Predictive factors of stable or progressive disease during anthracycline with/without taxane-based neoadjuvant chemotherapy in breast cancer

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- ABSTRACT -

Predictive factors of stable or progressive disease during anthracycline with/without taxane-based neoadjuvant chemotherapy in breast cancer

Purpose: Neoadjuvant chemotherapy (NAC) has been shown to effectively downstage locally advanced breast cancer; however, clinically, no response or a progression of the tumor can occur in some cases. Predictive factors of no response or progression are unknown compared to predictive factors of a response. We investigated predictive factors of stable (SD) or progressive disease (PD) during anthracycline with/without taxane based NAC.

Methods: From January 2012 to December 2015, data were collected retrospectively by reviewing medical records of patients who received NAC. Statistical analysis was performed to compare patients with a partial response and complete remission to patients with SD or PD after anthracycline- or taxane-based chemotherapy.

Results : In total, 242 patients received NAC with an anthracycline and cyclophosphamide (AC) regimen and 159 patients received anthracycline followed by taxane. Forty-one (17%) patients had SD or PD after anthracycline treatment, and 50 (31%) patients had SD or PD after taxane treatment. Factors related to SD/PD after an AC regimen included a large pretreatment tumor size (p = 0.001), clinical T3 status (p = 0.01) and high histologic grade (p < 0.001). In cases of a T regimen, clinical T3 status

(p = 0.04), estrogen receptor(ER)/progesterone receptor (PR) positivity (p = 0.04, 0.02, respectively), and human epidermal growth factor 2(HER2) negativity (p < 0.001) were predictors of no response.SD or PD after taxane was a negative predictor of disease-free survival. Moreover, SD or PD after anthracycline or taxane was a negative predictor of overall survival.

Conclusions: Clinical stage, ER/PR positivity and HER2 negativity were predictors of no response to NAC. We need a combination of predictive factors including clinical data, novel molecular markers, and genetic factors to identify patients who will show no response to the standard NAC regimen.

Key Words: *Breast neoplasms, Neoadjuvant therapy, Disease Progression*

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ABBREVIATION

NAC: Neoadjuvant chemotherapy

pCR: pathologic complete response

US: ultrasonography

MRI: magnetic resonance imaging

FDG PET-CT: fluoro-2-deoxyglucose positron emission tomography-computed Tomography

AC: anthracycline and cyclophosphamide

RECIST: Response Evaluation Criteria in Solid Tumors

T: taxane

LNs: lymph node

PR: partial response

CR: complete response

SD: stable disease

PD: progressive disease

ER: Estrogen receptor

PR: progesterone receptor

HER2: human epidermal growth factor receptor 2

TNBC: triple negative breast cancer

I. INTRODUCTION

Neoadjuvant chemotherapy (NAC) is the standard treatment for locally advanced breast cancer. NAC may have some clinical benefit for locally advanced breast cancer. because it can increase the likelihood of breast conservation and an improved cosmetic result from removal of less tissues. In addition, NAC can control non-visualized micrometastases and, the response to treatment can be observed *in-vivo*. According to the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18 and B-27 [1], NAC has no benefits for disease-free and overall survival compared to adjuvant chemotherapy. However, the pathologic response and tumor subtype influences the prognosis of patients who undergo NAC. Although the definition of a pathologic complete response (pCR) is not yet established, if patients achieve a pCR after NAC, they could have a significant improvement in long-term outcomes [2,3]. The factors that can predict a pCR are known, but factors that can predict progression during NAC have not been reported.

The objective of this study was to identify the predictive factors of no response or cancer progression during standard NAC and compare the disease-free and overall survival between the responsive group and the no response group. Although many other variables can affect the response to NAC, we can consider other treatment options for patients with expected disease progression during a standard NAC regimen.

II. METHODS

Study population

A total of 263 patients were treated with NAC for breast cancer in a single center between 2012 and 2015. We excluded patients who had distant metastasis at initial diagnosis of breast cancer (n=5), or who received another NAC regimen (n=9), had bilateral breast cancer (n=3), or were treated at another institute (n=4). The database including clinical, radiologic and pathologic assessment was reviewed retrospectively.

