the inclusion criteria in this study. The average utility value obtained for the doxorubicin and cyclophosphamide regimes is 0.637, and the average utility value for the docetaxel regimen is 0.704. Age did not affect utility ($p>0.05$), while recent education, occupation, and patient origin affected utility ($p<0.05$). Both regimens provided similar perceived quality of life and overall health status as measured by utility and VAS scores, suggesting comparable patient-reported quality of life outcomes between these chemotherapy treatments.

1. INTRODUCTION

Breast cancer is one of the most common cancers affecting women in the world National Cancer Control Committee) In 2018, the WHO noted that there were two million cases of breast cancer diagnosed globally. It is estimated that 30% of the total breast cancer patients are HER-2 type breast cancer, which is an invasive and aggressive type of breast cancer (Desriani *et al.*, 2021). Breast cancer is the cancer with the most cases in the world and in women, with a percentage of 11.7% or around 2.2 million cases in 2020, according to the Global Cancer Observatory (GLOBOCAN) (Adanu *et al.*, 2022). According to Histopathologic data from the Cancer Registration Agency of the Association of Indonesian Pathology Specialists (International Academy of Pathology, Indonesia division, IAPI) and the Indonesian Cancer Foundation (ICF), breast cancer ranks first with a relative frequency of 18.6% with an estimated incidence rate in Indonesia of 12/100,000 women (Ministry of Health, Republic of Indonesia, 2018). Based on basic health research data in 2018, the prevalence of cancer in Indonesia reached 1.79 per 1000 population, with the highest prevalence in the province of Yogyakarta, as much as 4.8 per 1000 population; West Sumatra occupies the second position at 2.4 per 1000 population (West Sumatera *Riskesdas*, 2018).

Breast cancer treatment uses chemotherapy bases such as doxorubicin, cyclophosphamide, and docetaxel. This combination shows a significant increase in breast cancer death and recurrence rates. Chemotherapy regimens containing anthracycline are slightly better at reducing recurrence and mortality compared to chemotherapy regimens without anthracycline. Intercalation of anthracycline with DNA stops topoisomerase II, leading to DNA damage and cell death. If cyclophosphamide is added as an alkylating agent, it can form cross-links in DNA, which stops DNA replication and leads to cell death. Compared to chemotherapy regimens that do not contain taxane, adding taxane can help the regimen by binding to microtubules, preventing depolymerization, and stopping cell division. This lowers the risk of death and long-term relapse (Dipiro *et al.*, 2020).

This article's selection of doxorubicin, cyclophosphamide, and docetaxel is based on their widespread use in breast cancer treatment protocols, particularly in combination regimens. Doxorubicin and cyclophosphamide are commonly used together in the adjuvant treatment of early-stage breast cancer. At the same time, docetaxel is frequently included in chemotherapy regimens for both early and advanced breast cancer due to its effectiveness in improving survival outcomes. These three chemotherapy agents are integral to the standard treatment for breast cancer in Indonesia. They are thus relevant for evaluating their cost-effectiveness and impact on patient's quality of life in the context of the country's healthcare system.

Breast cancer patients also experience depression and decreased quality of life, which includes the ability to walk, early treatment, usual activities, pain or discomfort, anxiety, or depression (Dipiro *et al.*, 2020). Utility or the level of satisfaction after getting a chemotherapy regimen can be expressed or calculated in Quality Adjusted Life Years (QALYs). Quality of life utility values have a scale of 0 to 1, where 0 means death and 1 for a perfect life (Fitria, 2023).

The use of the EQ-5D Instrument in this study is based on the Indonesian Technology Assessment Guidelines published by the Ministry of Health of the Republic of Indonesia in 2017, which stipulates the use of the EQ-5D instrument for utility measurement in Health Technology Assessment in Indonesia (Ministry of Health, Republic of Indonesia, 2017). The EQ-5D is a generic instrument developed by a European research team (The Euroqol Group) since 1990, designed to be self-administered and short enough to be combined with other measurement tools (Andayani, 2013). The EQ-5D has a simple approach that has been validated in various countries to measure a person's health status based on clinical and economic assessments. This instrument consists of 2 parts; the first part is the EQ-5D-5L sheet, which describes a 5-dimensional system (mobility, self-care, activity, pain/discomfort, and anxiety/depression) with five levels. The second part is a 20 cm Visual Analog Scale (VAS) sheet with the top endpoint being 'best health status' and the bottom is 'worst health status'.

