Neoadjuvant Weekly Paclitaxel with and without Trastuzumab in Locally Advanced or Metastatic Breast Cancer

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Abstract. *A phase II clinical trial was conducted to examine the clinical and pathologic efficacy and safety of neoadjuvant paclitaxel with or without trastuzumab in women with advanced or metastatic breast cancer. A total of 49 patients with advanced or metastatic breast cancer (clinical stage IIB -IV) were included. Patients with HER2-negative tumors received weekly paclitaxel 80 mg/m^2 (days 1, 8, 15) followed by a 1-week break for 4 cycles. Patients with HER2-positive tumors received weekly paclitaxel 80 mg/m^2 (days 1, 8, 15) followed by a 1-week break and a trastuzumab 4 mg/kg loading dose, intravenously, followed by 2 mg/kg weekly for 4 cycles. The age of the patients was 51.6±1.6 years (mean±SE) and the size of their tumors was 5.8±0.4 cm (mean±SE). Thirty-two patients had HER2-negative tumors and 17 had HER2-positive tumors. Of 49 patients, 13 (26.5%) had a clinical complete response and 24 (49.0%) had a clinical partial response. Five (10.2%) patients had a pathological complete response (pCR) and three (6.1%) patients had a near pCR in the breast. A total of eight (16.3%) patients had a pCR or near pCR in the breast. The pCR or near pCR rate was 3.1% in the HER2-negative group and 41.2% in the HER2-positive group. With a median follow-up of 28 months (range, 1-45), the 3-year overall survival was 88%. Clinical responders showed a significantly better overall survival than non-responders ($p<0.01$). Pathological responders showed a better overall survival than non-responders. There was no significant difference in overall survival between patients with HER2-positive and -negative tumors. In conclusion, combined neoadjuvant weekly paclitaxel and trastuzumab achieved high clinical and pathological response rates for HER2 -overexpressing breast cancers, despite the omission of an anthracycline.*

Paclitaxel is among the most active agents in the treatment of metastatic breast cancer, with response rates ranging from 30 to 60% when used as a single agent (1). Overall survival (OS) with single-agent paclitaxel is comparable to that with the previous gold-standard anthracycline, doxorubicin (2, 3). A few studies (4-6) have considered paclitaxel monotherapy in the neoadjuvant treatment of breast cancer. The results of these trials demonstrated that standard-dose paclitaxel has significant antitumor activity and is comparable to the 5-fluorouracil, doxorubicin and cyclophosphamide (FAC) regimen.

Human epidermal growth factor receptor-2 (HER2) is overexpressed in 25-30% of breast cancer (7). Breast cancer overexpressing HER2 typically has an aggressive course and high relapse and mortality rates. Trastuzumab is the first agent approved for use in patients with HER2-overexpressing breast cancer. Trastuzumab has been demonstrated to improve disease-free survival (DFS) and OS in metastatic cancer.

In the neoadjuvant setting, a number of small phase II trials have examined different combinations of preoperative trastuzumab and chemotherapy, in which the pathological complete response (pCR) rate ranged from 12 to 45% (8). Buzdar *et al*. (9) randomly assigned patients with HER2-positive operable breast cancer to either chemotherapy with simultaneous weekly trastuzumab for 24 weeks or chemotherapy alone. Of the

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42 randomized patients, 26% in the chemotherapy arm achieved pCR compared with 65.2% in the trastuzumab plus chemotherapy arm.

The simultaneous combination of doxorubicin and trastuzumab results in a high rate of clinical and subclinical cardiotoxicity (10), thus, subsequent studies have avoided the simultaneous administration of anthracyclines and trastuzumab. Some researchers, however, have investigated the possible use of the slightly less cardiotoxic epirubicin and liposomal doxorubicin (11). Combination therapy of paclitaxel with trastuzumab is well tolerated and effective for patients with HER2-positive breast cancer (12), and weekly paclitaxel administration is superior to every-three-weeks administration (13). Because there are concerns about cardiotoxicity of both the anthracyclines and trastuzumab, it is important to know whether trastuzumab can act sufficiently strongly in women with HER2-overexpressing tumors to make anthracycline therapy unnecessary. Several studies (14, 15) have reported that neoadjuvant chemotherapy with trastuzumab for patients with HER2-positive tumors achieved high pCR rates, despite the absence of an anthracycline.

