

Pathological Complete Response and Prognosis in Patients Receiving Neoadjuvant Paclitaxel and Trastuzumab with and without Anthracyclines for Stage II and III, HER2-positive Operable Breast Cancer: A Single-institute Experience

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Abstract. *Background:* Trastuzumab and various chemotherapy combinations have shown superior results in patients with primary and metastatic breast cancer. However, cardiotoxicity becomes a major adverse event when trastuzumab is used with anthracycline-containing regimens. The purpose of this study was to determine the clinical and pathological efficacy of neoadjuvant chemotherapy (NAC), using trastuzumab and chemotherapy, with or without anthracyclines, for patients with primary breast cancer and human epidermal growth factor receptor 2 (HER2)-positive tumors. *Patients and Methods:* A retrospective analysis of 41 patients with stage II and III primary breast cancer and HER2-positive tumors treated with NAC was performed. NAC consisted of weekly paclitaxel plus trastuzumab with (PTA group, n=21) or without anthracycline (PT group, n=20). Patients in the PTA group received four courses of 5-fluorouracil, epirubicin, and cyclophosphamide every 3 weeks followed by concomitant 80 mg/m² paclitaxel and trastuzumab weekly for 12 weeks, and those in the PT group received four courses of 80 mg/m² paclitaxel weekly (days 1, 8, and 15) followed by a 1-week break and trastuzumab weekly (days 1, 8, 15, and 29). *Results:* The median age of the patients was 50 years. Of 41 patients, 21 (51%) had a pathological complete response (pCR). Patients with clinical stage II cancer had a higher pCR rate compared with those with clinical stage III. Patients with estrogen receptor (ER)-negative tumors showed a trend toward a higher pCR rate. No significant difference was observed according age, clinical stage, ER status, clinical

response, or pathological response between the PTA and the PT groups. The pCR rate of the PTA and the PT groups was 47.6% and 55.0%, respectively. No significant difference in disease-free survival was observed between the two groups at a median follow-up of 32 months. *Conclusion:* Trastuzumab-containing NAC is effective irrespective of anthracycline use for treating patients with primary breast cancer and HER2-positive tumors.

Human epidermal growth factor receptor 2 (HER2)-gene amplification and protein overexpression occurs in about 20% of patients with breast cancer, resulting in a clinically aggressive tumor subtype which is associated with a poor prognosis (1). The monoclonal antibody trastuzumab, which is directed against an epitope on the external domain of the HER2 protein, improves survival of patients whose tumors overexpress HER2, in both a metastatic and adjuvant setting (2-6).

Neoadjuvant chemotherapy (NAC) has several advantages including down-staging of the primary tumor, thus allowing higher rates of breast-conserving surgery, as well as providing an *in vivo* assessment of tumor chemosensitivity (7). NAC also allows for determining the pathological complete response (pCR), which is a surrogate marker for disease-free survival (DFS). Several randomized studies have shown that NAC has the same effect on DFS and overall survival (OS) as adjuvant chemotherapy when the same chemotherapy is administered (8, 9).

Incorporation of trastuzumab into adjuvant chemotherapy regimens has improved outcomes in HER2-positive early breast cancer. Neoadjuvant trastuzumab and chemotherapy combinations also show superior results in patients with operable breast cancer (10, 11). However, cardiotoxicity becomes a major adverse event when trastuzumab is used with anthracycline-containing regimens. The incidence of congestive heart failure (CHF) when trastuzumab is used with anthracycline-based chemotherapy is 3.0%, whereas it is 1.5% for non-anthracycline-containing chemotherapy.

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Trastuzumab significantly increases the risk for CHF, with a risk ratio of 4.27 in patients receiving anthracycline-based chemotherapy (12).

The purpose of this study was to determine the clinical and pathological efficacy of NAC using trastuzumab and chemotherapy with or without anthracyclines in patients with stage II and III primary breast cancer and HER2-positive tumors.

