Doxorubicin-based Neoadjuvant Chemotherapy is Associated with Poorer Five-Year Survival in Patients with Locally Advanced Breast Cancer : A Retrospective Single-Center Study In Indonesia

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Abstract

One of the therapeutic modalities used to improve survival rate in breast cancer is neoadjuvant chemotherapy, which generally follows a doxorubicin-based regimen for patients with locally advanced breast cancer treated at Cipto Mangunkusumo General Hospital (CMGR). Five-year survival rates with doxorubicin-based versus non-doxorubicin-based neoadjuvant chemotherapy in locally advanced breast cancer are not known. To determine five-year overall survival (OS) in patients with locally advanced breast cancer who underwent doxorubicin or non-doxorubicin-based neoadjuvant chemotherapy at CMGR between 2011 and 2016. Clinical data of a total of 236 patients with locally advanced breast cancer who received neoadjuvant chemotherapy at CMGR during the study period were analyzed using the Kaplan–Meier method, log-rank test, and Cox proportional hazards regression analysis. Five-year OS rates were 37% and 48.9% in locally advanced breast cancer patients administered doxorubicin- and non-doxorubicin-based neoadjuvant chemotherapy, respectively. The probability of death was 1.38 times greater in locally advanced breast cancer patients receiving doxorubicin-based neoadjuvant chemotherapy [95% confidence interval (CI): 0.946–2.026] after controlling for lymphatic vascular invasion, clinical response, clinical stage, radiotherapy, histopathology, grade, and menopause status. Lymphatic vascular invasion had the greatest hazard ratio, at 4.74 (95% CI: 3.046–7.361). Five-year OS was higher in patients treated with non-doxorubicin-based neoadjuvant chemotherapy for locally advanced breast cancer.

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Introduction

Breast cancer, a malignant tumor of the breast tissue, has the highest incidence rate among all cancers in women, representing 43.3% of new cancer cases in this patient population. The estimated incidence of breast cancer in Indonesia is 12/100,000 women, compared with the higher rate of 92/100,000 women in the United States. Furthermore, approximately 12.9% of breast cancer cases result in death; this is the second highest cancer-related mortality rate, following only lung cancer.[1]

Locally advanced breast cancer is clinically defined as stage III breast cancer according to the tumor, node, and metastasis classification of the Union for International Cancer Control/The American Joint Committee on Cancer. Neoadjuvant chemotherapy is the currently recognized treatment strategy for locally advanced breast cancer. Although some studies suggest that neoadjuvant chemotherapy has shown benefits compared with adjuvant chemotherapy in short-term follow-up, a significant difference has not been observed in long-term follow up.[2]

Cipto Mangunkusumo General Hospital (CMGR) is one of the largest referral hospitals in Indonesia. Hospitalization rate of patients with breast cancer has been increasing since 2007 at this facility. According to the data from the Hospital Information System for Indonesia

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in 2008, hospitalized breast cancer cases ranked (18.4%) first among cancers at all hospitals in Indonesia, which was followed by cervical cancer (10.3%).[3]

In general, neoadjuvant chemotherapy for locally advanced breast cancer at CMGR is a doxorubicin-based regimen. However, no comparative studies have investigated the five-year overall survival (OS) in patients with locally advanced breast cancer receiving doxorubicin-based and non-doxorubicin-based neoadjuvant chemotherapy regimens. The current study was performed to address this gap in knowledge.

Materials and methods

This was a retrospective cohort study utilizing an observational, analytical design. Demographic and clinical data were collected from the medical histories of patients with breast cancer who received neoadjuvant chemotherapy at CMGR from January 2011 to December 2016, and followed up until May 2017. A total of 236 locally advanced breast cancer patients fulfilling the inclusion and exclusion criteria were included in the study (Figure 1). The inclusion criteria were female sex, age < 80 years, diagnosis of locally advanced breast cancer, and treatment with neoadjuvant chemotherapy. The exclusion criteria were incomplete medical records and recurrent breast cancer.

Five-year OS for breast cancer was determined based on cancer-related deaths. Data of patients who survived beyond the study period, those with relapse, and those who were lost to follow-up were censored. Univariate analysis was used to determine frequency distributions, and percentage value for each variable was presented. Bivariate analysis with the Kaplan–Meier method was used to determine the relationships of the dependent variable with independent variables. Hazard ratios (HRs) with 95% confidence interval (CIs) were calculated, and the log-rank test was used to determine significance. Next, proportional hazards assumption was tested using a goodness-of-fit test.