A non-randomized, phase II study was conducted in which patients with HER2-positive breast cancer were assigned to simultaneous weekly paclitaxel and trastuzumab and patients with HER2-negative breast cancer were administered single-agent weekly paclitaxel therapy. The primary aim was to evaluate the clinical and pathological efficacy and safety of the neoadjuvant chemotherapy. Secondarily, the prognosis between patients with HER2-negative tumors treated with neoadjuvant weekly paclitaxel and those with HER2-positive tumors treated with neoadjuvant weekly paclitaxel and trastuzumab was evaluated.

Patients and Methods

Patients with histologically confirmed noninflammatory clinical T3/4 or N2/3 untreated invasive carcinoma of the breast were eligible for the study. Invasive carcinomas were confirmed before chemotherapy in all patients by core needle biopsy. Patients were required to have disease measurable by physical examination and breast imaging (mammogram or ultrasound), with a primary tumor > 5 cm or metastatic regional lymph nodes (≥N2). All patients were ≥20 years of age. Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status ≤2, white blood cells ≥4,000 cells/mm^3, hemoglobin ≥9.0 g/dL, platelets ≥10×10^4, and adequate hepatic and renal function. Cardiac function was evaluated by cardiac ultrasound and a left ventricular ejection fraction of ≥50%. All patients gave written informed consent before entering the study. Ethics Committee approval was obtained at each center.

Treatment. Before treatment, core needle biopsies were performed in all eligible patients. Paraffin-embedded tumor specimens were used to evaluate estrogen receptor (ER), progesterone receptor (PgR) and HER2 status. HER2 status was analyzed by immunohistochemistry according to the HercepTest™ (DAKO Cytomation, Glostrup, Denmark). Scores 0 and 1+ were considered negative, and scores 2+ and 3+ were considered positive for HER2 expression.

Chemotherapy. Each patient received four cycles of weekly paclitaxel. Paclitaxel was administered at 80 mg/m^2 weekly for 3 weeks, followed by a 1-week break. Each patient was premedicated with dexamethasone 20 mg intravenously, diphenhydramine 50 mg intravenously, and cimetidine 300 mg intravenously 30 min before paclitaxel infusion. Patients were assigned to receive trastuzumab depending on their HER2 status. Tratuszumab was administered at a dose of 4 mg/kg intravenously on day 1 of the first treatment cycle, and subsequent doses of weekly trastuzumab were administered at 2 mg/kg. A total of 16 doses of trastuzumab were administered on a weekly basis. After the completion of 6 weeks of systemic therapy, patients received local therapy.

Dose modification criteria. The dose of paclitaxel was reduced by 10 mg/m^2 in subsequent cycles if a patient developed grade ≥2 neurotoxicity, nonhematological adverse events ≥3, <1,000 leukocytes/mm^3, febrile neutropenia, or <50,000 platelets/mm^3. Patients were required to have >3,000 leukocytes or 1,500 granulocytes/μl, ≥75,000 platelets/mm^3, grade ≤1 nonhematological adverse events (except for alopecia and peripheral neuropathy), and grade ≤2 peripheral neuropathy before administration of the next cycle of chemotherapy.

Local therapy. After the completion of neoadjuvant therapy, each patient was evaluated. Patients who were considered appropriate candidates for breast conservation therapy (BCT) were offered segmental mastectomies (lumpectomy). Patients who were considered inappropriate for BCT or who did not desire BCT underwent total mastectomies. All patients (mastectomy and BCT) underwent axillary lymph node dissection. All patients treated with a segmental mastectomy received whole-breast irradiation. The breast was treated with standard medial and lateral tangent fields using 6-15 MV photons to a total dose of 50 Gy, delivered in 25 fractions. Radiation treatment was not offered to patients who underwent total mastectomies. The treatment scheme is summarized in Figure 1.

