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Cost-Effectiveness of ACTH vs. ACT Chemotherapy Regimens at RSUP Dr. M. Djamil

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ABSTRACT: Introduction: Breast cancer is one of the most common cancers and is often diagnosed at a late stage, especially in Indonesia. This highlights the need for cost-effective treatment options. ACT (Adriamycin, Cyclophosphamide, and Taxane) and ACTH (ACT plus Herceptin/Trastuzumab) are used chemotherapy regimens, but studies comparing their cost-effectiveness are still limited. This study aimed to evaluate the cost-effectiveness of ACT versus ACTH for breast cancer treatment using tumor volume reduction. Method: A retrospective cost-effectiveness study was carried out at Dr. M. Djamil Hospital by comparing direct medical costs and tumor volume changes in breast cancer patients treated with ACT or ACTH regimens. Effectiveness was based on the average change in tumor volume, and cost-effectiveness was evaluated using the Incremental Cost-Effectiveness Ratio (ICER). Results: The mean tumor volume reduction in the ACT group was 2820.85 ± 11190.42 cm^3, and significantly higher at 9273.50 ± 60101.33 cm^3 in ACTH, although the difference was not statistically significant (p = 0.614). The average direct medical cost for ACTH was IDR 67,138,579, compared to IDR 13,005,027 for ACT. The ICER calculation resulted in IDR-838,935 per cm^3 of tumor reduction, while the negative ICER might suggest cost savings, it does not imply that ACTH is a dominant strategy indicating that ACTH incurred a higher cost with less effectiveness per unit of tumor reduction than ACT. Conclusion: The high associated cost leads to a negative ICER, suggesting that ACT may be more cost-effective in this setting. These findings are critical for optimizing chemotherapy choices within limited healthcare budgets.

Keywords: **ACT; ACTH; breast cancer; Cost-effectiveness analysis; tumor volume.**

Introduction

Breast cancer remains one of the leading causes of morbidity and mortality worldwide. In Indonesia, over 80% of breast cancer cases are diagnosed at an advanced stage, significantly limiting treatment options and reducing therapeutic outcomes [1,2]. According to data from the Indonesian National Health Insurance (BPJS) in 2022, breast cancer accounted for the highest number of cases and healthcare expenditures, totaling over 2.1 million cases with direct medical costs reaching IDR 45 billion [3]. This growing economic burden highlights the urgent need for cost-efficient treatment strategies.

Cost-effectiveness analysis (CEA) is crucial in health economic evaluations, particularly in resource-limited settings [4]. The CEA and the Incremental Cost-Effectiveness Ratio (ICER) are essential in resource-limited countries to ensure limited healthcare budgets are used for treatments that provide the most health benefit per cost. ICER supports decision-making by comparing the additional cost and effectiveness of treatments, helping prioritize affordable options with meaningful outcomes, such as selecting the most efficient chemotherapy regimen for breast cancer. This approach enables healthcare decision-makers to assess and compare the economic and clinical value of different therapeutic interventions. One of the primary metrics used in CEA is the Incremental Cost-Effectiveness Ratio (ICER), which quantifies the additional cost required to achieve a unit improvement in clinical outcomes [5,6]. This evaluation is essential in supporting policies that balance clinical effectiveness with cost efficiency, particularly in treating high-cost diseases like cancer.

Chemotherapy remains a cornerstone of breast cancer treatment and may involve single agents or combination regimens to optimize therapeutic efficacy [7,8]. Regimens commonly include anthracyclines (e.g., doxorubicin),

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alkylating agents (e.g., cyclophosphamide), and taxanes (e.g., docetaxel) [9–12]. For HER2-positive patients, the addition of targeted therapy such as trastuzumab (Herzumab) has been shown to improve clinical outcomes [13–15]. Trastuzumab, a monoclonal antibody approved by the U.S. Food and Drug Administration (FDA), selectively targets HER2-expressing cells through mechanisms including antibody-dependent cellular cytotoxicity (ADCC) [16], thereby enhancing tumor cell apoptosis [17]. Trastuzumab specifically targets HER2-positive cells by binding to the extracellular domain of the HER2 receptor, inhibiting cell proliferation and survival pathways while recruiting immune cells to mediate ADCC, making it particularly effective in treating HER2-overexpressing breast cancers.