Multivariate analysis with the Cox proportional hazards regression was used to distinguish the effect of neoadjuvant chemotherapy on five-year OS from that of other variables, including age, clinical stage, menopause status, radiatiotherapy, histological type, clinical response, lymphatic vascular invasion, grade, and molecular subtype. Prior to the analysis, evaluation of the potential for confounding variables was performed based not only on a p cutoff value of 0.10 but also on the correlation of the biological relevance of the variable and the outcome/dependent variable.

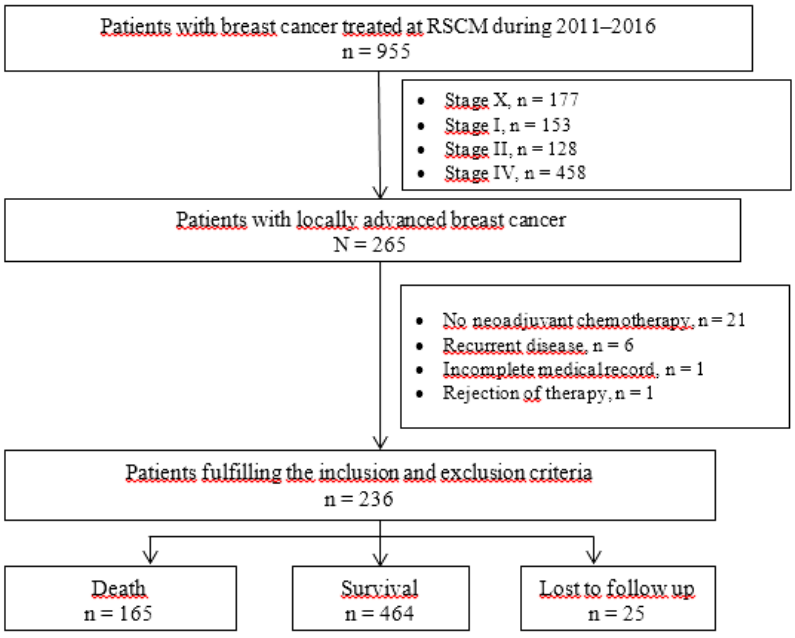

Figure 1. Flow Chart of the Subject Selection in This Study.

Results

The baseline and clinical characteristics of the patient cohort are as shown in Table 1. Among a total of 236 patients with locally advanced stage breast cancer treated at CMGR in the 2011–2016 period, 138 (58.47%) received doxorubicin-based neoadjuvant chemotherapy, whereas 98 (42.53%) patients received non-doxorubicin-based neoadjuvant chemotherapy. Doxorubicin-based therapy is the most widely prescribed type of neoadjuvant chemotherapy, which is administered as first-line by Indonesian oncologists.

The doxorubicin-based neoadjuvant chemotherapy at CMGR included either cyclophosphamide, Adriamycin, and 5-fluorouracil (CAF); cyclophosphamide, epirubicin, and 5-fluorouracil (CEF); or Adriamycin and cyclophosphamide (AC). In the study cohort, 127 (53.8%), 9 (3.8%), and 2 (0.8%) patients received CAF, CEF, and AC regimens, respectively.

The non-doxorubicin-based neoadjuvant chemotherapy at CMGR included either docetaxel or paclitaxel. Among the 98 patients who received non-doxorubicin-based neoadjuvant chemotherapy, 56 (23.7%) and 42 (17.8%) patients received paclitaxel-based (23.7%) and docetaxel-based neoadjuvant chemotherapy, respectively

The proportional hazards assumption test was performed based on the type of neoadjuvant chemotherapy, with the Kaplan–Meier curve and global test (Figure 2). The global test revealed a *p* value of 0.11. Figure 2 shows the Kaplan–Meier curve based on the neoadjuvant chemotherapy type.

The variable in neoadjuvant chemotherapy met the proportional hazards assumption, with a *P* > value > 0.05, and there was no intersection on the Kaplan–Meier curve. Median survival of the doxorubicin-based neoadjuvant chemotherapy group was 35 months, i.e., 50% of the patients died by the 35th month, whereas that of the non-doxorubicin-based neoadjuvant chemotherapy group was 44 months, i.e., 50% of the patients had died by the end of the 44th month. Table 2 shows HRs for OS based on the type of neoadjuvant chemotherapy in the study cohort.