Breast cancer is the most common cancer in Indonesia (National Cancer Control Committee, 2015), with a rising number of cases, making it crucial to assess the effectiveness and cost-efficiency of treatment options. Given the high cost of treatment, especially in advanced stages, utility analysis helps to determine whether the benefits justify the financial burden, enabling informed decisions on the most cost-effective use of healthcare resources. West Sumatra province ranks second with the highest prevalence of breast cancer in Indonesia. This study

aimed to determine the description of the quality of life of breast cancer patients at the national referral hospital in West Sumatra, specifically Dr. M. Djamil Padang Hospital, who underwent chemotherapy.

2.   MATERIAL AND METHODS

2.1 Research design, target population

This study used prospective techniques in data collection. Data collection was carried out using data collection sheet forms, EQ-5D-5L, and EQ-VAS of the Indonesian version of the EQ-5D-5L instrument on the website https://euroqol.org/. Each patient was asked to fill in the EQ-5D-5L form consisting of 5 questions in 5 levels according to the health condition that day. Respondents were also asked to mark and self-assess their health on the EQ-VAS form. Sociodemographic data were collected from respondents and the Register Form in the Chemotherapy Unit of Dr. M. Djamil Hospital Padang. The data collected included gender, age, education, domicile, occupation, marital status, presence or absence of other comorbidities, length of chemotherapy use, disease stage, chemotherapy cycle, and therapy regimen. Quality of life data was collected using the EQ-5D-5L and EQ-VAS questionnaire forms. This study has received ethical approval from the Research Ethics Committee of Dr. M. Djamil Padang Hospital with Number: DP.04.03/D.XVI.XI/55/2024. Respondents signed an informed consent form before the study began as proof of agreement to be involved in this study.

2.2 Inclusion and exclusion criteria

Sampling was determined by inclusion and exclusion criteria. The inclusion criteria were female breast cancer patients at Dr. M. Djamil Padang Hospital with an age range $\geq$ 20 years and who were willing to be respondents in the study. Exclusion criteria were breast cancer patients who refused to become respondents and did not complete the research form.

2.3 Time

This study was conducted at Dr. M. Djamil Padang Hospital from January to April 2024.

2.4 Data analysis

All data were inputted into Microsoft Excel form for analysis. Each data filled in the EQ-5D-5L value was converted into health status as a 5-digit number. The health status values were then converted into utility values using the Indonesian Value Data Sheet (Purba et al., 2017) EQ-VAS values were converted from a 0 - 100 data scale to a 0 - 1 data scale. Data analysis was performed using the IBM Statistic SPSS 26 application. Data normality tests were performed using the Kolmogorv-Sminorv and Shapiro Wilk tests. The test results showed that the EQ-5D and EQ-VAS utility data had an abnormal distribution, so the analysis of utility against sociodemographics was carried out using non-parametric tests, namely the Mann-Whitney Test (for two groups) and Kruskal Wallis (for more than two groups).

3.   RESULTS AND DISCUSSION

The target population for this study consisted of 59 breast cancer patients from the chemotherapy unit in February-March 2024. After applying the inclusion and exclusion criteria, 47 patients were selected as the final sample. The excluded patients did not receive the chemotherapy regimens of doxorubicin, cyclophosphamide, and docetaxel, had incomplete data, or were unwilling to participate in the interview. The final sample included 47 respondents: 24 patients who received the doxorubicin and cyclophosphamide regimen and 23 patients who received the docetaxel regimen.