While previous studies have demonstrated the superior clinical efficacy of trastuzumab-containing regimens, their high cost presents a challenge for widespread implementation in public health systems [18–20]. This study provides locally relevant cost and effectiveness data that can guide resource allocation and treatment decisions for breast cancer care in Indonesia, where economic constraints and high disease burden demand evidence-based prioritization. Therefore, it is imperative to conduct a cost-effectiveness comparison of the ACT regimen (doxorubicin, cyclophosphamide, and docetaxel) versus the ACTH regimen (ACT plus trastuzumab) to determine their relative value in clinical practice. This study aimed to evaluate the direct medical costs and tumor size reduction associated with both regimens and calculate the ICER, providing evidence to help clinicians choose affordable yet effective treatments and support policymakers in formulating cost-efficient breast cancer therapy guidelines within Indonesia's healthcare system.

Methods

Study Design, Target Population, Location

This study was conducted at Dr. M. Djamil Hospital in Padang, Indonesia, in 2024 using a descriptive research design. The data collected were retrospective and focused on breast cancer patients who had undergone chemotherapy. Sampling was performed using a non-random purposive sampling method, including only patients who met the inclusion criteria. The primary data source was the medical records of breast cancer patients treated at Dr. M. Djamil Hospital from 2023 to 2024. Cross-checking was conducted with billing data obtained from the hospital's Management Information System (SIM-RS) to ensure data validity and accuracy, allowing for a comprehensive understanding of treatment costs and chemotherapy regimens used. Although the sample size was limited by the number of eligible patient records available during the study period, it was sufficient to reflect real-world clinical and cost conditions in a tertiary care hospital setting. However, the sample size may limit the generalizability of the findings to broader populations.

Inclusion and Exclusion Criteria

The study included female breast cancer patients over the age of 20 who had completed eight cycles of chemotherapy, received the ACT regimen (doxorubicin, cyclophosphamide, and docetaxel) with or without trastuzumab, and had complete laboratory and medical cost data. Patients with metastatic disease or comorbidities were excluded to maintain sample homogeneity and analytical validity.

Perspective, Time Horizon, and Study Duration

The study evaluated costs from the hospital's perspective, focusing on direct medical expenditures. The sample consisted of BPJS-insured breast cancer patients who completed eight chemotherapy cycles in 2024 and met the inclusion criteria. Retrospective data from 2023–2024 were used for analysis. This period reflected the most recent and complete treatment and cost information available, ensuring relevance to current clinical practice. However, as with any retrospective study, there is potential for selection bias and incomplete documentation, which may affect data accuracy and limit the ability to control for confounding variables.

Cost Variables

The study analyzed direct medical costs, including administrative fees, medication costs, and supporting service charges. Data were retrieved from SIM-RS and the Health Insurance and Verification Division to ensure accuracy in the economic evaluation. In addition to financial variables, clinical effectiveness was assessed by measuring tumor volume, calculated using the ellipsoid formula.

Data Analysis

Patients were categorized based on the chemotherapy regimen received. A comparative analysis of baseline characteristics and therapeutic outcomes was conducted by calculating tumor volume changes. The compare means method was used to evaluate differences in effectiveness between groups. Inferential statistical tests (Chi-square, Mann-Whitney, and Kruskal-Wallis) were applied to assess the significance of observed differences. Subsequently, a

pharmacoeconomic analysis was carried out to calculate the Incremental Cost-Effectiveness Ratio (ICER), which indicates treatment cost-efficiency.

Cost-Effectiveness Analysis

The cost-effectiveness analysis evaluated the ICER between the new intervention and the comparator. The ICER was calculated using the following formula:

ICER = (Cost_intervention - Cost_comparator)/ (Effect_intervention - Effect_comparator)

In this study, ICER = (Cost_ACTH - Cost_ACT)/ (Effect_ACTH - Effect_ACT)

ICER = (Cost_ACTH - Cost_ACT)/(Decreasing tumor volume ACTH- Decreasing tumor volume_ ACT)

Result and Discussion

Study Sample and Analysis Approach

Following the application of inclusion and exclusion criteria, a total of 71 patient medical records met the inclusion criteria. In contrast, the remaining records were excluded following the study's exclusion parameters. Data from both intervention groups were subsequently analyzed, and their effectiveness was assessed by calculating the Incremental Cost-Effectiveness Ratio (ICER) to determine the more cost-effective therapeutic regimen. The findings of this study are expected to serve as a reference for hospital decision-making, particularly in the development of institutional formularies.

Sociodemographic Characteristics

The sociodemographic characteristics assessed in this study included age, occupation, marital status, and educational level. An overview of the breast cancer patients receiving either the ACT or ACTH regimen is presented in Table 1.

Table 1. Sociodemographic characteristics of breast cancer patients receiving ACT and ACTH Regimens.