The probability of death in patients who received doxorubicin-based chemotherapy was 1.46 times higher than in than those who received non-doxorubicin-based chemotherapy (95% CI: 1.031–2.058). This difference in probability was significant based on the log-rank test (*P*=0.007), indicating a significant effect of the type of neoadjuvant chemotherapy on five-year OS probability in patients with locally advanced breast cancer patients based on neoadjuvant chemotherapy.

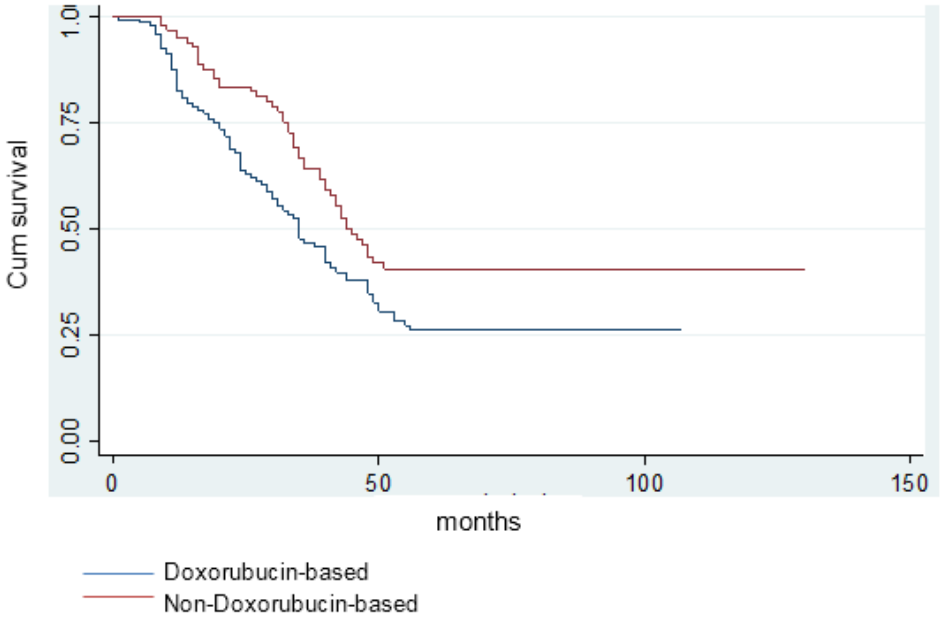

Figure 2. Kaplan–Meier Curve of Patient Survival Based on Two Types of Neoadjuvant Chemotherapy.

Variable	Number of Patients	Percentage
Neoadjuvant Chemotherapy		
Doxorubicin-based	138	58.47
Non-doxorubicin-based	98	42.53
Age		
< 35 years	17	44.92
35–50 years	113	47.88
> 50 years	106	7.20
Clinical Stage		
IIIA	28	11.86
IIIB	188	79.66
IIIC	20	8.47
Menopause Status		
Pre-menopause	81	34.32
Post-menopause	155	65.68
Radiatiotherapy		
Yes	155	65.6
No	81	34.32
Histological Type		
Nonspecific type	193	81.78
Other	43	18.22
Clinical Response		
Complete response	16	6.78
Partial response	32	13.56
No response	148	62.71
Progressive disease	40	16.95
Lymphatic Vascular Invasion		
Yes	127	53.81
No	109	46.19
Grade		
1	16	6.78
2	151	63.98
3	69	29.24
Intrinsic Subtype		
Luminal A	58	24.58
Luminal B	98	41.53
HER2 positive	42	17.80
Triple negative	38	17.79

Table 1. Characteristics of Patients Categorized According to Neoadjuvant Chemotherapy.

Neoadjuvant Chemotherapy	HR	95% CI	*p*
Non-doxorubicin-based	1		
Doxorubicin-based	1.46	1.031–2.058	0.033

Table 2. Bivariate Analysis for Overall Survival Based on the Type of Neoadjuvant Chemotherapy.

As presented in Table 3, bivariate analysis was performed to determine HRs for five-year OS for all study variables. Variables with significant HRs were clinical stage, type of neoadjuvant chemotherapy, clinical response, lymphatic vascular invasion, grade, and molecular subtype.

The confounding test was performed on all covariate variables. Potential confounding was determined for all covariate variables, which revealed that several covariate variables did not fit into the final model including molecular subtype and age.