Table 1: Frequency distribution data of respondents' sociodemographic characteristics (n=47)

Respondent Data	n	%
Age		
Young adult (15-40 years)	43	91.49
Elderly (≥60 years)	4	8.51
Educational Attainment		
Low	10	21.28
Intermediate	27	57.44
High	10	21.28
Occupation		
No Income	38	80.85
Earning Income	9	19.15
Domicile		
Padang	10	21.28
Outside Padang	37	78.72
Chemotherapy Regimen		
Doxorubicin and Cyclophosphamide	24	51.06
Docetaxel	23	48.94

Data on the sociodemographic characteristics of respondents in this study used data from 47 respondents, presented in Table 1 above. The data included age, latest education, occupation, origin, and chemotherapy regimen obtained. The data were grouped into 2 groups according to the chemotherapy regimen obtained: doxorubicin, cyclophosphamide, and docetaxel. All patients or respondents received doxorubicin, cyclophosphamide, and docetaxel chemotherapy regimens as additional information. Still, the regimen was divided into doxorubicin and cyclophosphamide regimens in cycles I-IV and the docetaxel regimen in cycles V-VIII.

The EQ-5D-5L instrument has five domains involving physical and psychological activities. Three domains on the EQ-5D-5L instrument involve physical activity, namely walking ability, self-care, and usual activities. The results of filling out the EQ-5D-5L questionnaire have obtained consent from the respondents involved in this study. Based on the research results in Table 2, more than half of the respondents have no problems with walking ability, as many as 80.85%. In the self-care domain, more than 50% of respondents did not experience difficulties in self-care. In these two domains, there were also no respondents who could walk or perform self-care. Generally, cancer patients will experience several side effects, such as fatigue, weakness, and unbearable pain. However, in this study, most patients had undergone surgery and recovered from their cancer, so patients had less difficulty in walking and self-care (Altun and Sonkaya, 2018). Doxorubicin, Cyclophosphamide, and Docetaxel can cause various adverse drug reactions (ADRs) such as nausea, vomiting, myelosuppression, cardiotoxicity, neuropathy, alopecia, and mucositis, with specific risks associated with each agent like heart damage from doxorubicin, bladder toxicity from cyclophosphamide, and peripheral neuropathy from

Table 2: EQ-5D-5L domain response of breast cancer patients

Domain	Level 1		Level 2		Level 3		Level 4		Level 5	
	n	%	n	%	n	%	n	%	n	%
Ability to walk	38	80.8	7	14.89	2	4.26	0	0	0	0
Self care	41	87.2	3	6.38	2	4.26	1	2.13	0	0
Normal activities	14	29.7	17	36.17	11	23.40	1	2.13	4	8.51
Uncomfortable pain	7	14.8	20	42.55	17	36.17	2	4.26	1	2.13
Anxiety/depression	13	27.6	10	21.28	17	36.17	6	12.77	1	2.13

Docetaxel (Altun and Sonkaya, 2018). However, we did not explore the ADR on this study.

In the domain of usual activities, it was found that almost 50% of the respondents experienced some difficulty. Through interviews conducted, most respondents experienced difficulties due to surgical wounds that sometimes hurt and were prohibited by the respondent's family to do heavy work such as housework or work. This was also due to the side effects of chemotherapy, such as fatigue and weakness, so respondents could not do heavy work as usual (Arora *et al.*, 2019).

Pain/ discomfort and anxiety/depression are the other two domains in the EQ-5D-5L instrument. Pain/discomfort that respondents often feel is in the form of headaches, breast surgery scars, and nausea after chemotherapy. The results showed that only seven respondents (14.89%) did not feel any pain/discomfort, and 40 others felt pain. This is in line with previous research where out of 393 patients, 41.5% experienced moderate to severe pain, 20.3%

relationship between the presence of pain and anxiety/depression in cancer patients undergoing chemotherapy (Arora *et al.*, 2019).

The anxiety/depression often experienced by respondents is because cancer is still the most feared disease in society and is known as the disease that takes the most lives (Gautama, 2022). Therefore, respondents often feel anxious and depressed because of their illness and also worry about their families, such as husbands and children. But not a few patients think positively and optimistically in undergoing treatment in order to recover. Based on the results of the study, there were 13 respondents (27.66%) who did not feel anxious/depressed.

A sociodemographic analysis of utility variables was conducted to find out which variables have the potential to cause differences in utility in this study. By knowing this, it can be estimated which variables need to be considered to increase utility.