Staging and Treatment

Patients underwent physical examination and breast imaging, such as mammogram and ultrasonography (US), of the breast and lymph nodes (LNs). After confirmation of breast cancer by core biopsy of the breast lesion and/or fine needle aspiration biopsy of the axilla LNs, magnetic resonance imaging (MRI) and fluoro-2-deoxyglucose positron emission tomography/computed tomography (FDG PET-CT) were performed for staging work-up. Breast cancer stages were based on the American Joint Committee on Cancer 7th edition. All patients had clinical stage II or III breast cancer. In our institution, the most common regimen for NAC is four cycles of AC (60mg/m² of adriamycin and 600mg/m² of cyclophosphamide) every 3 weeks. Subsequently, four cycles of T (150mg/m² of paclitaxel or 75mg/m² of docetaxel) were administered every 3 weeks. If the tumor was human epidermal growth factor receptor 2 (HER2) positive, trastuzumab (6mg/kg of Herceptin®) was added to the T regimen. About 3 to 4 weeks after the last administration of

chemotherapy, definite surgery was performed.

Assessment of tumor response

After four cycles of the AC regimen and/or 4 cycles of the T regimen, or during the treatment if a growing mass was identified by physical examination, breast US and MRI was performed for clinical response assessment. However, because proper validated criteria for monitoring of tumor response by MRI has not been established, we measured the tumor and LN size by MRI to determine the response using the Response Evaluation Criteria in Solid Tumors (RECIST) criteria (version 1.1) [3]. Therefore, the definition of progressive disease was at least a 20% increase in the sum of the target lesions and an absolute increase of at least 5mm.

The pathological response to NAC was determined by analyzing the surgical specimen. A pCR was defined as no residual cancer cells in the breast and axilla LNs. Residual ductal carcinoma *in situ* was included as a pCR.

Statistical analysis

Differences of characteristics of tumors and patients were analyzed using Student's t-test and the chi-square test. A logistic regression model and the backward elimination method were used in univariate and multivariate analysis of prognostic factors. Overall survival and disease free survival were determined using Kaplan-Meier methods. A $p<0.05$ was defined as statistically significant, and all statistical analyses were performed using SPSS 18.0 (SPSS Inc., Chicago, USA).

III. RESULTS

The data of 242 patients who received NAC before definite surgery were reviewed. One hundred fifty nine (66%) were treated with AC followed by T, and 83 (24.3%) received AC as NAC. According to the response to NAC, patients who had a partial response (PR) and a complete response (CR) were grouped together and compared with the group with stable disease (SD) and progressive disease (PD).

Response to an anthracycline-based regimen

Forty-one(17%) patients had SD/PD after or during the AC regimen. Median a ges were 47 years in the SD/PD group and 46 years in the PR/CR group. Patie nts and tumor characteristics at diagnosis are shown in Table 1. Menopausal st atus did not influence the response to AC. The histologic type of cancer showed a significant difference between the two groups. The SD/PD group had more non-ductal and lobular cancer than the PR/CR group (p = 0.001), but histologic type was not a predictive factor of response to the AC regimen. We also evalu ated clinical T and N stage. There was no difference in clinical T and N stage, but patients with SD/PD were more likely to have a larger tumor at diagnosis (p = 0.02).

After the definitive surgery, patients with SD/PD had a higher rate of mastecto mies for breast cancer (58.5% for SD/PD vs. 20.9% for PR/CR; p = 0.000). Po stoperative characteristics of the tumors are shown in Table 2. As expected, pa thological T stage (ypT stage), N stage (ypN stage), and cancer-stage had signi ficant differences between the two groups. Estrogen receptor (ER) and/or proge

sterone receptor (PR) and HER2 status were not different between the two gro ups, and being hormonal receptor positive did not predict a response to or prog ression during anthracycline treatment, We evaluated clinical tumor response to anthracycline according to intrinsic subtypes (Figure 1 a). Overall, 17.3% of ER/ PR+/HER2- patients, 18.5% of ER/PR+/HER2+ patients, 16.7% of ER/PR-/HE R2+ patients and 15.3% of ER/PR-/HER2- patients showed clinically SD/PD with no significant difference across groups (p = 0.120).

