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Survival Analysis in Metastasis Breast Cancer with HER-2 Type That Received Vinorelbine And Capecitabine Chemotherapy at Prof. Dr. I.G.N.G. Ngoerah Central General Hospital

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ABSTRACT

Introduction: Breast cancer remains a leading cause of cancer-related mortality globally, particularly in developing regions. The HER-2 subtype is known for its aggressive nature and poor prognosis. ***Methods:*** A retrospective cohort study was conducted involving 42 patients diagnosed with HER-2 positive metastatic breast cancer who received either Vinorelbine or Capecitabine as second-line chemotherapy between January 2015 and December 2021. Survival analysis was performed using Kaplan-Meier curves and Cox regression to assess the impact of chemotherapy type on overall survival (OS) and progression-free survival (PFS). ***Results:*** The average OS for patients receiving Vinorelbine was 436.62 days, while those on Capecitabine had an OS of 422.33 days, indicating no statistically significant difference (p=0.874). For PFS, Vinorelbine patients had an average of 280.81 days compared to 308.76 days for Capecitabine, with no significant difference (p=0.725). ***Discussion:*** Although both treatments showed similar survival outcomes, Vinorelbine demonstrated a marginally longer OS in this cohort. This suggests that while both agents are viable options, further research is needed to optimize treatment strategies for HER-2 positive metastatic breast cancer patients. ***Conclusion:*** The findings emphasize the need for individualized treatment approaches in managing metastatic breast cancer, particularly for HER-2 positive subtypes.

Keywords: HER-2 positive; metastatic breast cancer; Vinorelbine; Capecitabine; survival analysis.

INTRODUCTION

GLOBOCAN data for 2018 also shows 2,088,849 new cases of breast cancer (11.6%) out of a total of 18,078,957 all types of cancer cases in the world, and the mortality rate reached 626,679 cases (6.6%) (GLOBOCAN, 2018). Meanwhile, from GLOBOCAN data for 2020, there was an increase to 2,261,419 cases of breast cancer (11.7%), with a mortality rate reaching 684,996 cases (6.9%) from a total of 19,292,789 cases of all types of cancer in the world, where we can see an increase of 0.3%. The distribution of breast cancer in the world is not evenly distributed but is more common in developed countries. This is in accordance with the distribution pattern of non-communicable diseases which are more common and become a health burden in developed countries compared to developing countries (GLOBOCAN, 2020).

From GLOBOCAN 2020 data, in Asia, it was found that breast cancer ranks second among all cancer cases, the first being lung cancer with 3,521,907 (12.2%) new cases and breast cancer with 3,287,590 (11.4%) new cases (GLOBOCAN, 2020).

Meanwhile, from GLOBOCAN 2020 data, in Indonesia, breast cancer is in first place with 65,858 (16.6%) new cases with a mortality rate of 22,430 (9.6%), followed by second place cervical cancer with 36,633 (9.2%) new cases with a mortality rate of 21,003 (9.0%) (GLOBOCAN, 2020). Apart from that, in Bali itself, using secondary data reported by RSUP Prof. Dr. I.G.N.G. Ngoerah Denpasar obtained data on the average number of visits by breast cancer patients per year of around 668 cases. The number of patients who died in 2012 was 153 patients. Data obtained in the last three months, namely October-December 2012, contained 162 cases of breast cancer (Trisnadewi, 2012).

Breast cancer itself is classified into several subtypes based on mutation characteristics and immunohistochemistry. The most common classifications that can be used are luminal and non-luminal subtypes. Each of these breast cancer subtypes has a different clinical profile and responds differently to breast cancer management approaches (Cardoso, 2019).

In the HER-2 positive sub-type, human epidermal growth factor receptor 2 (HER-2) is overexpressed in approximately 20-30% of breast cancer tumors. It is associated with more aggressive disease, higher recurrence rates, and increased mortality and poor prognosis (Mitri, 2012).

Stage IV breast cancer (metastatic breast cancer) is when breast cancer spreads to other organs, most often spreading to the bones, liver and lungs, and can also spread to the brain or other organs. For patients with stage IV breast cancer, therapy includes: hormone therapy, chemotherapy, targeted therapy, immunotherapy, combination therapy, surgery and/or radiation therapy (Henry, 2020).

Although much progress has been made in the treatment of breast cancer, the prognosis for patients with metastatic breast cancer (MBC) remains poor, with a survival rate of 2–4 years. Meanwhile, approximately <10% of new patients diagnosed initially as locally advanced or metastatic, and 30% - 50% of patients diagnosed at an early stage will subsequently develop metastasises, despite using adjuvant endocrine and chemotherapy therapy. Ideally, MBC therapy is highly individualized, and oncologists rely on clinical trial data to make decisions about which therapy may be most beneficial (Roche et al, 2010).

Historically, metastatic breast cancer (MBC) with HER2 has been an aggressive cancer subtype although trastuzumab and pertuzumab have changed survival rates. In first-line therapy, Trastuzumab, can be combined with a taxane, and has shown significant improvement in results compared to standard chemotherapy, in terms of progression-free survival (PFS) and overall survival (OS). The regimen demonstrated improvements from 7.4 months PFS and 25 months OS to 18 months and 56.5 months, respectively. Once first-line therapy fails, patient management becomes more complex. Meanwhile, the second line can be used as a topoisomerase I inhibitor (deruxtecan) in combination with tratuzumab, kinase inhibitor (Tucatinib), Capecitabine or Vinorelbine (Cantini, 2017; Nader-Marta 2022)