In multivariate analysis, using the backward elimination method by entering all covariate variables, variables were added one at a time, starting with the one with the highest *p*-value to obtain the final model containing all variables that were statistically significant. Finally, clinical response, lymphatic vascular invasion, clinical stage, grade, histopathology, and radiatiotherapy were determined as variables that significantly impacted five-year survival in patients with locally advanced breast cancer receiving neoadjuvant chemotherapy.

As shown in Table 4, the HR for death in patients with locally advanced breast cancer receiving doxorubicin-based neoadjuvant chemotherapy was 1.38 (95% CI: 0.946–2.026), compared with those receiving non-doxorubicin-based neoadjuvant chemotherapy after controlling for clinical response, lymphatic vascular invasion, clinical stage, grade, histopathological type, radiatiotherapy, and menopause status as confounding variables.

Discussion

The findings of the current study are in agreement with that of a previous study demonstrating a significant improvement in disease-free survival following non-doxorubicin-based therapy compared with doxorubicin-based therapy (91% versus 86%) in which the patients achieved complete recovery for five years (HR: 0.66, 95% CI: 0.46–0.94, *P* = 0.0202). The five-year OS rates were 97% and 95% for non-doxorubicin and doxorubicin based chemotherapy, respectively (HR: 0.72, 95% CI: 0.40–1.30, *P* = 0.2677).[4]

According to a study by Anampa et al,[5] first-line chemotherapy could reduce mortality by 35% compared with no chemotherapy, they also determined that 20% reduction in mortality

Variables	Censored, *n* (%)	Event, *n* (%)	HR	95%CI	*p*
Neoadjuvant Chemotherapy					
Doxorubicin-based	48 (48.9)	50 (51.1)			
Non–doxorubicin-based	51 (37)	87 (63)	1.60	1.130–2.268	0.008*
Age					
< 35 years	45 (42.3)	61 (57.5)			
35–50 years	47 (41.6)	66 (58.4)	0.90	0.634–1.272	0.545
> 50 years	7 (41.2)	10 (58.8)	0.81	0.414–1.577	0.532
Clinical Stage					
IIIA	19 (67.9)	9 (32.1)			
IIIB	77 (40.9)	111 (59.1)	2.04	1.035–4.027	0.039
IIIC	3 (15)	17 (85)	4.97	2.212–11.182	0.000*
Menopause Status					
Pre-menopause	37 (45.7)	44 (54.3)			
Post-menopause	62 (40)	93 (60)	1.01	0.707–1.450	0.945
Radiotherapy					
Yes	62 (40)	93 (60)			
No	37 (45.7)	44 (54.3)	1.14	0.797–1.644	0.465
Histological Type					
Nonspecific type	15 (34.9)	28 (65.1)			
Other	84 (43.5)	109 (56.5)	1.03	0.678–1.557	0.898
Clinical Response					
Good response (complete response or partial response)	89 (54.3)	75 (45.7)			
Poor response (no response or progressive disease)	10 (13.9)	62 (86.1)	6.32	4.387–9.112	0.000*
Lymphatic Vascular Invasion					
No	67 (61.5)	42 (39.5)			
Yes	32 (25.2)	95 (74.8)	3.91	2.697–5.656	0.000*
Grade					
1	8 (50)	8 (50)			
2	70 (86.4)	81 (13.6)	1.10	0.532–2.275	0.797
3	21 (30.4)	48 (69.6)	1.98	0.935–4.184	0.075
Intrinsic Subtype					
Luminal A	32 (55.2)	26 (45.8)			
Luminal B	43 (48.9)	55 (51.1)	1.21	0.756–1.922	0.433
HER2-positive	13 (31.0)	29 (69.0)	1.64	0.964–2.779	0.068
Triple-negative	11 (28.9)	27 (71.1)	2.10	1.221–3.602	0.007*

*p<0.05

Table 3. Bivariate Analysis of Study Variables to Determine their Relationship with Overall Survival based on Type of Neoadjuvant Chemotherapy.

could be achieved with second-line chemotherapy compared with first-line chemotherapy; the mortality could be further reduced by 20% with the third-line chemotherapy compared with second-line chemotherapy.

In the current study, the HR for death was highest with lymphatic vascular invasion (4.74, 95% CI: 3.046–7.361), which means that locally advanced breast cancer patients with vascular invasion had a 4.74-times higher death rate than patients who did not have lymphatic vascular invasion.