Response to taxane-based regimen

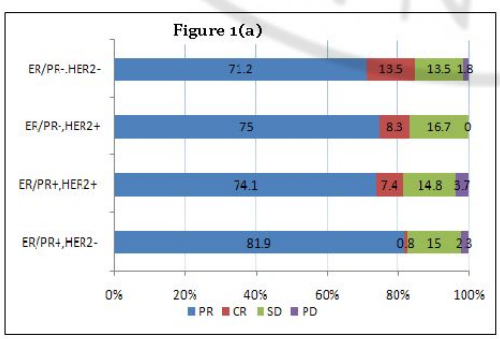
Fifty (31.4%) patients had SD/PD after or during the AC-T regimen. Median ages were 44 years in the SD/PD group and 47 years in the PR/CR group. Menopausal status did not influence the clinical response. Similar to the response to anthracycline, the histologic type of cancer showed significant difference between the two groups. However, unlike the response to anthracycline, clinical T and N stage influenced the cancer response to taxane (p = 0.001, p = 0.042, respectively) (Table 1). The postoperative characteristics of tumors and patients after taxane-based regimen were similar to those after an anthracycline-based regimen (Table 2). Clinical tumor response to taxane according to intrinsic subtypes is described in Fig ure 1 b. Overall, 31.4% of ER/PR+/HER2- patients, 22.2% of ER/PR+/HER2+ p atients, 20.0% of ER/PR+/HER2+ patients, and 45.5% of ER/PR-HER2- patie nts showed clinically SD/PD with a significant difference a cross groups ((p = 0.005).

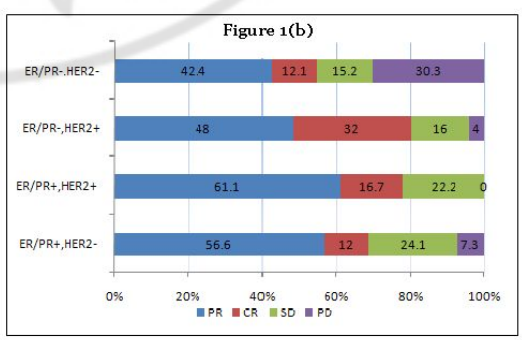
Table 1. Patients and tumor characteristics at diagnosis

Clinical characteristics		Anthracycline (n=242) SD/PD No. of patients (%)	PR/CR No. of patients (%)	p	Taxane (n=159) SD/PD No. of patients (%)	PR/CR No. of patients (%)	p
No.of patients		41 (16.9)	201 (83.1)		50 (31.4)	109 (68.6)	
Age, years							
	Mean ± SD	47.6 ± 9.5	46.8 ± 9.3		45.1 ± 10.0	47.9 ± 9.2	
	Median	47	46		44	47	
	Range	28-69	26-78		26-69	29-71	
Menopausal status				0.318			0.615
	Premenopause	26 (63.1)	136 (67.7)		35 (70.0)	68 (62.4)	
	Postmenopause	15 (36.9)	65 (32.3)		15 (30.0)	41 (37.6)	
BMI							
	Mean ± SD	23.1 ± 2.3	23.4 ± 2.9		23.1 ± 2.5	23.7 ± 3.0	
	Median	22.9	22.6		22.2	23.1	
	Range	18.5-28.2	18.2-32.0		20.1-30.1	18.5-32.0	
Histology				0.001			0.004
	Ductal	30 (73.2)	185 (92.0)		36 (72.0)	103 (94.5)	
	Lobular	1 (2.4)	12 (6.0)		5 (10.0)	3 (2.8)	
	Mucinous	3 (7.3)	1 (0.5)		0 (0.0)	2 (1.8)	
	Mixed	2 (4.9)	1 (0.5)		4 (8.0)	1 (0.9)	
	Other	5 (12.2)	2 (1.0)		5 (10.0)	0 (0.0)	
Tumor size,cm							
	Mean ± SD	4.4 ± 2.6	3.4 ± 1.8		4.2 ± 2.5	3.5 ± 2.0	
	Median	3.5	3		3.5	3	
	Range	1.4-10.9	1.0-11.0		1.2-10	1.2-12.0	
T stage				0.177			0.001
	T1	6 (14.6)	24 (11.9)		11 (22.0)	12 (11.0)	
	T2	23 (56.2)	146 (72.6)		21 (42.0)	81 (74.3)	
	T3	6 (14.6)	13 (6.5)		9 (18.0)	5 (4.6)	
	T4	6 (14.6)	18 (9.0)		9 (18.0)	11 (10.1)	
N stage				0.591			0.042
	N0	6 (14.6)	37 (18.4)		4 (8.0)	6 (5.5)	
	N1	29 (70.8)	152 (75.6)		35 (70.0)	97 (89.0)	
	N2	5 (12.2)	8 (3.9)		8 (16.0)	5 (4.6)	
	N3	1 (2.4)	4 (2.1)		3 (6.0)	1 (0.9)	