Vinorelbine is a type of chemotherapy drug that can be used in breast cancer. Specifically, Vinorelbine is indicated for metastatic breast cancer or breast cancer that does not respond to first-line chemotherapy regimens such as doxorubicin. In the evaluation of the effectiveness of Vinorelbine by Cybulska-Stopa (2013), Vinorelbine was proven to be effective as a second or more-line chemotherapy agent, either as a single agent or in combination with 5-flourouracil. In addition, oral capecitabine is a chemotherapy drug that is quite effective and tolerable in patients with prostate, renal cell, ovarian and pancreatic cancer, and metastatic breast and colorectal cancer (Christine, 2005; Xiu Cen, 2019). Capecitabine is among the most successful agents against MBC, both in monotherapy and in combination with several other agents (Roche, 2010).Based on the decree of the Minister of Health of the Republic of Indonesia number HK.02.02/MENKES/137/2016 Capecitabine and Vinorelbine are indicated as therapy for patients with advanced or metastatic breast cancer. However, further research on Vinorelbine and Capecitabine has not yet been conducted. Looking at RSUP Prof. Dr. I.G.N.G Ngoerah, these two regimens are quite widely used and their funding is guaranteed by the Health Social Security Administering Agency (BPJS). The effectiveness of this regimen as a treatment modality for metastatic breast cancer with HER-2 positive and second line has also never been carried out at RSUP Prof. Dr. I.G.N.G Ngoerah. Apart from that, advanced breast cancer is still a major challenge for surgeons and oncologists.

METHODS

Study Design, time and place of study

This study used an analytical observational design with a longitudinal approach, namely a retrospective cohort, to determine the role of breast cancer subtype as a predictor of survival in breast cancer patients undergoing Vinorelbine and Capecitabine chemotherapy. The research sample was recruited during observation by looking back (retrospective) regarding the subtype of breast cancer suffered at the time of diagnosis. The observation endpoint was defined as mortality (death) or survival. This research was conducted at RSUP Prof. Dr. I.G.N.G. Ngoerah Denpasar starts from May 2023 to December 2023.

Samples Characteristic

The accessible population in this study were metastatic breast cancer patients undergoing Vinorelbine and Capecitabine chemotherapy at Prof. Hospital. Dr. I.G.N.G. Ngoerah, Denpasar in the period observed, namely from January 2015 to December 2021. The minimum sample size was found to be 21 people per observation group. With two observation groups, the minimum sample size for the two groups is 42 people.

This study includes (1) HER-2 type breast cancer patients who have received first-line chemotherapy and targeted therapy (trastuzumab) according to the national formulary; and (2) aforementioned patients who underwent Vinorelbine chemotherapy and Capecitabine chemotherapy at Prof. Dr. I.G.N.G. Ngoerah Hospital, Denpasar during the study period. Exclusion criteria for this study were (1) breast cancer patients stage 0 to III; (2) patients who do not have immunohistochemistry results; (3) incomplete medical record data; and (4) have not received first-line chemotherapy and trastuzumab.

Data Analysis

Research analysis begins with a description of the sample characteristics. Then a Kaplan-Meyer curve analysis will be carried out to describe the survival of HER-2 subtype breast cancer patients undergoing Vinorelbine and Capecitabine chemotherapy. Finally, a Cox regression analysis was carried out to determine whether the HER-2 subtype affected the survival of breast cancer patients undergoing Vinorelbine and Capecitabine chemotherapy.

RESULTS

Characteristics of the study

This study obtained 42 samples that met the inclusion and exclusion criteria with detailed characteristics can be seen in Table 1. The age variable is known to have a normal distribution (Shapiro-Wilk, p>0.05) with an average age of 51.76 years. The lowest age is 31 years old, while the highest age is 67 years old. Of the 42 samples obtained, 21 samples were metastatic breast cancer patients with HER-2 subtype who received Vinorelbine chemotherapy and 21 other samples were patients who received Capecitabine chemotherapy.

In organ metastasis that occurred in the entire sample, metastasis in the lungs was the most, namely 21 patients, 1 patient in contralateral metastasis and lungs, 1 patient in the brain and lungs, 3 patients in the lungs and liver, 4 patients with lungs and bone, and 13 patients only in the lungs.

In the characteristics of the menstrual status of the samples studied, there were 24 samples with menstrual status pre-menopause and 18 samples with post-menopause. In the characteristics of tumor location, there were 26 samples with tumor location in Central, 9 samples with tumor location in an upper outer quadrant, 3 samples with tumor location in upper inner quadrant, 3 samples with tumor location in lower outer quadrant, and 1 sample with tumor location in lower inner quadrant. In terms of side tumor, 28 samples were found in the left breast and 14 samples in the right breast. In the characteristics of worsening seen from radiology or Karnofsky Score, it is known that the most worsening is a decrease in KS >20 in as many as 13 samples and bilateral massive pleural effusion in as many as 5 samples.

TABLE 1: Sample Characteristics.