Patients and Methods

All patients with HER2-positive operable breast cancer who were administered NAC containing trastuzumab between 2004 and 2010 at Breast and Endocrine Surgery, Gunma University Hospital were evaluated. Patients with multifocal or multicentric tumors were excluded. Forty-one patients with primary breast cancer (stages IIA-IIIc), with HER2-positive tumors, were treated by NAC. NAC consisted of weekly paclitaxel plus trastuzumab with (PTA group, n=21) or without anthracycline (PT group, n=20). Patients in the PTA group received four courses of 500 mg/m² 5-fluorouracil, 100 mg/m² epirubicin, and 500 mg/m² cyclophosphamide every 3 weeks followed by concomitant 80 mg/m² paclitaxel and trastuzumab weekly for 12 weeks, and those in the PT group received four courses of 80 mg/m² paclitaxel weekly (days 1, 8, and 15) followed by a 1-week break and trastuzumab weekly (days 1, 8, 15, and 29).

Clinical and radiological evaluation. Before the initiation of therapy, all patients underwent an evaluation that included a complete medical history and physical examination, a complete blood count, chemistry profile, and computed tomography scans of the lung, liver, and bone.

A complete clinical response (CR) was defined as the clinical absence of all evidence of active tumor in the breast. A partial response was defined as a 30% reduction in the product of the maximal diameter of the measurable tumor without progression of any lesion or appearance of any new disease. Stable disease was defined as no change or as a decrease in tumor measurements insufficient to qualify as partial remission. Progressive disease was defined as a 20% increase in maximal size of the tumor and/or the appearance of new lesions. The combined clinical response included mammographic and ultrasound evaluations combined with physical examinations.

Surgery and radiation therapy. All patients received a partial mastectomy or total mastectomy with axillary lymph node dissection. Patients who underwent a partial mastectomy received 50 Gy of breast irradiation.

Pathological assessment. All patients underwent a core-needle biopsy before receiving NAC. The presence of hormone receptors (estrogen receptor, ER; progesterone receptor, PgR) was assessed by immunohistochemistry (IHC). ER and PgR positivity was determined by the Allred score. HER2 positivity was indicated by 3+ staining intensity on IHC for the HER2 protein or amplification of the HER2 gene by fluorescent *in situ* hybridization.

The breast and all excised axillary lymph nodes were fully evaluated at the time of surgery. The tumor and all axillary lymph nodes were submitted for histopathological analysis.

Pathological response was evaluated only from histological changes in the invasive area by Japan Breast Cancer Society criteria (13). If only ductal components remained, the pathological response

was evaluated as grade 3. Classification of response criteria was as follows: Grade 0, no response: almost no change in cancer cells after treatment; grade 1: slight response, 1a: mild response, mild changes in cancer cells regardless of the extent and/or marked changes in fewer than one-third of cancer cells, 1b: moderate response, marked changes in one-third or more but fewer than two-thirds of cancer cells; grade 2: marked response, 2a: high-grade changes, marked changes in two-thirds or more of tumor cells, with apparent remaining cancer cells, 2b: extremely high grade, marked changes approaching a complete response, with only a few remaining cancer cells; grade 3 complete response: necrosis and/or disappearance of all tumor cells and/or the replacement of cancer cells by granulation and/or fibrosis. The criteria for pCR were that invasive cancer cells in the tumor had completely disappeared irrespective of the presence of lymph node metastases, but the presence of ductal components was not evaluated.

Statistical analysis. The influence of baseline characteristics on the likelihood of achieving a pCR was tested in a univariate analysis using the chi-square or Fisher's exact test. OS and DFS were measured from the date of first treatment until death or recurrence, respectively. Survival curves were calculated by the Kaplan-Meier method, and differences were assessed by the log-rank test.