Table 2. Postoperative characteristics of tumor and patients

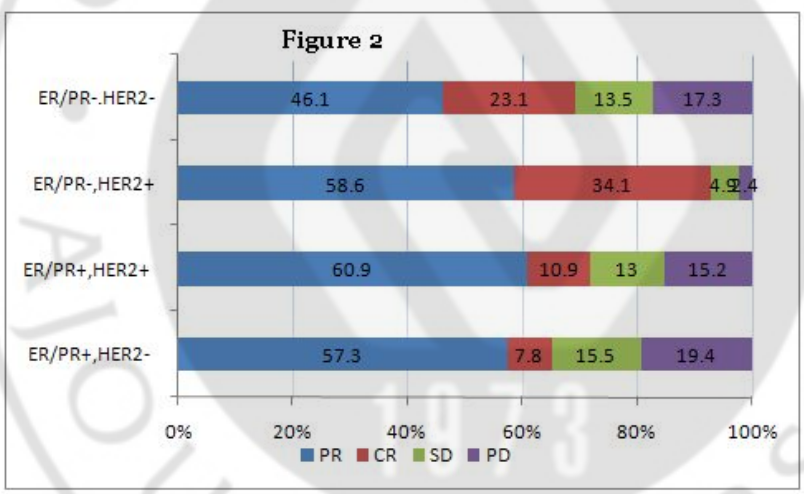
Treatment and Tumor characteristics		Anthracycline SD/PD (n=41) No. of patients (%)	Anthracycline PR/CR (n=201) No. of patients (%)	p	Taxane SD/PD (n=50) No. of patients (%)	Taxane PR/CR (n=109) No. of patients (%)	p
Surgery				0			0
	Mastectomy	24 (58.5)	42 (20.9)		28 (56.0)	23 (21.1)	
	BCS	17 (41.5)	159 (79.1)		22 (44.0)	86 (78.9)	
Tumor size, cm							
	Mean ± SD	3.5 ± 2.4	2.0 ± 2.3		3.8 ± 3.2	1.7 ± 2.1	
	Median	3	1.5		2.9	1.3	
	Range	0-10.0	0-19.0		0-19.0	0-16.0	
ypTstage				0.006			0
	T0	1 (2.4)	33 (16.4)		1 (2.0)	22 (20.2)	
	Tis	2 (4.9)	15 (7.5)		0 (0.0)	9 (8.3)	
	T1	7 (17.1)	89 (44.3)		16 (32.0)	50 (45.9)	
	T2	23 (56.1)	51 (25.4)		21 (42.0)	24 (22.0)	
	T3	6 (14.6)	10 (5.0)		8 (16.0)	3 (2.8)	
	T4	2 (4.9)	3 (1.4)		4 (8.0)	1 (0.8)	
ypNstage				0.021			0.001
	N0	11 (26.8)	108 (53.7)		12 (24.0)	56 (51.4)	
	N1	17 (41.5)	64 (31.8)		20 (40.0)	38 (34.9)	
	N2	10 (24.4)	18 (9.0)		9 (18.0)	14 (12.8)	
	N3	3 (7.3)	11 (5.5)		9 (18.0)	1 (0.9)	
AJCC stage				0.002			0.001
	0 (pCR)	2 (4.9)	13 (6.5)		0 (0.0)	8 (7.3)	
	I	0 (0.0)	42 (20.9)		4 (8.0)	20 (18.3)	
	II	21 (53.6)	83 (41.3)		22 (44.0)	45 (41.3)	
	III	17 (41.5)	33 (31.3)		23 (48.0)	16 (33.1)	
Histologic grade				0.094			0.101
	I	8 (19.5)	31 (15.4)		8 (16.0)	17 (15.6)	
	II	11 (26.8)	101 (50.2)		18 (36.0)	56 (51.4)	
	III	22 (53.7)	91 (34.4)		24 (48.0)	36 (33.0)	
Nuclear grade				0.694			0.682
	I	25 (61.0)	107 (53.2)		28 (56.0)	59 (54.1)	
	II	13 (31.7)	85 (42.3)		20 (40.0)	43 (39.4)	
	III	3 (7.3)	9 (4.5)		2 (4.0)	7 (6.5)	
LVI				0.011			0.001
	Present	17 (41.5)	42 (20.9)		23 (48.0)	17 (15.6)	
	Non/unknown	24 (58.5)	159 (79.1)		27 (52.0)	92 (84.4)	
ER status				0.879			0.334
	Positive	26 (63.4)	125 (62.2)		29 (58.0)	71 (65.1)	
	Negative	15 (36.6)	76 (37.8)		21 (42.0)	38 (34.9)	
PR status				0.42			0.374
	Positive	24 (58.5)	92 (45.8)		22 (44.0)	56 (51.4)	
	Negative	17 (41.5)	109 (54.2)		28 (56.0)	53 (48.6)	
HER2 status				0.267			0.257
	Positive	11 (26.8)	52 (25.9)		9 (18.0)	34 (31.2)	
	Negative	30 (73.2)	149 (74.1)		41 (82.0)	75 (68.8)	
Ki-67 score							
	Median	30	10		30	9	
	Range	1-90	0-90		0-90	1-80	





