

RESEARCH COMMUNICATION

Prognostic Factors of Locally Advanced Breast Cancer Patients Receiving Neoadjuvant and Adjuvant Chemotherapy

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Abstract

Background: Neoadjuvant chemotherapy is known to be beneficial for down-staging patients with locally advanced breast cancer. Clinical stage, degree of cell differentiation and expression of estrogen/progesterone receptors and HER2/neu are all prognostic factors that may effect survival of patients with locally advanced breast cancer. The present study was conducted to determine their influence in a series of Indonesian patients **Materials and Methods:** The subjects were a total of 52 patients with locally advanced breast cancer in Sardjito General Hospital Yogyakarta, from January 2003 to June 2006. Survival analysis with Kaplan Meier was tested for age, clinical stage, degree of histological differentiation, estrogen-progesterone receptor (ER/PR), HER-2 expression and neoadjuvant as well as adjuvant chemotherapy. To find the most important influencing factors, significant variables were tested with multivariate Cox regression. **Result:** Of the 52 patients with locally advanced breast cancer, most were between 40-60 years old (41, 78%), almost half were stage IIIA (23, 44%), and the majority were negative for ER and PR (32, 61%). Her2 positivity was found in 29 patients (55%) and a moderate histological grade in 26 (50%). Thirty-nine patients were alive at the end of the study period (75%). There were no significant differences in survival between patients with and without adjuvant and neoadjuvant chemotherapy. Tumor characteristics that did influence survival were advanced stage ($p < 0.001$) and histological grade ($p < 0.001$), while HER-2 and ER/PR hormonal status had no effect. **Conclusion:** Clinical stage and degree of histological grade are the most significant prognostic factors for Indonesian locally advanced breast cancer cases, while hormonal status and HER-2 did not appear impact on our patient's survival.

Keywords: Locally advanced breast cancer - clinical stage - histological grade - HER-2 - ER/PR - Indonesia

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Introduction

Breast cancer is the most common malignant disease in women around the world, comprise 18% of cancer cases in women. Each year, there are one million new cases around the world and almost 60.000 patients die from this disease. In the US, there were 600,000 cases per year, in other developed countries there were 350,000 cases, while in developing countries, there were 250,000 cases per year (Rustogi et al., 2005).

Breast cancer is the fifth leading cause of cancer death around the world (after lung cancer, gastric cancer, hepatocellular cancer, and colon cancer). Despite its high incidence, overall deaths have been reduced, among others by administration and success of early therapy in breast cancer (Coleman, 2001; Rakha et al., 2007). Five years survival rate is increasing to 80% in 2003, compared to 52% in a 1971-1975 studies (Coleman, 2001).

Breast cancer is classified into two groups based on therapeutic management: the operable patients and patients who are no longer appropriate for surgery (Rustagi et al., 2005). Locally advanced breast cancer is included in the advanced breast cancer group. Clinical appearance

of this cancer is marked by tumor size of more than 5 cm, with or without involvement of chest wall and skin, accompanied by involvement of axillary lymph nodes or internal mammary nodes and supraclavicular nodes (Rakha et al., 2007).

Therapy of advanced breast cancer consists of radical surgery, radiotherapy, and chemotherapy with or without hormonal therapy. It has developed from using single modality to multiple modalities. Neoadjuvant chemotherapy is used in the management of advanced breast cancer. Initial chemotherapy with anthracycline or taxane is the standard therapy (Rustogi et al., 2005).

The success of locally advanced breast cancer treatment depends on some prognostic factors. Some researches indicated that clinical prognostic factors such as clinical stage (involvement of regional lymph node, size of tumor, and absence or presence of distant metastasis) and other prognostic factors (histological type, degree of histological grade, mitotic index) played significant role in recurrence of the disease and patient's survival (Pasqualini et al., 2003).

Some prognostic factors in patients with locally advanced breast cancer are: involvement of axillary lymph

node, tumor size, number of axillary lymph node involved, histological grade, hormonal status, expression of HER-2 and some other factors (Pasqualini et al., 2003).