Results

The median age of the patients was 50 years (range, 29-76 years). Patient and tumor characteristics are shown in Table I. No difference in clinical factors was observed between the PA and PTA groups. The histological subtype was invasive ductal carcinoma in all patients.

The clinical response of the two groups is shown in Table II. Either treatment resulted in a good clinical response. Twenty-one (51.2%) out of 41 patients achieved a clinical CR after NAC. In total, 45% of patients in the PT group and 57% of patients in the PTA group obtained a clinical CR. No patient had disease progression after treatment. No statistical difference in clinical response was observed based on the treatment schedule.

The pathological responses in relation to clinicopathological factors are shown in Table III. Of 41 patients, 21 (51%) had a pathologically complete response. The pCR rate in the PTA and the PT groups was 47.6% and 55.0%, respectively. No statistical difference was observed between the pathological responses of the two treatment groups.

Patients with an earlier clinical stage or those who obtained clinical CR had a higher pCR rate compared with those with advanced clinical stage disease or those who did not achieve clinical CR. Patients with ER-negative tumors showed a trend towards a higher pCR rate.

No CHF was observed in each group. LVEF evaluated by cardiac ultrasound remained more than 50% at the baseline and after NAC.

At a median follow-up of 32 months, the 5-year DFS in all patients was 81.5%, and the 5-year OS was 86.4% (Figures 1 and 2). Only two patients, who experienced a recurrence in the

Table I. Patient characteristics by treatment groups.

	Total	PT	PTA
Number of patients	41	20	21
Age, years	50.4	52.4	48.6
Median	50	49.5	50
Range	29-76	37-76	29-71
Initial clinical stage			
IIA	5	1	4
IIB	15	6	9
IIIA	14	9	5
IIIB	5	3	2
IIIC	2	1	1
Estrogen receptor			
Positive	16	9	7
Negative	25	11	14
Surgery			
Partial	26	12	14
Mastectomy	15	8	7
Pathological node			
Negative	34	17	17
Positive	7	3	4

PTA, Patients received weekly paclitaxel plus trastuzumab with anthracycline; PT, patients received weekly paclitaxel plus trastuzumab without anthracycline. Differences between PTA and PT groups were not significant.

Table II. Clinical response by treatment group.

Clinical response	Total	PT	PTA
CR	21	9	12
PR	19	11	8
SD	1	0	1
PD	0	0	0

PTA, Patients received weekly paclitaxel plus trastuzumab with anthracycline; PT, patients received weekly paclitaxel plus trastuzumab without anthracycline. CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease. Differences between PTA and PT groups were not significant.

Table III. Pathological response by treatment group.

Pathological response	Total	PT	PTA
1a	1	1	0
1b	4	2	2
2a	4	1	3
2b	8	2	6
pCR	21	11	10

PTA, Patients received weekly paclitaxel plus trastuzumab with anthracycline; PT, patients received weekly paclitaxel plus trastuzumab without anthracycline; pCR, pathological complete response. Differences between PTA and PT groups were not significant.

Table IV. Clinicopathological factors and pathological complete response.

Factor	non-pCR	pCR	P-value
Number of patients	20	21	
Age			
<51 years	11	11	0.9999
≥51 years	9	10	
Clinical stage			
II	5	15	0.0048
III	15	6	
ER			
Negative	9	16	0.0578
Positive	11	5	
Clinical response			
Non-cCR	14	6	0.0126
cCR	6	15	
NAC			
PT	9	11	0.7579
PTA	11	10	

ER, Estrogen receptor; cCR, clinical complete response; PTA, patients received weekly paclitaxel plus trastuzumab with anthracycline; NAC, neoadjuvant chemotherapy; PT, patients received weekly paclitaxel plus trastuzumab without anthracycline; NS, not significant.

brain, died. Negative ER status was associated with a worse DFS, with a 5-year DFS of 88.5% in ER-negative patients compared with 100% in ER-positive patients (Figure 3). Patients with stage II disease had a better DFS than those with stage III disease (Figure 4). However, the pathological response and the preoperative chemotherapy regimen had no significant influence on DFS (Figures 5 and 6).