Pathologic response after neoadjuvant chemotherapy

The final pathologic response after NAC was confirmed after definite surgery; 31 patients (12.8%) had SD, 37 patients (15.3%) had PD, and 39 patients (16.1%) had a pCR. We analyzed these results according to the intrinsic subtypes and found that 34.9% of ER/PR+/HER2- patients,28.2% of ER/PR+/HER2+ patients,7.3% of ER/PR-/HER2+ patients and 30.8% of ER/PR-/HER2- patients had pathologically SD/PD with a significant difference among groups (p = 0.003) (Figure 2).



Predictive factors of no response to neoadjuvant chemotherapy

Univariate analysis results of potential predictors of no response to anthracycline/taxane and multivariate analysis results using possible predictive variables are shown in Table 3 and 4. Factors that correlate SD/PD after an AC regimen include a large pretreatment tumor size (OR = 2.19; 95%CI, 1.02 to 3.25; p = 0.001), clinical T3 status (OR = 6.34; 95%CI, 1.04 to 24.06; p = 0.01), and high histologic grade (OR = 2.01; 95%CI, 1.34 to 4.49; p < 0.001). For the T regimen,

clinical T3 status (OR = 2.09; 95%CI, 0.55 to 9.87; p = 0.04), ER/PR positivity (p = 0.04, 0.02) and HER2 negativity (p < 0.001) were predictors of no response.

Table 3. Predictive factors of no response or progression of tumor after anthracycline based neoadjuvant chemotherapy

Factor	Univariate Analysis			Multivariate Analysis		
	Odds Ratio	95% CI	P	Odds Ratio	95% CI	P
Age	0.98	0.94 - 1.02	0.32			
BMI	0.81	0.67 - 1.54	0.48			
Menopausal status						
Premenopause	1	—	—	1	—	—
Postmenopause	0.72	0.52 - 1.23	0.15	0.8	0.63 - 1.51	0.24
Clinical tumor size	2.19	1.02 - 3.25	0.001			
Clinical T stage						
T1	1	—	—	1	—	—
T2	2.64	0.41 - 6.58	0.21	2.01	1.29 - 4.97	0.55
T3	5.87	0.98 - 19.26	0.01	6.34	1.04 - 24.06	0.02
T4	4.21	1.51 - 16.24	0.13	4.08	1.87 - 15.97	0.21
Clinical N stage						
N0	1	—	—			
N1	1.02	0.59 - 1.87	0.79			
N2	1.33	0.42 - 3.62	0.26			
N3	1.97	0.84 - 4.28	0.45			
Clinical stage						
I	1	—	—	1	—	—
II	1.49	0.87 - 4.29	0.12	1.62	0.67 - 3.79	0.19
III	1.72	1.01 - 6.37	0.07	1.68	0.97 - 6.02	0.1
Histologic type						
Ductal	1	—	—	1	—	—
Lobular	0.98	0.58 - 2.19	0.88	0.9	0.54 - 1.83	0.72
Mucinous	0.71	0.19 - 2.44	0.29	0.76	0.22 - 2.46	0.24
Other	1.82	0.49 - 5.21	0.91	1.53	0.31 - 4.93	0.83
Histologic grade						
I/II	1	—	—	1	—	—
III	1.73	1.01 - 4.08	0.001	2.01	1.34 - 4.49	<0.001
Nuclear grade						
I/II	1	—	—			
III	1.04	0.58 - 2.67	0.24	1.07	0.54 - 2.60	0.21
ER status						
Positive	1	—	—	1	—	—
Negative	0.51	0.19 - 0.87	0.02	0.58	0.24 - 0.89	0.03
PR status						
Positive	1	—	—	1	—	—
Negative	0.45	0.21 - 1.58	0.04	0.41	0.34 - 1.97	0.02
HER2 status						
Negative	1	—	—	1	—	—
Positive	0.78	0.19 - 2.54	0.19	0.64	0.27 - 1.49	0.22
Ki-67 score	0.89	0.26 - 3.14	0.82			