From the description above, it was clear that neoadjuvant therapy is a standard therapy in patients with locally advanced breast cancer. However, there was no enough data that support the importance of neoadjuvant therapy on improving survival. The prognostic factors that may influence survival in patients with locally advanced breast cancer haven't also been well defined. This study aimed to further understand whether the neoadjuvant chemotherapy may have better effect on survival as compared with adjuvant therapy, and which prognostic factors that might have role in survival of patients with locally advanced breast cancer.

Materials and Methods

Study was conducted in January 2003 until December 2006 for 52 patients with locally advanced breast cancer in Sardjito General University Hospital Yogyakarta. Kaplan-Meier survival analysis was tested for age, clinical stage, degree of histological grade, estrogen-progesterone receptor (ER/PR), HER-2 and also neoadjuvant as well as adjuvant chemotherapy. To assess the most influencing prognostic factor, significant variables were tested with multivariate Cox regression.

Results

From 52 patients with locally advanced breast cancer, mostly were between 40-60 years old in 41 patients (78%). According to stage, mostly of stage IIIA in 23 patients (44%), while 32 patients with negative ER and PR (61%).

Tabel 1. Characteristics of Locally Advanced Breast Cancer Patients

Variable	Age	Neoadjuvant		Adjuvant	
		n	%	n	%
Age (years old)	< 40	2	7.4	3	12
	40-60	21	77.8	20	80
	>60	4	14.8	2	8
Stage	II B	0	0	5	0
	III A	15	55.6	8	32
	III B	10	37	12	48
	III C	2	7.4	0	0
Hormonal Status	ER+/PR +	5	18.5	7	28
	ER+/PR -	3	11.1	3	12
	ER-/PR+	2	7.4	0	0
	ER-/PR-	17	63	15	60
HER2	+	11	40.7	18	34.6
	-	16	59.3	7	19.2
Histological grade	Poor	5	18.5	5	20
	Intermediate	14	51.9	12	48
	Good	8	29.6	8	32
Death	Alive	22	81.5	17	68
	Death	5	18.5	8	32

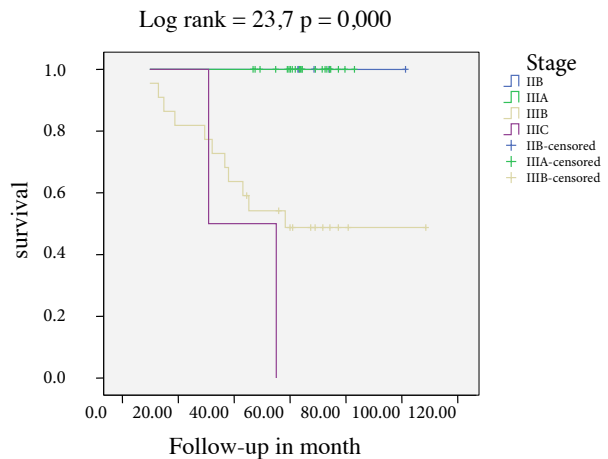


Figure 1. Kaplan Meier Curve of Clinical Stage for Survival

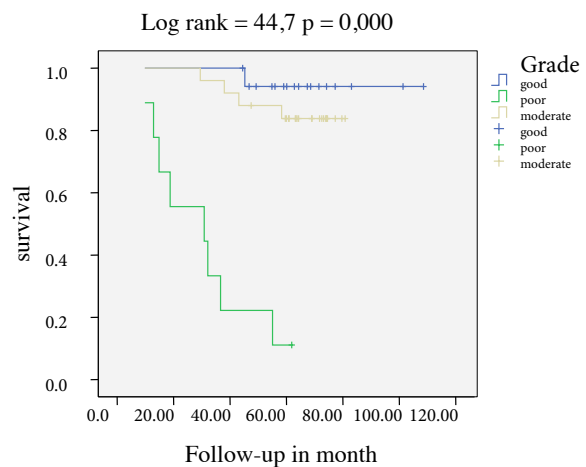


Figure 2. Kaplan Meier Curve of Histological Grade to Survival

Her2 positive found in 29 patients (55%), moderate histological grade in 26 patients (50%). Thirty-nine patients were alive (75%). No significant difference in survival between patients with adjuvant and neoadjuvant chemotherapy. Tumor characteristic that might influence survival, were advanced stage ($p < 0,001$) and degree of histological grade ($p < 0,001$), while HER-2 and hormonal status of ER/PR had no effect on survival (Table 1).