Discussion

HER2 is one of the best markers for predicting a better response to neoadjuvant anthracycline- and taxane-based chemotherapy (14). A high pCR rate has been reported when trastuzumab-containing NAC was administered to patients with HER2-positive tumors. Buzdar *et al.* (10) evaluated whether adding trastuzumab to chemotherapy in the neoadjuvant setting could increase the pCR rate in patients with HER2-positive disease. Of the 42 randomized patients, 26% in the chemotherapy arm achieved pCR compared with 65.2% in the trastuzumab plus chemotherapy arm. Paluch-Shimon *et al.* (15) reviewed patients with HER2-overexpressing breast cancer who received neoadjuvant therapy. Thirty-seven patients received chemotherapy alone, and 24 patients received chemotherapy and trastuzumab. The pCR rate was significantly higher among the trastuzumab-treated group compared with that in the chemotherapy-alone group. Therefore, trastuzumab should be incorporated into the regimen for patients with HER2-positive disease.

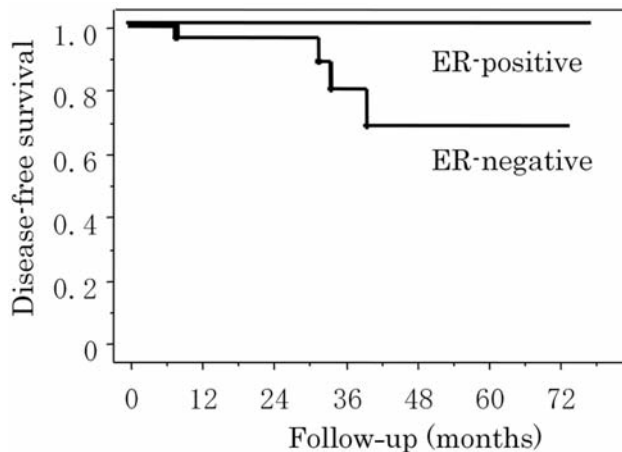


Figure 1. Disease-free survival (DFS) in relation to estrogen receptor (ER) status. Patients with ER-positive tumors had a better DFS than those with ER-negative tumors ($p=0.082$).

Cardiotoxicity is a major adverse event when trastuzumab is used with anthracycline-containing regimens. In our study, anthracycline was not concomitantly used with trastuzumab. In anthracycline-containing regimens, anthracycline-containing chemotherapy only is administered and followed by a combination therapy of taxane and trastuzumab. Chumsri *et al.* (16) reviewed the rate of pCR and changes in left ventricular ejection fraction in women with operable HER2-positive breast cancer who were treated with doxorubicin and cyclophosphamide followed by a taxane with or without trastuzumab before definitive breast surgery. The pCR rates were 28.6% and 52.6% in the group that received chemotherapy alone and with trastuzumab, respectively. Severe cardiac events or treatment delays as a result of cardiac toxicity were not observed. Sequential administration of preoperative doxorubicin and cyclophosphamide followed by a taxane and trastuzumab combination may be safe for women with primary operable HER2-positive breast cancer.

HER2 is one of the strongest predictive factors for obtaining pCR. However, predictive factors for pCR in patients with HER2-positive tumors have not been fully evaluated. In our study, clinical stage II patients had a higher pCR rate than did those with clinical stage III. Tumors that were ER-negative also tended to have a higher pathologic response rate to chemotherapy than did ER-positive tumors.