Variable	Result
Age (Year), average (CI95%)	51,76 (49,47-54,05)
Overall Survival (Day), average (CI95%)	429,48 (332,70-526,25)
Progression-Free Survival (Day), average (CI95%)	294,79 (219,99-369,58)
Chemotherapy, n (%)	
Vinorelbine	21 (50)
Capecitabine	21 (50)
Metastasis (Organ), n (%)	
Liver	6 (14,3)
Contralateral metastasis	2 (4,8)
Contralateral metastasis, lungs	1 (2,4)
Neck lymph node metastasis	1 (2,4)
Brain	1 (2,4)
Brain, lungs	1 (2,4)
Lungs	13 (31)
Lungs, liver	3 (7,1)
Lungs, bone	4 (9,5)
Bone	9 (21,4)
Bone, liver	1 (2,4)
Menstrual State, n (%)	
Pre menopause	24 (57,1)
Post menopause	18 (42,9)
Location of Tumor, n (%)	
Central	26 (61,9)
Upper outer quadrant	9 (21,4)
Upper inner quadrant	3 (7,1)
Lower outer quadrant	3 (7,1)
Lower inner quadrant	1 (2,4)
Side of Tumor, n (%)	
Left breast	28 (66,7)
Right breast	14 (33,3)
Progression-Free Survival (Decreased of Karnofsky Score or aggravation in radiology)	
Brain metastasis	4 (9,5)
Brain metastasis, pleural effusion	1 (2,4)
Bilateral massive pleural effusion	5 (11,9)
Bilateral massive pleural effusion, Metastatic type pneumonic	4 (9,5)
Bilateral massive pleural effusion, Pneumonic type and subpleural type	2 (4,8)
Pleural effusion bilateral, Pneumonic type and subpleural type	1 (2,4)
Pleural effusion, pleural type metastasis	1 (2,4)
Liver metastasis	4 (9,5)
Local recurrence	1 (2,4)
Lungs metastasis	1 (2,4)
Liver metastasis	1 (2,4)
Metastatic type pneumonic	1 (2,4)
Metastatic type pneumonic, liver metastasis	1 (2,4)
Miliary type pulmonary metastasis	1 (2,4)
Decreased of KS >20	13 (31,0)
Subpleural type metastatic, bone	1 (2,4)

Throughout the study period, 42 deaths were found, which in this survival study is an event or event that is assessed as an outcome or final status. In stratification based on metastatic breast cancer patients with HER-2 subtype who received Vinorelbine and Capecitabine chemotherapy which can be seen in Table 2, it was found that there was no significant difference between metastatic breast cancer patients with HER-2 subtype who received Vinorelbine and Capecitabine chemotherapy in the characteristics of age, Overall Survival, Progression-Free Survival, metastasis, menstrual status, tumor location, and radiological worsening/Karnofsky Score.

TABLE 2: Sample Characteristics and Difference Test of Vinorelbine and Capecitabine Chemotherapy.

Variable	Vinorelbine Chemotherapy (n=21)	Capecitabine Chemotherapy (n=21)	p-value
Age (year), average (CI95%)	50,38 (46,34-54,42)	53,14 (50,74-55,54)	0,229
Overall Survival (day), average (CI95%)	436,62 (312,40-560,84)	422,33 (262,62-582,05)	0,563
Progression-Free Survival (day), average (CI95%)	280,81 (177,95-383,67)	308,76 (191,26-426,27)	0,920
Metastasis (Organ), n (%)			
Liver	1 (4,8)	5 (23,8)	
Contralateral metastasis	1 (4,8)	1 (4,8)	
Contralateral metastasis, lungs	1 (4,8)	0 (0)	
Neck lymph node metastases	0 (0)	0 (0)	
Brain	0 (0)	1 (4,8)	
Brain, lungs	1 (4,8)	0 (0)	0,662
Lungs	12 (57,1)	1 (4,8)	
Lungs, liver	1 (4,8)	2 (9,5)	
Lungs, bone	2 (9,5)	2 (9,5)	
Bone	2 (9,5)	7 (33,3)	
Bone, liver	0 (0)	1 (4,8)	
Menstrual State, n (%)			
Pre menopause	13 (61,9)	11 (52,4)	0,466
Post menopause	8 (38,1)	10 (47,6)	
Location of Tumor, n (%)			
Central	11 (52,4)	15 (71,4)	
Upper outer quadrant	6 (28,6)	3 (14,3)	
Upper inner quadrant	2 (9,5)	1 (4,8)	0,790
Lower outer quadrant	1 (4,8)	2 (9,5)	
Lower inner quadrant	1 (4,8)	0 (0)	
Side of Tumor, n (%)			
Left Breast	14 (66,7)	14 (66,7)	0,743
Right Breast	7 (33,3)	7 (33,3)	
Progression-Free Survival (Decreased of Karnofsky Score or aggravation in radiology)			
Brain metastasis	1 (4,8)	3 (14,3)	
Brain metastasis, pleural effusion	0 (0)	1 (4,8)	
Bilateral massive pleural effusion	5 (23,8)	0 (0)	
Bilateral massive pleural effusion, Metastatic type pneumonic	2 (9,5)	2 (9,5)	
Bilateral massive pleural effusion, Pneumonic type and subpleural type	0 (0)	2 (9,5)	0,672
Pleural effusion bilateral, Pneumonic type dan subpleural type	1 (4,8)	0 (0)	
Pleural effusion, pleural type metastasis	0 (0)	1 (4,8)	
Liver metastasis	3 (14,3)	1 (4,8)	

Variable	Vinorelbine Chemotherapy (n=21)	Capecitabine Chemotherapy (n=21)	p-value
Progression-Free Survival (Decreased of Karnofsky Score or aggravation in radiology)			
Local recurrence	1 (4,8)	0 (0)	
Lungs metastasis	0 (0)	1 (4,8)	
Liver metastasis	1 (4,8)	0 (0)	
Metastatic type pneumonic	1 (4,8)	0 (0)	
Metastatic type pneumonic, Liver metastasis	0 (0)	1 (4,8)	
Miliary type pulmonary metastasis	0 (0)	1 (4,8)	
Decreased of KS >20	6 (28,6)	7 (33,3)	
Subpleural type metastatic, bone	0 (0)	1 (4,8)	
MBC Primary dan Secondary	12 (57,1)	13 (61,9)	
MBC De-Novo	9 (42,9)	8 (38,1)	