Pathological evaluation. After chemotherapy, resected specimens were evaluated by breast pathologists using the standard protocol of the Japanese Breast Cancer Society. Briefly, the surgeon oriented the specimen with sutures and accompanied it to the pathology suite. The specimen was sectioned into 5-mm slices. The pathologist examined the sliced specimen grossly to identify suspicious areas and noted their proximity to the margins. Permanent paraffin sections of suspicious areas and margins were obtained. The number of sections taken was based on the gross inspection and the size of the resected specimen. The entire breast tissue was submitted for histological evaluation. A pathologist examined the slices and determined the tumor size and gross evaluation and confirmed the tumor size by microscopic evaluation. The largest area of residual disease was included to document the extent of disease in a patient with multiple foci of persistent invasive cancer. All axillary lymph nodes were also carefully evaluated by serial gross sectioning. One or two representative histological sections were evaluated in lymph nodes that contained grossly identifiable metastatic carcinomas. Lymph nodes that did not

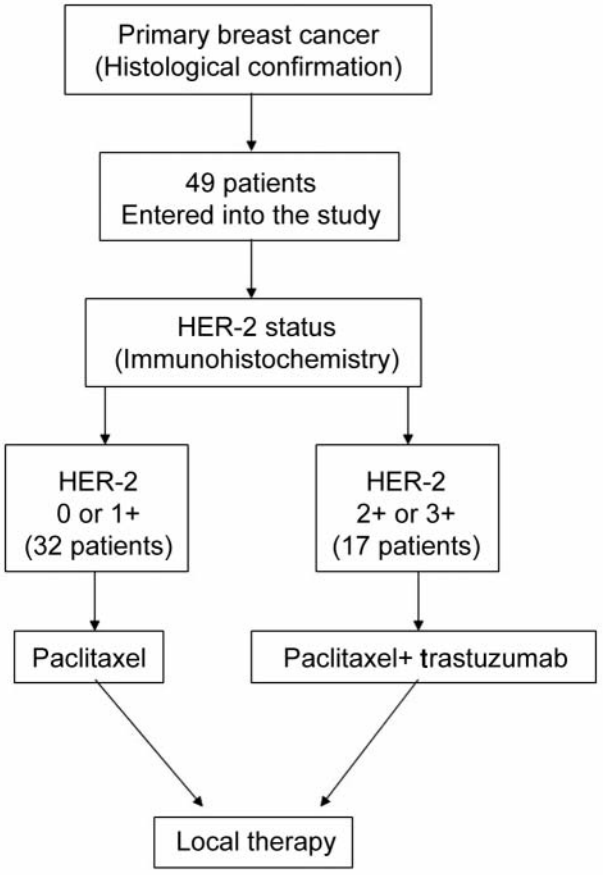

Figure 1. *Treatment scheme*.

show grossly identifiable tumors were submitted for histological evaluation in their entirety. One representative histological section was evaluated per paraffin block. Immunohistochemical staining for cytokeratin was not routinely performed on negative nodes.

Adjuvant therapy. After surgery, patients who underwent breast-conserving surgery received 50 Gy of radiation therapy. No patient who underwent total mastectomy received radiation therapy. Postoperative adjuvant therapy was left to the discretion of the treating physician, however, most patients were treated as follows. Trastuzumab was continued for 1 year after the surgery for patients with HER2-positive tumors. FEC (5-FU 500 mg/m^2, epirubicin 75 mg/m^2, cyclophosphamide 500 mg/m^2, intravenous, once per 3 weeks) was administered to patients with HER2-negative tumors and pathological non-responders with HER2-positive tumors. Adjuvant endocrine therapy was administered to patients with hormone receptor-positive tumors.

Safety assessments. Adverse events and toxic effects were evaluated weekly and recorded every cycle. They were graded according to the National Cancer Institute Common Toxicity Criteria, version 2.0.

Statistical methods. Survival was calculated using the Kaplan-Meier method. A log-rank test was used to compare survival between groups. A p-value <0.05 was considered significant.

Table I. *Patient characteristics*.