Characteristics	Number of Patients (%)	P Value*
	ACT	ACTH
Age (years)		
26–35	3 (42.9)	4 (57.1)
36–45	7 (41.2)	10 (58.8)
46–55	12 (35.3)	22 (64.7)
56–65	4 (33.3)	8 (66.7)
>65	1 (100.0)	0 (0.0)
Education		
Low (No schooling, primary school)	11 (61.1)	7 (38.9)
Intermediate (Junior and senior high school)	9 (27.3)	24 (72.7)
High (Diploma, Bachelor's, Master's, Doctorate)	7 (35.0)	13 (65.0)
Marital Status		
Married	22 (37.3)	37 (62.7)
Unmarried	5 (41.7)	7 (58.3)
Occupation		
Employed	9 (30.0)	21 (70.0)
Unemployed	18 (43.9)	23 (56.1)

Table 2. Effectiveness of ACT and ACTH therapies in breast cancer treatment.

Effect Parameters	ACT (Mean ± SD, 95% CI)	ACTH (Mean ± SD, 95% CI)	P Value
Tumor Volume Reduction (cm^3)	2820.85 ± 11,190.42 (-16,050.93 to 7,247.63)	9,273.50 ± 60,101.33 (-899,897 to 27,545.97)	0.614

The sociodemographic characteristics of the patients, including age, educational level, marital status, and employment status, were analyzed. While most variables showed no statistically significant differences between the two treatment groups, educational level approached statistical significance (p= 0.056), suggesting a potential influence on the selection or accessibility of more advanced therapies such as ACTH. The majority of patients fell within the 46–55 year age group, which is consistent with the age range commonly affected by breast cancer in developing countries [21–23].

Clinical Parameters

The effectiveness of breast cancer therapy was evaluated based on the average change in tumor volume measured at the beginning and end of the chemotherapy cycle, as seen in Table 2.

Tumor volume was calculated using the ellipsoid formula, which incorporates three key dimensions: length, width, and height. This method is widely utilized for tumor volume estimation and has been validated through water displacement techniques to ensure measurement accuracy during therapy. In terms of clinical effectiveness, tumor volume reduction was used as the primary outcome. Although the mean reduction in tumor volume was greater in the ACTH group (9273.50 cm^3) compared to the ACT group (2820.85 cm^3), the difference was not statistically significant (p = 0.614). This result may be attributed to the high variability observed in tumor response, as reflected in the large standard deviations, particularly in the ACTH group [1,24]. These findings suggest that while ACTH may offer greater tumor shrinkage, its effect is not uniformly observed across all patients, potentially due to biological variability or differences in HER2 status [25].

Cost Analysis

Cost analysis conducted at Dr. M. Djamil Hospital in Padang compared the direct medical costs associated with the ACT regimen against those with the addition of trastuzumab (ACTH). These results are summarized in Table 3.

The cost-effectiveness analysis of breast cancer treatment in this study was performed by calculating the Incremental Cost-Effectiveness Ratio (ICER), which represents the ratio between the difference in costs and the difference in treatment outcomes between the interventions. The ICER serves as an indicator to assess whether the cost differences between interventions are justified by their clinical benefits [5,13,15]. From an economic perspective, the mean direct medical cost for patients receiving ACTH was considerably higher (IDR 67,138,579) compared to ACT (IDR 13,005,027). When adjusted for the effectiveness in terms of tumor volume reduction, the calculated ICER was IDR -838,935/cm^3, indicating that ACTH incurs significantly higher costs without a commensurate gain in clinical effectiveness, thus questioning its cost-effectiveness in this patient population. In this context, it is important to note that a negative ICER does not indicate dominance [26], but rather highlights that the more expensive treatment is less effective in terms of tumor volume reduction [18,27].

The ICER for tumor volume reduction was derived by comparing the average direct medical costs and the mean tumor volume changes between the ACTH and ACT intervention groups. The resulting ICER was IDR -838,935 per unit of tumor size reduction, indicating the

Table 3. ICER calculation for tumor volume reduction in ACT and ACTH chemotherapy regimens.