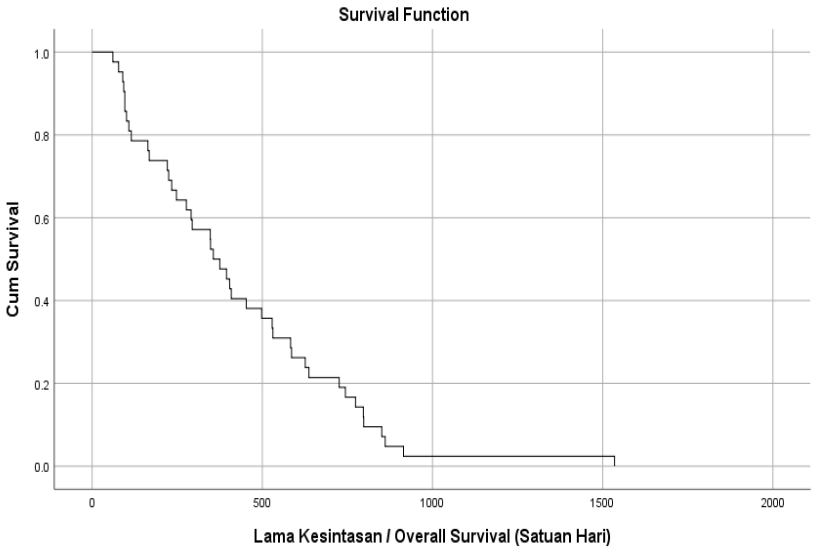

FIGURE 1: Kaplan-Meyer Overall Survival Curve for the Whole Sample.

In the analysis using the Kaplan-Meyer trajectory curve on the length of survival (Overall Survival) without stratification which can be seen in Figure 1, it was found that the average length of survival in all patients with metastatic breast cancer with HER-2 subtype was 429.48 days (95% CI 332.70-526.25). In Figure 1, it can be seen that the survival line shows the percentage of patients until the occurrence of an event or event which is the final status. In the analysis using the Kaplan-Meyer trajectory curve of overall survival, the overall survival rate of the sample was 0%. This indicates that the overall final status of metastatic breast cancer patients with the HER-2 subtype is death.

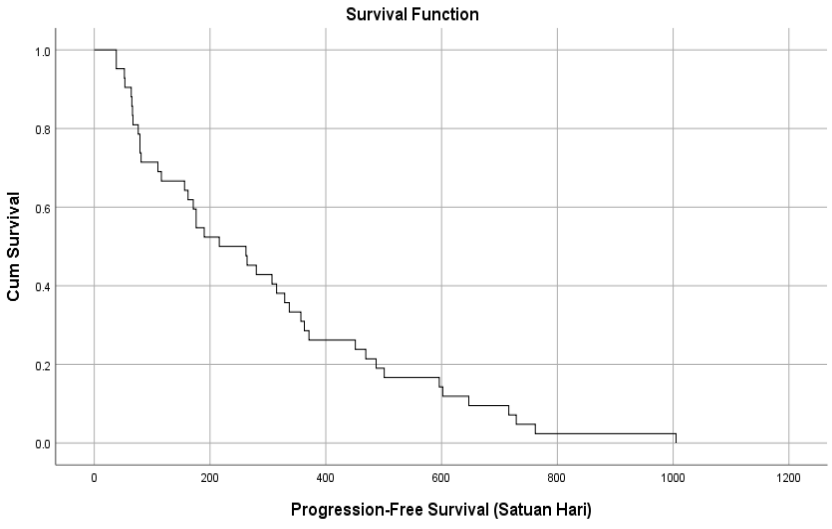

FIGURE 2: Kaplan-Meyer Progression-Free Survival Curve for the Whole Sample.

In the analysis using the Kaplan-Meyer trajectory curve of Progression-Free Survival without stratification which can be seen in Figure 2, it was found that the average length of survival in all patients with metastatic breast cancer with HER-2 subtype was 294.79 days (CI 95% 219.99-369.58).

In Figure 2, it can be seen the survival line that shows the percentage of patients until the occurrence of events or worsening in patients. In the analysis using Kaplan-Meyer curves of Progression-Free Survival, the overall survival rate of the sample was 0%.

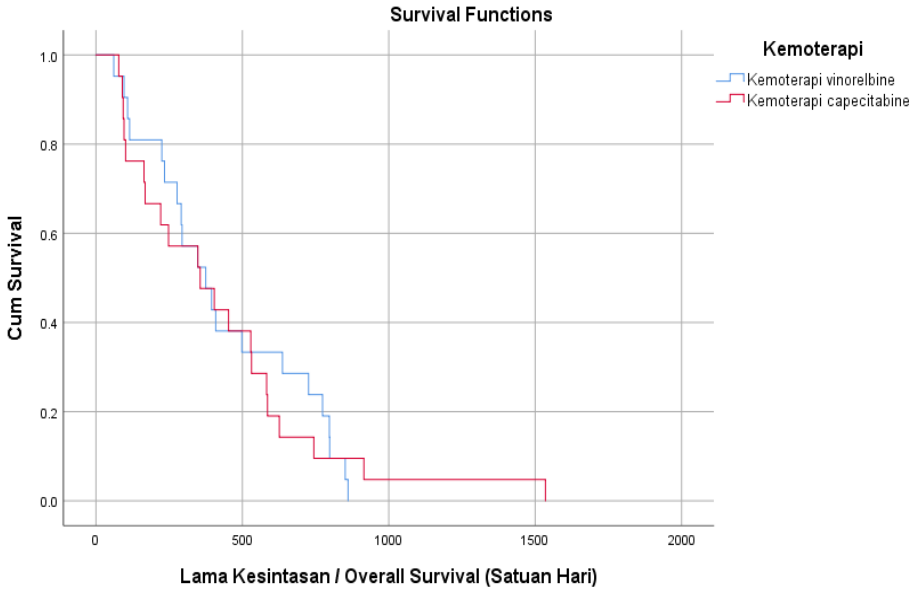

FIGURE 3: Kaplan-Meyer Overall Survival Curve Based on Vinorelbine and Capecitabine Chemotherapy.