	All patients	Paclitaxel	Paclitaxel + trastuzumab
Number of patients	49	32	17
Age, mean±SE (years)	51.6±1.6	52±1.9	50.6±2.6
Tumor size, mean±SE (cm)	5.8±0.4	5.7±0.3	6.2±1.0
Disease stage			
IIB	5	4	1
IIIA	20	11	9
IIIB	14	11	3
IIIC	5	2	3
IV	5	4	1
Menopausal status			
Pre	30	18	12
Post	19	14	5
Hormone receptor			
ER+/PR+	19	15	4
ER+/PR–	12	9	3
ER–/PR+	1	0	1
ER–/PR–	17	8	9

Results

Patients. Forty-nine previously untreated patients with Stage IIB, IIIA, IIIB, IIIC, or IV breast cancer were enrolled in the study between April 2004 and February 2006. Detailed patients characteristics are summarized in Table I. All patients were evaluated for efficacy and safety on an intention-to-treat basis. Five patients with metastatic disease were included. One patient with multiple tumors was not evaluable for clinical and pathologic responses. Four patients were excluded from the study: three with progressive disease and one with an adverse event. Four patients rejected surgery, thus, a total of 41 patients were evaluated for pathologic responses.

Safety. A total of 582 infusions of weekly paclitaxel were administered, with a median of 12 per patient (range, 3-12), and a total of 254 infusions of trastuzumab were administered with a median of 16 per patient (range, 14-16). Of the 49 patients, 45 completed four cycles of treatment. The dose of paclitaxel was reduced in two patients because of liver dysfunction (increased GOT and GPT). The median paclitaxel dose administered was 60.0 mg/m^2/week. Toxicity was assessed in 49 patients (Table II). Most toxicity was within grade 2, including leukocytopenia, anemia, alopecia, nausea, fatigue, peripheral neuropathy, and increased liver transaminase. One patient was excluded because of suspicion of interstitial pneumonia; this patient was treated with corticosteroids and promptly improved.

Table II. *Toxicity.*

Adverse event	Paclitaxel		Paclitaxel + trastuzumab	
	Grade 1	Grade 2	Grade 1	Grade 2
Hematological				
Anemia	8	4	5	3
Leukopenia	8	7	3	4
Thrombocytopenia	0	0	1	0
Nonhematological				
Alopecia	8	21	3	13
Peripheral neuropathy	11	5	8	1
Myalgia/arthralgia	4	2	3	2
Nausea	10	2	5	2
Fatigue	8	1	7	0
Rash	5	1	2	0
Diarrhea	4	0	2	0
Constipation	5	2	3	0
Taste alteration	2	0	2	0
Appetite loss	0	0	1	1
Mucositis	0	0	1	0
Laryngitis	0	0	2	0
Nail change	0	0	1	0
Flushing	1	0	0	0
Allergy	0	1	0	0

Table III. *Clinical and pathological responses.*

Clinical response			Pathological response		
	Paclitaxel	Paclitaxel + trastuzumab		Paclitaxel	Paclitaxel + trastuzumab
CR	2	11	pCR	0	5
PR	19	5	near pCR	1	2
SD	7	0	No pCR	26	7
PD	4	0	NE	5	3
NE	0	1			

CR: Complete response; PR: partial response; SD: stable disease; PD: progressive disease; NE: non evaluable; pCR: pathological complete response.

Efficacy. The overall clinical response rate was 75.5%; 65.6% in patients treated with paclitaxel and 94.1% in patients treated with paclitaxel and trastuzumab. Patients treated with paclitaxel and trastuzumab showed a significantly higher clinical response rate than those treated with paclitaxel alone (p=0.0014). A CR was obtained in 13 patients and a partial response was obtained in 24 patients (Table III). Surgery was performed in 41 patients, with breast-conserving surgery in 17. A pCR, with no evidence of invasive tumor in the breast was confirmed in 5 (10.2%) of 49 patients, including 4 patients with residual carcinoma *in situ* only. A near pCR (16), with a small number of scattered tumor cells in the breast, was confirmed in 3 (6.1%) of 49 patients. The pCR or near pCR rate was 3.1% in the HER2-negative group and 41.2% in the HER2-positive group. Patients who were treated with paclitaxel and trastuzumab showed a significantly higher pCR or near pCR rate than those treated with paclitaxel alone (p=0.037).