Table 4. Predictive factors of no response or progression of tumor after taxane based neoadjuvant chemotherapy

Factor		Univariate Analysis			Multivariate Analysis		
		Odds Ratio	95% CI	P	Odds Ratio	95% CI	P
Age		0.86	0.67 - 1.51	0.49			
BMI		0.97	0.24 - 2.68	0.73			
Menopausal status							
	Premenopause	1	—	—	1	—	—
	Postmenopause	0.83	0.21 - 2.15	0.28	0.8	0.63 - 1.51	0.19
Clinical tumor size		1.58	0.87 - 3.19	0.01			
Clinical T stage							
	T1	1	—	—	1	—	—
	T2	1.26	0.41 - 4.28	0.45	1.24	0.47 - 5.16	0.34
	T3	3.24	0.67 - 12.51	0.09	2.09	0.55 - 9.87	0.05
	T4	2.29	0.49 - 9.58	0.21	2.31	0.69 - 12.46	0.26
Clinical N stage							
	N0	1	—	—			
	N1	1.13	0.49 - 2.01	0.88			
	N2	1.26	0.24 - 3.62	0.73			
	N3	1.18	0.62 - 2.59	0.79			
Clinical stage							
	I	1	—	—	1	—	—
	II	1.11	0.28 - 2.56	0.39	1.29	0.34 - 2.48	0.28
	III	1.36	0.59 - 3.14	0.51	1.31	0.54 - 4.26	0.62
Histologic type							
	Ductal	1	—	—	1	—	—
	Lobular	1.02	0.67 - 1.67	0.26	1.02	0.62 - 1.78	0.25
	Mucinous	0.99	0.89 - 1.53	0.82	0.82	0.75 - 1.98	0.8
	Other	1.31	0.25 - 2.68	0.72	1.29	0.24 - 2.61	0.69
Histologic grade							
	I/II	1	—	—	1	—	—
	III	1.26	0.91 - 2.16	0.16	1.34	0.87 - 2.42	0.09
Nuclear grade							
	I/II	1	—	—			
	III	1.38	0.27 - 2.21	0.36	1.29	0.25 - 2.59	0.35
ER status							
	Positive	1	—	—	1	—	—
	Negative	0.46	0.04 - 1.01	0.04	0.44	0.06 - 1.31	0.02
PR status							
	Positive	1	—	—	1	—	—
	Negative	0.53	0.16 - 1.08	0.01	0.49	0.19 - 1.15	0.02
HER2 status							
	Negative	1	—	—	1	—	—
	Positive	0.18	0.02 - 0.87	<0.001	0.19	0.04 - 0.91	<0.001
Ki-67 score		0.97	0.18 - 4.14	0.68			

Clinical outcomes

Disease-free survival and overall survival were evaluated with a median follow-up time of 36.5 months (range,8 to 66 months).SD/PD after an AC regimen did not influence disease-free survival (p = 0.155), but SD/PD after a T regimen were correlated with a worse disease-free survival (p = 0.001)(Figure 3). In addition, SD/PD after an AC and/or T regimen had a significanly worse overall survival (p = 0.001 for AC, ; p < 0.001 for T) (Figure 4).

Figure 3. (a) Kaplan-Meier curve of disease-free survival in patients with anthracycline (p=0.155; log-rank test) (b) Kaplan-Meier curve of disease-free survival in patients with taxane (p=0.001; log-rank test)