In the analysis using the Kaplan-Meyer trajectory curve on the length of survival (Overall Survival) based on Vinorelbine and Capecitabine chemotherapy which can be seen in Figure 3, it was found that the average length of survival in metastatic breast cancer patients with HER-2 subtype who underwent Vinorelbine chemotherapy was 436.62 days (CI 95% 312.40-560.84), while the average length of survival in patients undergoing Capecitabine chemotherapy was 422.33 days (CI 95% 262.62-582.05). In Figure 3, we can see the survival line that shows the percentage of metastatic breast cancer patients who received vinorelbine or capecitabine chemotherapy until death.

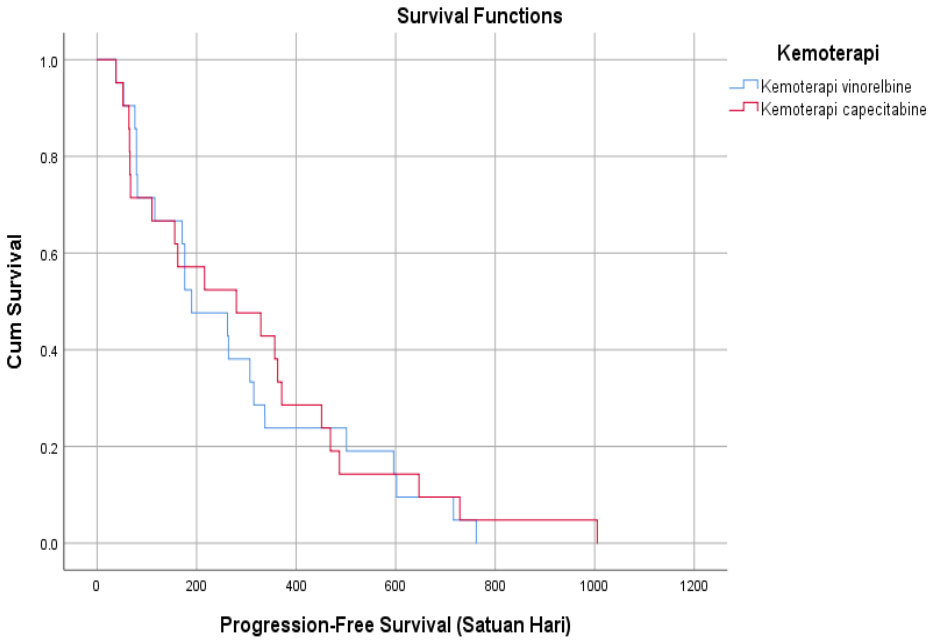

FIGURE 4: Kaplan-Meyer Progression-Free Survival Curve-Based on Vinorelbine And Capecitabine Chemotherapy.

In the analysis using the Kaplan-Meyer trajectory curve of Progression-Free Survival based on Vinorelbine and Capecitabine chemotherapy which can be seen in Figure 4, it was found that the average length of survival in metastatic breast cancer patients with HER-2 subtype undergoing Vinorelbine chemotherapy was 280.81 days (CI 95% 177.95-383.67), while the average Progression-Free

Survival in patients undergoing Capecitabine chemotherapy was 308.76 days (CI 95% 191.26-426.27). In Figure 4, it can be seen the survival line that shows the percentage of patients until the occurrence of events or worsening in patients. In the analysis using Kaplan-Meyer curves of Progression-Free Survival, it can be seen that the survival rate of Vinorelbine chemotherapy group reached 0% earlier than Capecitabine chemotherapy group.

In the analysis using Kaplan-Meyer curves of Overall Survival based on Vinorelbine and Capecitabine chemotherapy which can be seen in Figure 5, it was found that the average length of survival in metastatic breast cancer patients with HER-2 subtype who underwent Vinorelbine chemotherapy with Lungs metastasis was 15.233 months (CI 95% 10.896-19.570), while the average Overall Survival in patients who underwent Capecitabine chemotherapy with Lungs metastasis was 6.527 months (CI 95% 2.776 - 10.277). This shows that Her-2 subtype breast cancer patients with lung metastasis who received vinorelbine had an average period of 15,233 months from diagnosis to death, compared to capecitabine which was only 6,527 months.

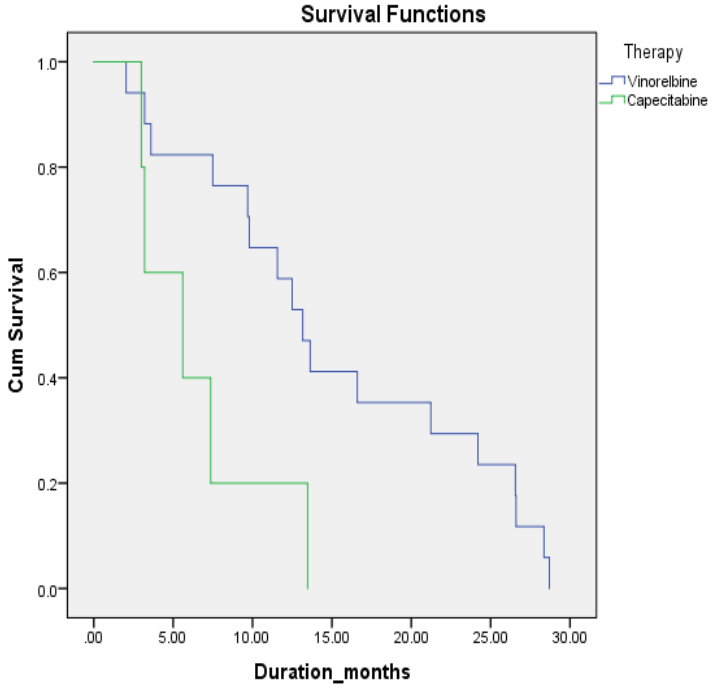

FIGURE 5: Kaplan-Meyer Overall Survival curve based on Vinorelbine and Capecitabine chemotherapy in patients with metastatic Lungs.