Discussion

Since January 2003 until December 2006 there were 106 patients diagnosed as having locally advanced breast cancer. From those 106 patients, 52 patients showed the inclusion criteria and then were enrolled in the study, all were women. Patients with locally advanced breast cancer, 26 patients received adjuvant chemotherapy, while the other 26 patients received neoadjuvant chemotherapy. During follow up, there were five deceased patients from the neoadjuvant group (9.6%) and 8 patients (14.4%) with adjuvant therapy.

Survival analysis to assess effect of adjuvant as compared to neoadjuvant therapy on patients survival showed no statistically significant difference with log rank value of 1.127 and $p = 0.288$. Mean duration of follow up for patients with adjuvant therapy is 63 months and

61 months for neoadjuvant group. This finding was in concordance with previous study that concludes that there were no statistically significant difference in ten years survival rate of neoadjuvant as compared to the adjuvant group, with the value of 68% vs. 65% (n=329; p=0.21), also no difference in mean survival between patients who received adjuvant and neoadjuvant chemotherapy (Chang et al., 2009).

Patients with locally advanced breast cancer mostly presented in age of 40-60 years old (n=41; 78.8%), while the other patients presented in the age of less than 40 years old and more than 60 years old were 5 patients (9.65%) and 6 patients (11%), respectively. In survival analysis to assess patients survival for each age group, no statistically significant result was obtained (p=0.852; log rank=0.319). No statistically significant correlation between age and survival in patients with locally advanced breast cancer was found. A literature stated that the effect of age of breast cancer diagnosis on prognosis was still controversial (Clark, 2000).

Regarding the tumor characteristic, it was found that most patients presented in clinically advanced stage. In this study most patients presented in stage IIIA (n=23; 44%) and IIIB (n=22; p=42%), followed by 2 patients (3%) that presented in stage IIIC and 5 patients (9%) in stage IIIB.

Survival analysis on the effect of clinical stage on survival showed significant correlation (p value of 0.000 and log rank=23.749) (Figure 1).

Prognosis for patients with earlier stage without lymph node metastasis was favorable compared with patients with advanced stage with lymph node involvement (Giardino, 2003).

In this study, most patients have a moderate degree of histological grade (n=26; 48,1%). Patients with well-differentiated cancer cells was 16 (34,6%), while the other 10 patients (17.3%) had poor differentiation. The result of survival analysis for effect of histological grade on survival showed a significant value (p=0.000 and log rank=44.74) (Figure 2).

Histological grade was one of the most important prognostic factors. A poor degree of differentiation had adverse effect on recurrence, metastasis, and death (Schniff & Guidi, 2000).

Expression of HER-2 was positive in most patients (n=29; 55%) and negative in 23 patients (44%). Survival analysis of type of chemotherapy on survival showed no significant difference (p=0.070 and log rank 3,291).

Some researches found that expression of HER-2 was associated with death hazard in breast cancer patients (HR: 1.6, 95% CI: 1.0-2.6) (Beeghly et al., 2008).

There were two significant variables: clinical stage, degree of histological differentiation that were statistically significant (p<0,05) on survival. With Cox regression analysis, those two variables did not show concomitant effect on survival.

In conclusion, No significant difference in survival between therapy of locally advanced breast cancer with adjuvant or neoadjuvant treatment. Prognostic factors that showed significant correlation with survival were clinical stage and histological grade. Prognostic factors such as

ER/PR and HER-2 had no effect on survival.

Further study that involved other departments with more patients should be conducted and medical record should be improved in order to obtain a comprehensive data. Larger sample size and longer duration of follow up is required to further evaluate the locally advanced breast cancer patients survival.

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