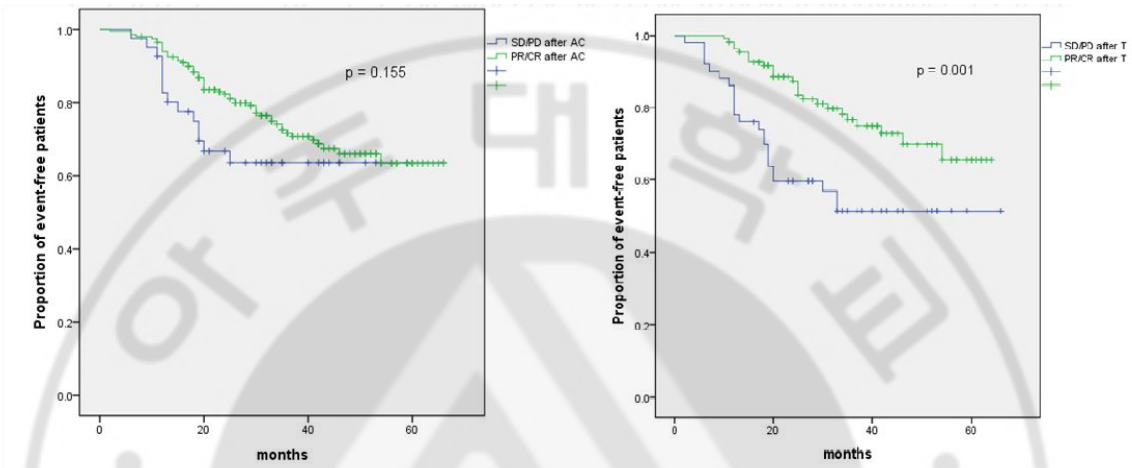
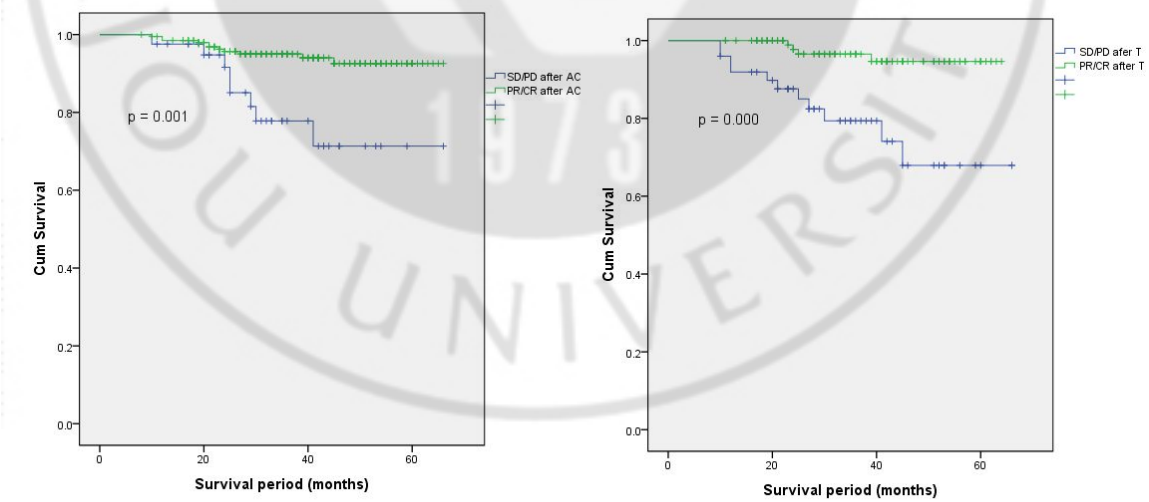


Figure 4. (a) Kaplan-Meier curve of overall survival in patients with anthracyc line (b) Kaplan-Meier curve of overall survival in patients with taxane



IV. DISCUSSION

NAC is the standard treatment for locally advanced breast cancer, providing an increased chance for breast conservation surgery and an improved cosmetic result by removal less of tissues; however, it is unclear if achieving a pCR predicts long term outcomes [7]. Although many studies cannot prove an obvious survival gain for patients who receive NAC, a meta-analysis of 12 neoadjuvant randomized controlled trials reported that individual patients who attain a pCR have a more favorable long-term outcome [5, 6]. However if patients show unexpected results from NAC, it could do harm to patients such as shifting them to an inoperable status or developing metastatic disease and eventually having a worse survival. Therefore, identifying predictive factors of no response or progression during NAC is necessary in addition to identifying factors predicting a pCR.

NSABP B-18 identified an 80% response rate, 36% clinical complete remission, and 9% pCR after a preoperative AC regimen [1]. Caudle et al. reported retrospectively reviewed data of 1,928 patients who received NAC including an anthracycline-based regimen or taxane-based regimen. Among them, 6% had a clinically SD and 3% had PD while receiving a NAC regimen. Of these, 3% had PD and 88.7% had R/SD (response/stable disease) after the AC based regimen, 3% had PD and 73.8% had R/SD after a taxane-based regimen [8]. In our study, 17% and 31% had SD/PD after an AC regimen and AC following a taxane regimen, respectively.