Table 3 shows no significant difference in utility values (p=0.789; p>0.05) between adults and older

Table 3: Relationship between sociodemographic characteristics and utility of breast cancer patients undergoing chemotherapy at Dr. M. Djamil Hospital Padang

Sociodemographic characteristics	Respondents (n=47)	Utility value				*p-value*
		Median	**SD**	**Min.**	**Maks.**	
Age						
Adult	43	0.663	0.216	0.008	1.000	0.789[a]
Elderly	4	0.735	0.130	0.655	1.000	
Education Attainment						
Low	10	0.712	0.221	0.181	0.929	
Intermediate	27	0.606	0.207	0.008	0.904	0.022[b]
High	10	0.797	0.141	0.593	1.000	
Income						
No Income	38	0.625	0.202	0.008	0.911	0.002[a]
Earning Income	9	0.855	0.129	0.655	1.000	
Domicile						
Padang	10	0.563	0.195	0.174	0.770	0.048[a]
Outside Padang	37	0.698	0.207	0.008	1.000	

a Analysed using Mann-Whitney
b Analysed using Kruskal-Wallis

experienced anxiety, and 24.8% experienced depression. It can be concluded that there is a

people. This means that the utility value in adults is no significantly different from that of older people.

However, the average utility value in elderly patients was higher than in adult patients. This result is not in line with the results of a study conducted by Leinert et al., where their study stated that there was only a small difference in utility in patients aged <65 years compared to patients aged 65-70 who received chemotherapy. Younger patients may experience a decrease in quality of life compared to older patients because they have more social, work, or family commitments that are disrupted due to the patient undergoing chemotherapy. However, Leinert et al.'s study used the European Organization for Research and Treatment for Cancer (EORTC) Quality of Life Core Questionnaire (QLQ-C30) instrument, allowing this difference in results. The unbalanced number of adult and elderly patients may also cause a difference in results (Leinert *et al.*, 2017). Kouwenberg et al. stated that the EQ-5D-5L questionnaire can be used to assess and compare the quality of life between different patient groups (Kouwenberg *et al.*, 2019). Alava et al. demonstrated that the EQ-5D-5L questionnaire has the potential to capture smaller changes in health status and improvements in quality of life more accurately (Hernandez Alava *et al.*, 2018). Battisti et al., conducted research related to the effect of chemotherapy on elderly early breast cancer patients in 56 UK hospitals. The result is that chemotherapy has a negative impact on patients in the first 6 months, thereby affecting the patient's quality of life. However, this negative impact will disappear in the 18th month (Battisti *et al.*, 2021).

The results of utility statistical calculations showed a significant difference in utility values (p=0.022; p<0.05) in the last education variable. This means that the utility value in the low-education respondent group is different from the utility value of the medium and high-education respondent groups. Judging from the average value of each education group, the higher education group has a higher utility value than the low and middle education groups, namely 0.797. These results are in line with research conducted by Ngo et al., where it was found that a higher level of education provided a better quality of life to patients (Ngo *et al.*, 2023). This is because patients with higher education have better knowledge about their health conditions and are better able to communicate with doctors so that it helps them make better decisions for the treatment they undergo. In addition, patients are also able to manage the side effects of chemotherapy better, thus improving their quality of life (Ngo *et al.*, 2023).

There is a significant difference in utility value (p=0.002; p<0.05) in the employment variable. This means that the utility value in the non-income respondent group is different from the utility value of the income respondent group. Judging from the average utility value, the group of patients who earn income has a higher utility than those who do not. These results are in accordance with research conducted by Binotto et al., where the results state that socioeconomic factors such as income affect the quality of life of breast cancer patients. Higher-income gives patients a better quality of life (Binotto *et al.*, 2020).

There is a significant difference in utility value (p=0.048; p<0.05) in the origin/domicile variable. This means that the utility value of the respondent group from Padang differs from the value of the respondent group from outside Padang. Judging from the average utility value, the group of patients from outside the field had a higher utility than those who came from inside the field. This is not in line with research conducted by Ligt et al., where the results of their research state that the further the distance from the patient's home to a health facility or hospital will make his utility or quality of life lower (de Ligt *et al.*, 2019). However, the research of Novianti et al. stated

that environmental factors such as living outside the city provide life satisfaction, thereby improving quality of life. This is in line with the found utility value in patients who come from outside Padang, which is higher than in patients who come from Padang (Novianti, Wungu, and Purba, 2020).