Chemotherapy Regimen	Average Direct Medical Cost (IDR)	Average Tumor Volume Reduction (cm^3)	ICER (IDR/cm^3)
ACTH	67,138,579	-92,735	-838,935
ACT	13,005,027	-282,085	

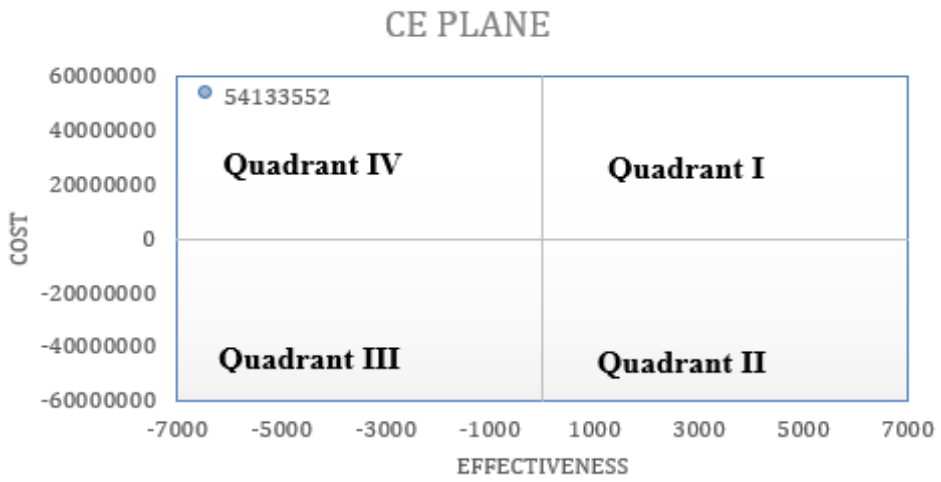

Figure 1. Cost-effectiveness diagram of breast cancer treatment using ACT-ACTH.

cost-effectiveness of each treatment regimen. A negative ICER of IDR -838.935 per cm^3 tumor reduction means that the ACTH regimen is both more expensive and less effective in reducing tumor volume compared to the ACT regimen, based on the data analyzed. In the context of decision-making, this suggests that ACTH is a dominated strategy—it costs more but delivers less benefit in terms of tumor size reduction. The Cost-Effectiveness (CE) Plane in Figure 1 presents a graphical representation of the cost-effectiveness distribution between the ACT and ACTH groups.

These findings are consistent with previous studies emphasizing the high economic burden of incorporating biologic agents such as Trastuzumab into chemotherapy regimens [6,15,28]. Although Trastuzumab has been demonstrated to improve survival outcomes in HER2-positive breast cancer patients significantly, its cost remains a critical barrier in resource-limited settings [5,6,19,21]. This underscores the need for careful patient selection based on HER2 expression and the potential implementation of pharmacogenomic testing to ensure targeted and efficient resource allocation.

Furthermore, the use of tumor volume reduction as the sole clinical endpoint may not fully capture the long-term benefits of therapy [1]. Parameters such as disease-free survival, overall survival, and quality of life may provide a more comprehensive assessment of treatment value. Future research should incorporate these outcomes, along with stratification based on HER2 status, to more accurately assess the cost-effectiveness of ACTH in appropriate patient subgroups.

Strengths and limitations

This study has several strengths that enhance its value, particularly in the Indonesian healthcare setting. It uses real-world data from a tertiary hospital, reflecting actual treatment patterns and costs. The analysis focuses on direct medical costs, offering practical insights for decision-makers and formulary development. By comparing ACT and ACTH chemotherapy regimens, it provides useful information on cost-effective options for breast cancer treatment, especially where local pharmacoeconomic data is limited.

However, some limitations should be noted. The study only measures tumor volume reduction as an outcome, not overall survival or quality of life. Its retrospective design may introduce bias due to incomplete data and lack of randomization. The small sample size (71 patients) limits generalizability, and the lack of HER2 status stratification may affect interpretation of Trastuzumab's effectiveness. Additionally, the economic analysis excludes indirect costs, potentially underestimating the true financial impact of the treatments.

Conclusion

In conclusion, while the ACTH regimen may offer greater tumor volume reduction in some patients, its significantly higher cost is not justified by a proportional increase in effectiveness based on current findings. These findings can inform hospital formulary decisions and resource allocation by prioritizing ACT as a more cost-effective regimen for the general breast cancer population, while highlighting the need for further

analyses incorporating survival, quality of life, and long-term outcomes to fully assess treatment value, thereby supporting more evidence-based national health policies on drug subsidies and the selective use of high-cost therapies like trastuzumab.

Ethical Approval

This research was conducted at Andalas University Hospital, making ethical clearance (ethical clearance) at the Research Ethics Committee of the M. Djamil Hospital No. DP.04.03/D.XVI.XI/109/2024.

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Competing Interests

The author(s) declare no conflict of interest regarding this manuscript. No funding was provided for this study.

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Author Contributions

NF designed the study. NAZR conducted the fieldwork. NF and DP supervised data collection in the field. NF and FH checked conceptual variables and wrote the manuscript. RA checked the language use. All authors read and approved the final version.

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