Several trials have reported the predictive factors for clinical and pathological responses to NAC [10,11]. According to these studies, predictive factors of pCR are a

young age, lower BMI, hormone receptor negative tumor, a grade 3 tumor, high Ki-67, HER2 positive, and other molecular subgroup specific predictors. However, only a few studies have evaluated the predictive factors of progression during NAC.

In our study, we found that larger clinical stage (large tumor size and metastatic nodal status), worse histologic grade, and ER/PR positivity could be predictive factors of tumor progression during anthracycline treatment with/without a taxane regimen and age was not a predictive factor.

Loibi et al. reported ER positivity and increased tumor size were associated with no response [12]. Our study also reflected the same result. However, Abigail et al. reported being ER and PR negativity were predictive factors of no response [8]. This result seemed to be associated with aggressive histologic types. In other words, when aggressive cancer types, such as inflammatory breast cancer connect ed with BRCA mutations and metaplastic breast cancer, were included in the study, the results were influenced by the numbers of aggressive histologic types in regards to ER and PR hormone receptor negativity. To avoid selection bias, we excluded inflammatory breast cancer and metaplastic breast cancer patients from our study.

Recent studies have reported that the AC-T regimen for triple negative breast cancer (TNBC) has increased pCR rates compared with other subtypes. Histologic grade, tumor stage, and tumor response ratio were significantly associated with disease-free survival in another study [15]. pCR was observed in 45% of TNBC and in 6% of luminal type breast cancer [17]. Similar to the previous study, pCR was observed in 23.1% of TNBC patients and in 7.8% of luminal type breast cancer in our study. An

MD Anderson Cancer Center study evaluated 1,118 patients (23% with TNBC) treated with neoadjuvant therapy. The pCR rates were significantly higher in TNBC treated with anthracycline-based regimens. Anthracycline and taxane-based regimens were more active, but both progression-free survival and 3-year overall survival were significantly worse in TNBC (hazard ratio [HR] 1.86, 95% confidence interval [CI] 1.39-2.50, p < 0.0001; and HR 2.53, 95% CI 1.77-3.57, p < 0.0001, respectively) [13,14]. In our study, the pCR rate showed that there was a similar difference of 13.5% in the AC based regimen and 12.1% in the taxane-based regimen. Many studies have focused on the pCR rates in TNBC but our study focused on the non-response factors of NAC. Only 15.3% of ER/PR-/HER2- patients showed clinically SD/PD after an AC regimen but when we used AC followed by a taxane regimen for TNBC, 45.5% of ER/PR-/HER2- patients showed SD/PD, a significant difference (p = 0.005). The final pathologic response rate was confirmed after definite surgery and 30.8% of ER/PR-/HER2- patients had pathologically SD/PD, a significant difference (p = 0.003). Therefore, we can conclude that in TNBC a taxane-based regimen can predict a worse response to NAC. Additionally, Liedtke et al. reported that patients with SD/PD after NAC in the ER/PR-/HER2- group have a worse survival than other subtypes of breast cancer [13]. This study and our study definitely showed more SD/PD response when using a taxane-based regimen. Therefore, we need additional studies of the combination of predictive factors of clinical data, novel molecular markers, and genetic factors when use taxane-based regimen.

The Ki-67 count was a predictive factor of no response in NAC in another study. [8]

However, Tan, Qi-Xing et al. reported that the Ki-67 labeling index also could be used as a means to better reflect tumor response to NAC in ER/PR negative breast cancer [16]. However, in our study, Ki-67 was not included because of the lack of patient data. Ki-67 pathologic data has subjective characteristics for each pathologist and the results have the problem of lack of reproducibility. We need more studies on standardization and automatization of Ki-67 data when using it as a predictive factor for NAC.

The limitation of our study is that it is a retrospective study using a non-randomized control, and its small numbers and a lack of Ki-67 data.

V. CONCLUSION

Clinical stage, ER/PR positivity, and HER2 negativity were predictors of no response to NAC. In TNBC, our study showed that a taxane-based regimen was predictive of no response to NAC. We might want to use only AC regimens for NAC. We need a combination of predictive factors of clinical data, novel molecular markers, and genetic factors to identify patients who are predicted to have no response to standard NAC regimens. Based on these predictive factors, patients should consider surgery first or another NAC regimen.

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