At the median follow-up duration of 28 months (range, 1-45), 5 of the 49 patients had died. The 3-year overall survival rate was 88% (Figure 2). Patients with a clinical response showed a significantly (p<0.01) better overall survival than non-responders (Figure 3). Moreover, patients with a pathological response showed a better overall survival than non-responders (Figure 4). There was no significant difference in the overall survival between patients treated with paclitaxel and trastuzumab and those treated with paclitaxel alone (Figure 5).

Discussion

Combination neoadjuvant chemotherapy with paclitaxel and trastuzumab achieved high clinical and pathological response rates for patients with HER2-positive tumors. However, a very low pathological response rate was achieved with single-agent paclitaxel neoadjuvant chemotherapy in patients with HER2-negative breast cancers. One reason for the low pathological response of neoadjuvant paclitaxel monotherapy for HER2-negative breast cancer may be that patients had advanced breast cancer. Indeed, the mean size of the tumors investigated was 5.8 cm. Secondly, patients with HER2-negative breast cancer are typically resistant to chemotherapy. Thirdly, paclitaxel monotherapy is often insufficient to allow patients with advanced breast cancer to achieve pCR.

Factors associated with a higher likelihood of pCR include tumor size, histology (ductal>lobular), tumor intrinsic subtype (basaloid or HER2>luminal), hormone receptor status (ER negative>ER positive), and grade (high>low) (17). Clinical tumor size is a factor associated with clinical or pathological CR (18-24). Bonadonna *et al.* (20) showed an inverse relationship: a complete response was observed in 50% of patients with tumors <2 cm in size, in 38% with tumors 2-4 cm, and in only 18% with tumors >5 cm. Patients with large tumors and N2 nodes (*i.e.* higher stage breast cancer) are less likely to have a pCR compared with those with tumors at lesser stages (25). Penault-Llorca *et al.* (26) reported that a pCR in breast and nodes was achieved three times more frequently in HER2-positive patients than in HER2-negative patients when preoperative chemotherapy without an anti-HER2-specific biological agent was

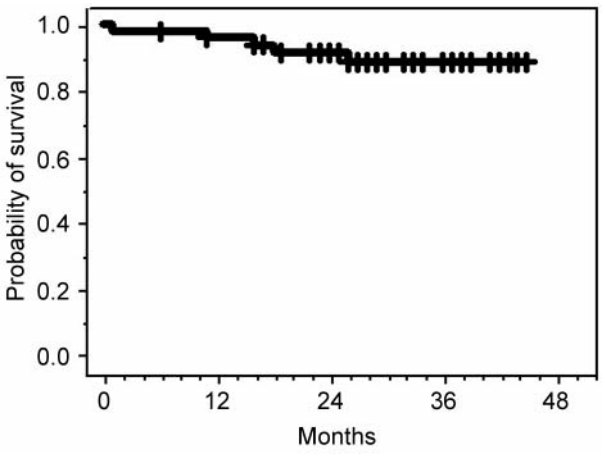

Figure 2. *Overall survival for all patients (n=49). The 3-year overall survival rate was 88%.*

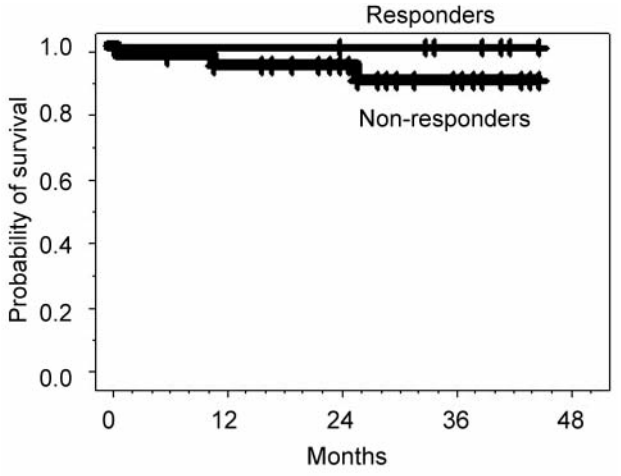

Figure 4. *Comparison of survival between pathological responders (pathological CR or near pathological CR) and non-responders (no pathological CR).*