TABLE 3: Kaplan-Meyer Overall Survival Analysis based on Vinorelbine and Capecitabine chemotherapy.

Variable	Overall Survival (CI 95%)	p-value
Chemotherapy		
Vinorelbine	436,62 (312,40-560,84)	0,874
Capecitabine	422,33 (262,62-582,05)	

Kaplan-Meyer analysis of overall survival with further stratification based on the use of vinorelbine and capecitabine chemotherapy in patients with metastatic breast cancer with HER-2 subtype, obtained an average length of survival in patients with vinorelbine chemotherapy of 436.62 days (CI 95% 312.40-560.84), longer than the length of survival in patients with capecitabine chemotherapy of 422.33 days (CI 95% 262.62-582.05).

Furthermore, to support the hypothesis on the Kaplan-Meyer survival curve that has been obtained in the previous subchapter, it is necessary to conduct a log rank test. The log rank test is used to determine whether there are differences between survival curves in each factor group. From the test results, the p-value is 0.874. Since the p-value is >0.05, it can be concluded that there is no significant difference between the survival curves in the overall survival of metastatic breast cancer patients with HER-2 subtype undergoing vinorelbine chemotherapy and patients undergoing capecitabine chemotherapy.

TABLE 4: Kaplan-Meyer Progression-Free Survival Analysis based on Vinorelbine and Capecitabine chemotherapy.

Variable	Overall Survival (CI 95%)	p-value
Chemotherapy		
Vinorelbine	280,81 (177,95-383,67)	0,725
Capecitabine	308,76 (191,26-426,27)	

Kaplan-Meyer analysis of Progression-Free Survival with further stratification based on the use of vinorelbine and capecitabine chemotherapy in patients with metastatic breast cancer with HER-2 subtype, obtained an average Progression-Free Survival in patients with vinorelbine chemotherapy of 280.81 days (177.95-383.67), faster than the average Progression-Free Survival in patients with capecitabine chemotherapy of 308.76 days (191.26-426.27).

Furthermore, to support the hypothesis on the Kaplan-Meyer survival curve that has been obtained in the previous subchapter, it is necessary to conduct a log rank test. The log rank test is used to determine whether there are differences between survival curves in each factor group. From the test results, the p-value is 0.725. Since the p-value is >0.05, it can be concluded that there is no significant difference between the curves in Progression-Free Survival of metastatic breast cancer patients with HER-2 subtype undergoing vinorelbine chemotherapy and patients undergoing capecitabine chemotherapy.

TABLE 5: Cost-Effectiveness Comparison of Breast Cancer Treatment Based on Vinorelbine Chemotherapy.

Drug	Form	Dosage	Price / Unit (Rp)	Cycle	Total Cost (Rp)
Vinorelbine	50 mg/5 ml	25 mg/m^2 daily, twice a week (day-1 and 7)	1.927.039/vial	8 cycles	15.416.312
Capecitabine	500 mg/tab	Twice daily for 14 days	6.235/tablet	8 cycles	4.189.920