Bhargava *et al.* (17) evaluated 104 patients who were HER2-positive and received NAC. The patients were classified into three groups based on semiquantitative hormone receptor and HER2 results: HER2 (ER-/PR- [H-score, ≤ 10]/HER2+); luminal B-HER2 Hybrid (LBHH; weak to moderate ER + [H-score, 11-199]/HER2+); and luminal A-HER2 hybrid (LAHH; strong ER + [H-score, ≥ 200]/HER2+). The pCR was 52% (25 out of 48 cases) in the HER2 group,

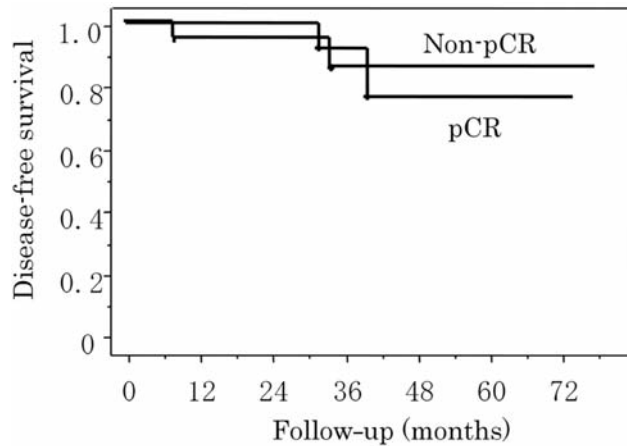


Figure 3. Disease-free survival (DFS) in relation to pathological response. No statistically significant difference was observed in DFS between patients, who obtained a pathological complete response and those who did not ($p=0.9347$).

which was significantly higher than that in the LBHH (33%; 10 out of 30) and LAHH (8%; 2 out of 26) groups. The benefit of adding trastuzumab to NAC is highest in ER-negative tumors and progressively decreases with an increase in tumor ER expression. ER-negativity is a possible predictive factor of pCR in patients with HER2-positive breast cancer.

Adjuvant regimens without anthracyclines have been evaluated. In the 5-year results of the first adjuvant chemotherapy trial for early breast cancer by US Oncology Research (18), among 1,016 patients with operable breast cancer, the non-anthracycline regimen of docetaxel plus cyclophosphamide given for four cycles was superior to standard doxorubicin and cyclophosphamide (AC) for the primary end-point of DFS. The Breast Cancer International Research Group 006 study (19) recruited 3,222 women with node-positive or high-risk node-negative breast cancer and randomly allocated them to one of three therapy arms. No significant difference was found for DFS or OS between patients receiving AC therapy followed by docetaxel (anthracycline-containing regimen) and trastuzumab compared with those receiving docetaxel, carboplatin and trastuzumab (non-anthracycline-containing regimen). Patients receiving the non-anthracycline-containing regimen showed significantly less grade 3/4 CHF than did those who received the anthracycline-containing regimen. However, no randomized study has been published comparing the efficacy of anthracycline-containing trastuzumab NAC with non-anthracycline-containing trastuzumab NAC. Coudert *et al.* (20) evaluated non-anthracycline-containing NAC with trastuzumab in patients with HER2-positive, stage II/III, noninflammatory, operable breast cancer who received six cycles of trastuzumab, docetaxel and carboplatin. A complete or partial objective clinical response occurred in 95% of these patients (85% and

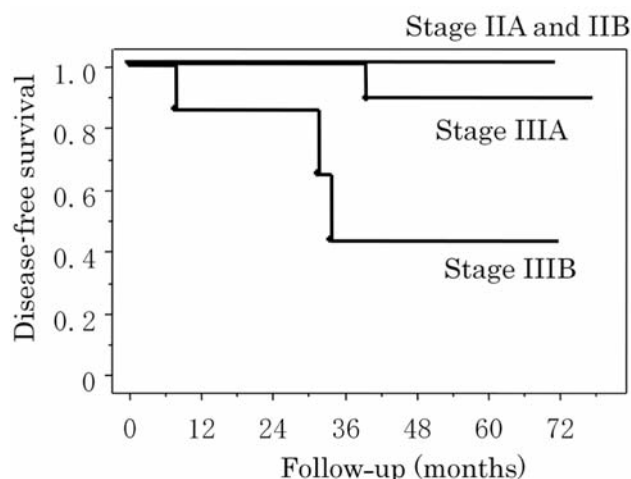


Figure 2. Disease-free survival (DFS) in relation to clinical stage. Patients with clinical stage II tumors had a better DFS than those with clinical stage III tumors ($p=0.094$).