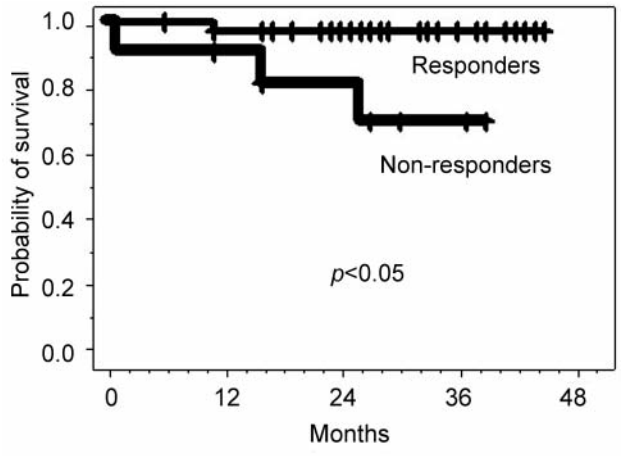

Figure 3. *Comparison of survival between clinical responders (clinical CR or PR) and non-responders (SD or PD).*

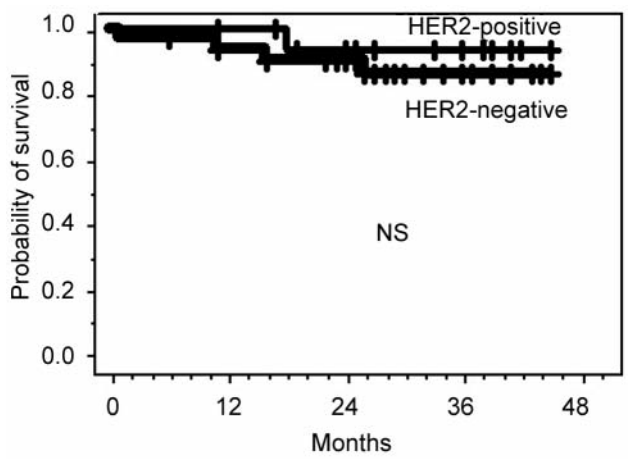

Figure 5. *Comparison of survival between HER2-positive and -negative groups.*

administered. Rouzier *et al*. (27) investigated whether the molecular subtype of a tumor affected chemotherapy sensitivity. They evaluated the gene expression profile of 82 patients treated with neoadjuvant paclitaxel, followed by FAC. The pCR rate was 45% for the basal-like and HER2-positive subtypes and 6% for the luminal tumors. These results support the finding that ER-negative or HER2-positive tumors are more responsive to chemotherapy. Mazouni *et al*. (21) examined whether the inclusion of a taxane and more prolonged preoperative chemotherapy improved the pCR rate in ER-positive breast cancer compared with three or four courses of FAC. Patients with ER-negative cancer had higher overall pCR rates than did patients with ER-positive tumors. In ER-negative patients, the pCR rates were 29% and 15% with and without a taxane, respectively. In ER-positive patients, the pCR rates were 8.8% and 2.0% with and without a taxane, respectively. In a multivariate analysis, clinical tumor size, ER-negative status and the inclusion of a taxane were independently associated with pCR. This indicates that a subset of patients with ER-positive breast cancer benefits from more aggressive chemotherapy, similarly to patients with ER-negative tumors.

In tumors with overexpressed or amplified HER2, some phase II studies have shown that adding trastuzumab to the preoperative regimen produces a high pCR rate. Buzdar *et al*. (9) reported significantly higher pCR rates with four cycles of paclitaxel followed by four cycles of FEC with