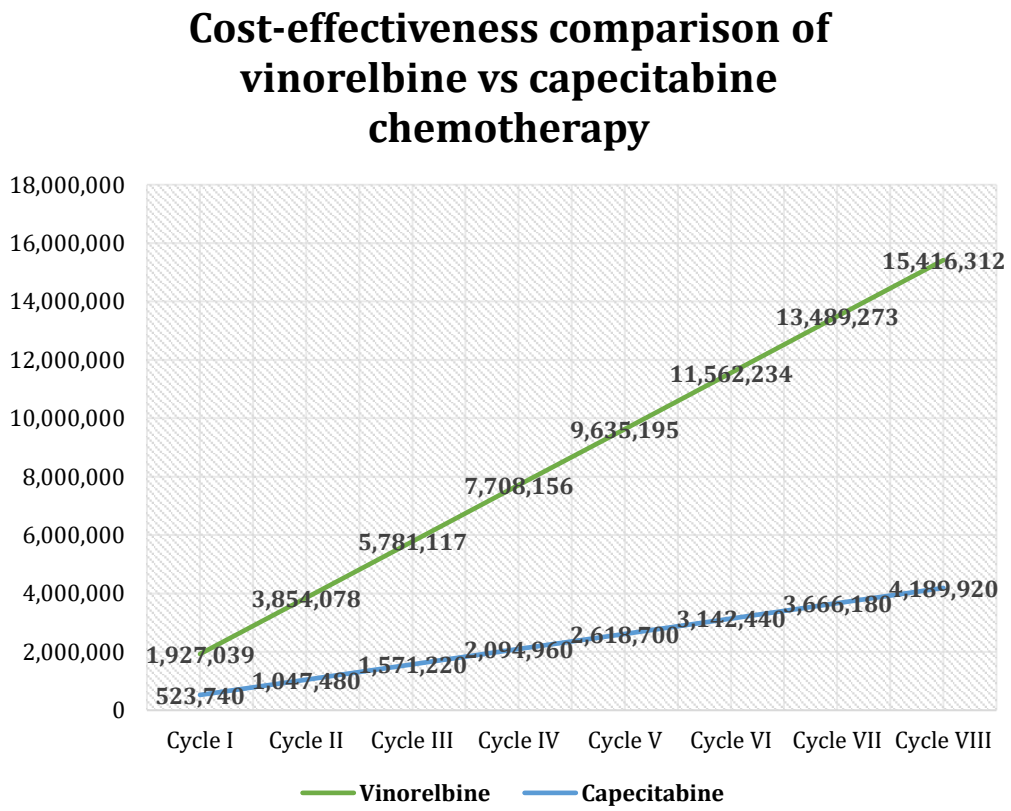

Figure 6: Cost-Effectiveness Comparison Curve of Vinorelbine and Capecitabine Chemotherapy Administration in HER-2 Type MBC.

Based on the comparison of the cost burden required in the chemotherapy treatment of breast cancer using vinorelbine and capecitabine for eight cycles, by taking the cut-off that the length of therapy required by each patient is 8 cycles, it was found that chemotherapy-based treatment using vinorelbine has a cost burden 3.67 times higher than that of capecitabine which can be seen in Figure 6.

DISCUSSION

In this study, there were 42 metastatic breast cancer patients with HER-2 subtype undergoing vinorelbine chemotherapy and patients undergoing capecitabine chemotherapy who were then used as samples. From the calculation results, the average age of the sample was 51.76 years, with the lowest age known to be 31 years while the highest age was 67 years. This age distribution is not much different from previous research on a population of women with advanced breast cancer, which found the average age of 36 thousand women with advanced breast cancer was 54.7 years, with a minimum age of 16 years and the oldest age of 70 years (Eng et al, 2016). Meanwhile, in a study by Frank (2020), advanced breast cancer patients with a total sample of 14 thousand patients found that the average advanced breast cancer patient was a patient aged > 60 years (47.8%), followed by 40-60 years (44.7%) and < 40 years (7.5%) (Frank et al, 2020). In addition, a study by Hai-long Chen (2016), out of 133 thousand patients, found that the average advanced breast cancer patient was aged 50-59 years (26.4%), 40-49 years (20.9%), and 60-60 years (22.1%) (Hai-long Chen at al, 2016).

From this study, it was found that the youngest advanced breast cancer patient was 31 years old and had a poor or fastest survival time of 96 days. This is related to age, where young breast cancer patients (<40 years) are more aggressive and have poor overall survival and prognosis (Hai-long Chen at al, 2016). Study by Sharma (2017), young breast cancer patients are more aggressive and have a poor prognosis. Compared to older breast cancer patients due to larger tumor size, more axillary lymph node involvement, higher grade of differentiation, positive lymphovascular invasion, and low ER/PR expression (Sharma et al, 2017).

In organ metastasis that occurred in the entire sample, metastasis to the lung organ was the most common, namely 21 patients, of which 1 patient had contralateral metastasis and lungs, 1 patient had brain and lungs, 3 patients had lungs and liver, 4 patients had lungs and bones, and 13 patients only had lungs. The most common organ locations of metastasis in breast cancer are bone, lung and liver (Xin Jin et al, 2015). While the study by Miranti (2022), with a total sample of 93 patients at Muhammad Husein Hospital in 2018, the most common location of metastasis in breast cancer patients is the lung followed by the second is bone. Then, based on the subtype of breast cancer, the HER-2 subtype most often metastasizes to the lung as much as 50% (Miranti et al, 2022).

In terms of the characteristics of the menstrual status of the studied samples, there were 24 samples with pre-menopause and 18 samples with post-menstrual status. In terms of tumor location, there were 26 samples with tumors located in the central, 9 samples with tumors located in the upper outer quadrant, 3 samples with tumors located in the upper inner quadrant, 3 samples with tumors located in the lower outer quadrant, and 1 sample with tumors located in the lower inner quadrant. In terms of tumor location characteristics, 28 samples were found in the left breast and 14 samples in the right breast. In the characteristics of worsening seen from radiology or Karnofsky Score, it is known that the most worsening is a decrease in KS >20 in as many as 13 samples and worsening of bilateral massive pleural effusion in as many as 5 samples.

The main result of this study, on Kaplan-Meyer survival curve analysis, found a mean length of survival of 429.48 days (332.70-526.25) for the entire sample without stratification. Meanwhile, Kaplan-Meyer analysis of overall survival with further stratification based on the use of vinorelbine and capecitabine chemotherapy in patients with metastatic breast cancer with HER-2 subtype, the mean length of survival in patients with vinorelbine chemotherapy was 436.62 days (CI 95% 312.40-560.84), longer than the length of survival in patients with capecitabine chemotherapy which was 422.33 days (CI 95% 262.62-582.05), but there was no statistically significant difference. However, there was a retrospective study by Chan (2009), which stated that capecitabine was more effective than vinorelbine (Chan et al, 2009). In addition, there is also other literature comparing vinorelbine with capecitabine used as second line and found no difference in effectiveness but found the most common side effect of vinorelbine is toxicity to the blood and capecitabine is toxicity to the skin, then pharmacoeconomically found capecitabine is more cost-effective than vinorelbine (Brunello et al, 2009).

While the Kaplan-Meyer analysis of Progression-Free Survival with further stratification based on the use of vinorelbine and capecitabine chemotherapy in patients with metastatic breast cancer with HER-2 subtype, the average Progression-Free Survival in patients with vinorelbine chemotherapy was 280.81 days (177.95-383.67), faster than the Progression-Free Survival in patients with capecitabine chemotherapy which was 308.76 days (191.26-426.27), but statistically, there was no significant difference.