Table 4 shows the value of utility and VAS of the chemotherapy dosage form. The comparison between the Doxorubicin and Cyclophosphamide regimen and the Docetaxel regimen revealed no statistically significant differences in utility values (p=0.882) or VAS scores (p=0.862) among breast cancer patients receiving chemotherapy. Both treatment regimens yielded similar results regarding perceived quality of life and overall health status, as indicated by utility and VAS measurements, suggesting that patient-reported quality of life outcomes are comparable between these two chemotherapy options. The comparison between the Doxorubicin and Cyclophosphamide regimen and the Docetaxel regimen revealed no statistically significant differences in utility values (p=0.882) or VAS scores (p=0.862) among breast cancer patients receiving chemotherapy. Both treatment regimens yielded similar results in terms of perceived quality of life and overall health status, as indicated by utility and VAS measurements, suggesting that patient-reported quality of life outcomes are comparable between these two chemotherapy options.

The study on breast cancer patients undergoing chemotherapy demonstrated several strengths, including comprehensive data collection that

encompassed a wide range of sociodemographic factors, the use of the validated EQ-5D-5L instrument to ensure the reliable and valid quality of life assessments, and comparative analysis between different chemotherapy regimens (doxorubicin and cyclophosphamide vs. docetaxel), providing insights into treatment impacts. Detailed sociodemographic insights highlighted the influence of education and income on quality of life, and the significant sample size of 47 patients added robustness to the findings. However, the study also had weaknesses, such as potential sample selection bias due to the reduction from 59 to 47 patients, unbalanced age groups, limited geographical scope as it was conducted at a single hospital in Padang, and potential recall bias from patient interviews. The cross-sectional design limited the assessment of long-term impacts, and the lack of longitudinal data made it difficult to evaluate changes in quality of life over time. Future research can build on these findings while addressing these limitations to enhance the understanding of the quality of life in breast cancer patients undergoing chemotherapy. These results are in line with the results in this study where the utility of the Docetaxel regimen was higher than the Doxorubicin and Cyclophosphamide regimen (Saptaningsih *et al.*, 2022). The selection of doxorubicin, cyclophosphamide, and docetaxel in this study is based on their prominence in current breast cancer treatment regimens, particularly for their effectiveness in various stages of the disease.

Table 4: Calculation of utility and VAS values of chemotherapy regimens

Component	Doxorubicin and Cyclophosphamide Regimen (n=24)		Docetaxel Regimen (n=23)		*p-value*
	Median	SD	Median	SD	
Utility value	0.637	0.254	0.704	0.148	0.882[a]
VAS value	76.25	11.44	76.30	14.71	0.862[a]

a Analysed using Mann-Whitney

including comprehensive data collection that

Doxorubicin and cyclophosphamide are standard

drugs used in combination chemotherapy for early-stage breast cancer. At the same time, docetaxel is often included in regimens for both early and metastatic breast cancer due to its proven efficacy in improving survival rates. However, while these treatments are widely used, this study aims to assess whether these chemotherapy regimens are the most cost-effective and beneficial in terms of overall health outcomes, quality of life, and the financial burden on the healthcare system. Although docetaxel is an important treatment option, the study will explore whether it provides the best balance of efficacy, cost, and patient quality of life compared to other available treatments, given the unique healthcare context of Indonesia.

4. CONCLUSION

Comparing the utility and VAS values between the doxorubicin and cyclophosphamide regimen and docetaxel regimen groups revealed no significant differences, although the docetaxel regimen group had slightly higher average values. The comparison between the Doxorubicin and Cyclophosphamide regimen and the Docetaxel regimen showed no statistically significant difference in either utility values or VAS values for breast cancer patients undergoing chemotherapy. Both regimens provided similar perceived quality of life and overall health status as measured by utility and VAS scores, suggesting comparable patient-reported quality of life outcomes between these chemotherapy treatments.

5. ACKNOWLEDGMENT

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