weekly trastuzumab in 18 patients, compared with 16 patients treated with chemotherapy alone. Their trial was originally intended to accrue 164 patients, but the trial's Data Monitoring Committee stopped the trial because of the superiority of trastuzumab plus chemotherapy. A recent update (28) showed that the efficacy remained unchanged after the inclusion of the results of 22 additional patients. Another neoadjuvant trial (14) tested the efficacy of docetaxel/carboplatin with or without trastuzumab in stage II/III BC patients with HER2-positive tumors. Of 70 patients, 27 (39%) showed tumor and nodal pCR. A centralized retrospective analysis of HER2 status demonstrated a 43% pCR rate in 24 of 56 confirmed HER2-overexpressing (3+) and/or fluorescence *in situ* hybridization-positive tumors. Cardiac adverse events increased in HER2-positive breast cancer when administering combination therapy of anthracycline-containing regimens and trastuzumab. When trastuzumab is administered, it is unclear whether an anthracycline-containing regimen is actually necessary for HER2-positive breast cancer. It is also unclear whether additional chemotherapy should be given, in the adjuvant setting, for patients who have achieved pCR after preoperative non-anthracycline-containing chemotherapy.

Here, the response rate of single-agent chemotherapy with paclitaxel for HER2-negative breast cancer and of combination therapy with paclitaxel and trastuzumab for HER2-positive breast cancer was evaluated. The pCR was 29.4% in HER2-positive patients. Neoadjuvant paclitaxel and trastuzumab therapy is an effective therapy for HER2-positive advanced breast cancer. Neoadjuvant chemotherapy for breast cancer is equal to postoperative adjuvant chemotherapy in prognosis when using the same regimen. Patients with HER2-positive tumors have been reported to show poor prognoses. A higher pCR was obtained in patients with HER2-positive tumors than in those with HER2-negative tumors when chemotherapy without trastuzumab was administered. However, there was a significant difference in favor of HER2-negative patients compared with HER2-positive patients. It is unknown whether there is any difference in the prognosis between patients with or without HER2 positive tumors when patients with HER2-positive tumors are treated with trastuzumab-containing regimens.

Overall survival was a secondary endpoint in this study, although postoperative adjuvant therapy was not defined. Most patients with hormone receptor-positive tumors received adjuvant endocrine therapy; those with HER2-positive tumors received adjuvant trastuzumab therapy, and non-responders and some responders received adjuvant FEC therapy. There was no difference in overall survival between patients with HER2-negative tumors treated with neoadjuvant weekly paclitaxel and those with HER2-positive tumors treated with neoadjuvant paclitaxel and trastuzumab. Postoperative adjuvant therapy differed among patients: patients with HER2-positive and hormone receptor (HR)-negative tumors received adjuvant trastuzumab for 1 year and HER2-positive and HR-positive patients received adjuvant endocrine therapy. Patients with HER2-negative and HR-positive tumors received postoperative adjuvant endocrine therapy with or without an anthracycline-containing regimen, and those with HER2-negative and HR-negative tumors received an anthracycline-containing regimen. Patients who did not respond to neoadjuvant paclitaxel did not respond to the next anthracycline-containing regimen. Neoadjuvant paclitaxel may be a predictive factor for the next chemotherapy. Paclitaxel responders indicated good prognoses comparing with non-responders.

Several clinical trials have attempted to apply information on drug sensitivity to clinical management. The design of these trials is based on the hypothesis that non-cross-resistant chemotherapeutic agents increase the pCR rate and ultimately improve survival. The German Preoperative Adriamycin and Docetaxel Study II (GEPARTRIO) (29, 30) and Aberdeen trial (31) indicated that the results of using non-cross-resistant chemotherapeutic agents to improve disease outcome were disappointing. It seems that tumors that are insensitive to one class of neoadjuvant chemotherapeutic agents may also be insensitive to other classes of agents. It remains unclear, however, whether patients treated preoperatively with taxane-based therapy should also receive postoperative adjuvant chemotherapy to improve survival, and the decision to administer adjuvant chemotherapy in addition to neoadjuvant chemotherapy is currently left to the discretion of the physician. In contrast, it is accepted practice to treat patients with residual tumors at surgery with a non-cross-resistant chemotherapy regimen. Treatment could be tailored to be of greatest benefit to the individual patient and ultimately should improve long-term outcomes for women with breast cancer.