Based on a study by Roche (2010), capecitabine is a second-line option for MBC patients that has been approved in the USA and Europe. The advantage of capecitabine is that the chemotherapy is available in oral form and can be used as monotherapy as second and third line. Overall Survival (OS) of patients who received capecitabine as monotherapy and second-line who previously received anthracycline and taxane chemotherapy had an OS of 10-15 months or 300 - 450 days with Progression-Free Survival (PFS)

of 3-5 months or 90 - 150 days. Another study by Montagna (2017) reported that capecitabine as monotherapy obtained OS of 22 months or 660 days with a total of 323 MBC patients (Montagna et al, 2017). In addition, there is a study by Vernieri (2020) where MBC patients with triple-positive who received capecitabine as monotherapy obtained OS 20.9 months or 627 days and PFS 5.96 months or 178 days (Vernieri et al, 2020). Meanwhile, MBC patients who received vinorelbine as monotherapy and second-line who previously received anthracycline and taxane chemotherapy obtained OS 6 - 16 months or 180 - 480 days with PFS 4 months or 120 days (Roche et al, 2010).

In a previous study by Eng (2016), it was found that the average survival of patients with advanced breast cancer was 2.3 years (820 days). Another study that specifically evaluated survival in advanced breast cancer patients receiving vinorelbine chemotherapy, either as a single agent or in combination, found a mean survival of 11.5 months or 345 days (Stravodimou, 2014). Another study that specifically studied survival in women with breast cancer receiving vinorelbine as second-line chemotherapy found a mean progression-free survival of 18 weeks or 180 days (Cybulska-Stopa, 2013).

Various sources and studies have shown that the duration of survival of individuals with advanced breast cancer can vary. This is because many factors can affect the duration of survival, and differences in the clinical situation at different research centers can affect the survival of the study population at that site.

Some factors that may affect the survival of metastatic breast cancer patients with the HER-2 subtype include high expression of HER-2 receptor in breast cancer tumors, which has been associated with poor prognosis. Patients with high HER-2 expression may have a higher risk of disease progression and may have lower survival (Slamon et al, 1987). In addition, the presence or absence of estrogen (ER) and progesterone (PR) hormone receptors in breast tumors may affect prognosis and response to therapy. Patients with HER-2 positive metastatic breast cancer who are also positive for ER or PR may have a better survival rate compared to patients who are negative for ER/PR (Nielsen et al, 2004; Sharma et al, 2017). A study by Qin (2013) of 243 HER-2 positive MBC patients in southern China found that a history of anti-HER2 therapy (trastuzumab or lapatinib), history of endocrine therapy, and history of surgical intervention were prognostic factors for OS in these patients, while poor PS (Karnofsky Score) and brain metastasis were the most important factors in determining patient survival (Qin et al, 2013). In another study by Mengyu (2021), the factors affecting patient prognostic are the characteristics of the tumor itself such as tumor size and histological grade (Mengyu et al, 2021).

Based on a cost comparison study in breast cancer chemotherapy treatment using vinorelbine and capecitabine, it was found that treatment with capecitabine had a lower cost. In eight treatment cycles, the cost of using vinorelbine was 3.67 times higher than capecitabine. The study concluded that although there was no significant difference in Overall Survival and Progression-Free Survival, capecitabine offered an advantage in terms of cost savings. These results were supported by a systematic review study conducted by Jones et al., which found that capecitabine had better cost-effectiveness than vinorelbine (Jones et al, 2004). In a recent study, capecitabine was found to be the most cost-effective therapy compared to vinorelbine, 5-fluorouracil and gemcitabine (Lewis et al, 2002), this was also reinforced by a study by Brunello, where pharmacoeconomically capecitabine was more cost-effective than vinorelbine (Brunello et al, 2009).

Response to chemotherapy: The patient's response rate to chemotherapy, including vinorelbine and capecitabine, may also affect survival. Patients who respond well to chemotherapy are likely to have a better prognosis compared to those who do not respond well (O'Shaughnessy, 2002). Another influencing factor is the extent to which the cancer has spread to other organs (metastasis), which can affect the patient's prognosis and survival. Patients with few or no distant metastasis may have a better prognosis compared to those with more extensive metastasis (Kennecke, 2010).

The main limitation of this research lies in its narrow focus on HER-2 subtype metastatic breast cancer patients without a comprehensive analysis of therapy side effects, quality of life impacts, or comparative effectiveness against other treatments. To address these gaps, it is suggested that future studies should expand their scope to include a detailed analysis of vinorelbine and capecitabine chemotherapy's response rates and survival impacts, identify predictive factors for optimal therapeutic response, evaluate treatment-related side effects and quality-of-life measures, and conduct comparative studies with alternative therapies to understand better the relative benefits of different treatment options for metastatic breast cancer patients with HER-2 subtype.

CONCLUSION

In this study of HER-2 positive breast cancer patients at Prof. I.G.N.G. Ngoerah General Hospital, demographic and clinical profiles aligned with previous research findings, with pulmonary metastases being the predominant metastatic presentation. Statistical analysis revealed no significant differences in Overall Survival and Progression-Free Survival between patients treated with vinorelbine versus capecitabine chemotherapy ($p>0.05$ for both parameters). The cost-effectiveness analysis demonstrated that capecitabine chemotherapy presents a substantially more economical option, with accumulated costs approximately one-fourth of those of vinorelbine treatment for equivalent therapeutic cycles, suggesting it may be the more pragmatic choice for resource-conscious clinical settings.

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