10%, respectively). In an intent-to-treat analysis, tumor and nodal pCR were seen in 27 (39%) out of 70 patients. NAC with trastuzumab plus docetaxel and carboplatin achieved promising efficacy, with a good pCR rate and favorable tolerability in patients with stage II or III HER2-positive breast cancer. In our study, the pCR rate for patients receiving non-anthracycline NAC was 55.0%, which was almost the same as the pCR rate for those who received anthracycline-containing NAC. Trastuzumab-containing NAC without anthracycline may be an effective option for patients with HER2-positive disease, who have problems with cardiovascular organs.

In our study, the use of adjuvant therapy depended on the decision by the physician, and patients with hormone receptor-positive tumors received endocrine therapy. Most patients received adjuvant trastuzumab for 1 year. For some patients, the non-anthracycline regimen was followed by an anthracycline-containing regimen as an adjuvant. No difference in DFS was seen between the two groups. Stage II and ER-positive patients had better DFS than stage III and ER-negative patients. Patients with ER-positive tumors had a favorable prognosis, although their pCR rate in response to NAC was lower than that of ER-negative patients. Long-term follow-up data have not been well evaluated in patients with HER2-positive breast cancer who received NAC containing trastuzumab. Guu *et al.* (21) studied the long-term follow-up of patients with stage II/III HER2-positive breast cancer, treated with trastuzumab-associated NAC. Among 135 patients with a median follow-up of 48 months, the relapse-free survival (RFS) rate was 73% and the OS rate was 91%. Adjuvant trastuzumab favorably influenced RFS in univariate analysis, whereas pathological nodal invasion unfavorably influenced RFS and OS. Our study demonstrated that a trastuzumab-containing chemotherapy without anthracycline conferred almost the same prognosis as that with

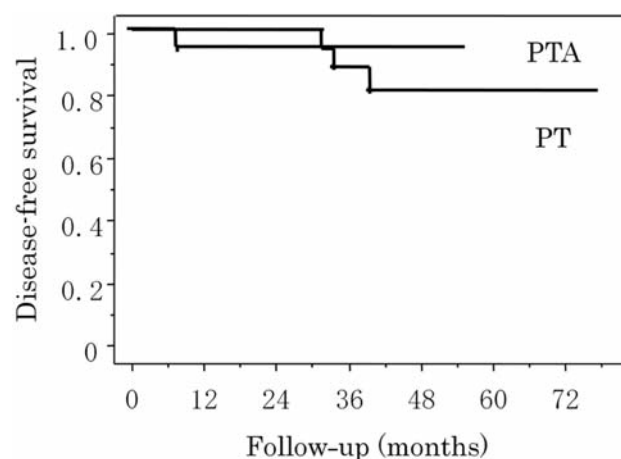


Figure 4. Disease-free survival (DFS) in relation to preoperative chemotherapy regimens. No statistically significant difference was observed in DFS between patients who received a preoperative anthracycline-containing regimen and those who received a preoperative non-anthracycline-containing regimen ($p=0.9553$).

anthracycline. The choice of trastuzumab-containing chemotherapy without anthracycline could be proposed to patients with vascular contraindication for anthracyclines or for those who prefer a taxane-only schedule.

In conclusion, trastuzumab-containing NAC is effective irrespective of anthracycline use for treating patients with primary breast cancer and HER2-positive tumors. A good pCR rate can be achieved for patients with HER2-positive breast cancer with trastuzumab-containing NAC irrespective of anthracyclines.

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