According to a study by Vohrerr,[6] prognosis was worse in patients with lymphatic vascular invasion than those with positive axillary lymph nodes. One of the three patients with lymphatic vascular invasion experienced disease recurrence after 3 years of surgery in the current study.

The current study also found that the probability of death was 4.57 times higher among patients with poor clinical response compared with those with good clinical

response (95% CI: 3.030–6.905), which was similar to the findings of a study by Takahashi, et al who demonstrated that younger patients and those receiving doxorubicin-based chemotherapy had a worse clinical response and were more likely to die earlier than those with good clinical response.[7]

We also found that the HRs for death in patients with stage IIIB and IIIC cancer were 1.23 (95% CI: 0.604-2.516) and 2.93 (95% CI: 1.442-4.157) compared with those with stage IIIA disease. Our analysis indicated that the patients who did not receive radiotherapy were 1.88 times more likely to die than those who received radiotherapy (95% CI: 1.225-2.888). Arkoob et al.[8] reported that the highest survival rate in patients undergoing surgical treatment followed by radiotherapy was 69%.

Variable	HR	95% CI	*P*
Chemotherapy Neoadjuvant			
Non-doxorubicin-based	1		
Doxorubicin-based	1.38	0.946–2.026	0.095
Lymphatic Vascular Invasion			
No	1		
Yes	4.74	3.046–7.361	0.000*
Clinical Response			
Good response (complete or partial response)	1		
Poor response (no response or progressive)	4.57	3.030–6.905	0.000*
Clinical Stage			
IIIA	1		
IIIB	1.23	0.604–2.516	0.566
IIIC	2.93	1.442–4.157	0.001*
Radiatiotheraphy			
Yes	1		
No	1.88	1.225–2.888	0.004*
Histological Type			
Others	1		
Nonspecific type	1.63	1.043–2.533	0.032*
Grade			
1–2	1		
3	1.34	0.924–1.951	0.123
Menopause Status			
Post-menopause	1		
Pre-menopause	1.21	0.837–1.754	0.310

*P<0.05

Table 4. Final Model of the Multivariate Analysis for Five-Year Overall Survival in Patients with Locally Advanced Breast Cancer Based on the Type of Neoadjuvant Chemotherapy.

Furthermore, the patients with nonspecific histological type were 1.63 times more likely to die than those with other histological types (95% CI: 1.043–2.533). This finding is in agreement with the findings of a study by Ridolfi et al.[9] who reported that the ten-year survival of patients with medullary carcinoma was 84% compared with the 63% rate in patients with nonspecific histological-type cancer.Our analysis revealed that the HR for death was 1.34 in patients with grade 3 cancer compared with those with grade 1 or 2 disease (95%CI 0.924-1.951). Similar results were reported by Arkoob et al. (2007), who found that the rate of survival was lowest in patients with grade 3 breast cancer (43.2%).

Finally, our results indicated that the premenopausal patients were 1.21 times more likely to die than postmenopausal patients (95%CI 0.837-1.754). Menopause after the age of 55 years increases the risk of breast cancer. A study by Azamris[10] conducted at M. Djamil Padang Hospital in Indonesia reported that the estimated risk of breast cancer in postmenopausal women older than 55 years of age was 1.86 times higher than postmenopausal women younger than 55 years of age.

The major weakness of the current study was the exclusion of 10.6% of the subjects due to missing data or loss to follow-up during the study period, which might have affected the outcomes. Only the last hospital visit was included in the final analyses for those patients.

Conclusions

Among patients with locally advanced breast cancer, the probability of death was 1.38 times higher with the doxorubicin-based neoadjuvant chemotherapy compared with non-doxorubicin-based neoadjuvant chemot-hemotherapy (95%CI 0.946-2.026) after controlling for lymphatic vascular invasion, clinical response, clinical stage, radiotherapy, histopathology, grade, and menopause status. Furthermore, lymphatic vascular invasion, clinical response, clinical stage, radiotherapy, histopathology, grade, and menopause status affected survival rate in patients with locally advanced breast cancer who received doxorubicin-based neoadjuvant chemotherapy patients. The HR was highest

at 4.74 (95%CI 3.046–7.361) with lymphatic vascular invasion as the variable.

Declaration of Interest

The authors report no conflict of interest.

Acknowledgments

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