Fenton *et al*. (32) reported data on the addition of the monoclonal antibody trastuzumab to paclitaxel by comparing two different two-agent neoadjuvant chemotherapy regimens. Paclitaxel/carboplatin in patients with HER2-negative breast cancer was compared with paclitaxel/trastuzumab in patients with HER2-positive breast cancer. Patients with HER2-positive breast cancer were more likely to achieve a pCR than were those with HER2-negative breast cancer. It was also found that the pCR rate was significantly higher in patients with HER2-positive than in those with HER2-negative cancer when trastuzumab was added to paclitaxel monotherapy. Moreover, patients with HER2-positve breast cancer showed almost the same prognosis as those with HER2-negative breast cancer. HR negativity and HER2 amplification are both associated with more aggressive phenotypes such as high grade and high proliferation. The apparent paradox in breast cancer treatment is that more aggressive tumors are more responsive to chemotherapy, whereas less aggressive tumors are less responsive to chemotherapy, but have better long-

term disease outcome. As knowledge accumulates, physicians will be able to identify specific molecular markers to guide treatment selection, develop more effective targeted treatment, and make individualized therapy a reality.

In conclusion, HER2-positive breast cancer has aggressive potential. However, it is sensitive to combination trastuzumab and paclitaxel chemotherapy, resulting in a high rate of pCR. Trastuzumab-containing chemotherapy has the possibility of improving the prognosis of patients with HER2-positive tumors.

References

1 Eniu A, Palmieri FM and Perez EA: Weekly administration of docetaxel and paclitaxel in metastatic or advanced breast cancer. Oncologist *10*: 665-685, 2005.

2 Sledge GW, Neuberg D, Bernard P *et al*: Phase III trial of doxorubicin, paclitaxel, and the combination of doxorubicin and paclitaxel as front-line chemotherapy for metastatic breast cancer: an intergroup trial (E1193). J Clin Oncol *21*: 588-592, 2003.

3 Parideans R, Biganzoli L, Bruning P *et al*: Paclitaxel *versus* doxorubicin as first-line single-agent chemotherapy for metastatic breast cancer: a European Organization for Research and Treatment of Cancer randomized study with cross-over. J Clin Oncol *18*: 724-733, 2000.

4 Buzdar AU, Singletary SE, Theriault RL *et al*: Prospective evaluation of paclitaxel *versus* combination chemotherapy with fluorouracil, doxorubicin, and cyclophosphamide as neoadjuvant therapy in patients with operable breast cancer. J Clin Oncol *17*: 3412-3417, 1999.

5 Dittrich C, Jakesz R and Gnant M: Preoperative paclitaxel (TOL) in the first-line therapy of patients with breast cancer T3/4, N0-3, M0, followed by surgery, CMF±tamoxifen and radiotherapy: Phase II trial. Proc Am Soc Clin Oncol *16*: 166a (Abstr 581), 1997.

6 Volm M, Forment S, Symmans F *et al*: Neo-adjuvant paclitaxel for locally advanced breast cancer (LABC): Preliminary results. Proc Am Soc Clin Oncol *17*: 181 (Abstr 695), 1998.

7 Slamon DJ, Godolphin W, Jones LA *et al*: Studies of the *HER-2/neu* proto-oncogene in human breast and ovarian cancer. Science *244*: 707-712, 1989.

8 Sachelarie I, Grossbard ML, Chadha M *et al*: Primary systemic therapy of breast cancer. The Oncologist *11*: 574-589, 2006.

9 Buzdar AU, Ibrahim NK, Francis D *et al*: Significantly higher pathologic complete remission rate after neoadjuvant therapy with trastuzumab, paclitaxel, and epirubicin chemotherapy: Results of a randomized trial in human epidermal growth factor receptor 2-positive operable breast cancer. J Clin Oncol *23*: 3676-3685, 2005.

10 Slamon DJ, Leyland-Jones B, Shak S *et al*: Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpress HER2. N Engl J Med *344*: 783-792, 2001.

11 Robert NJ, Vogel CL, Henderson IC *et al*: The role of the liposomal anthracyclines and other systemic therapies in the management of advanced breast cancer. Semin Oncol *31*: 106-146, 2004.

12 Bullock K and Blackwell K: Clinical efficacy of taxane-trastuzumab combination regimen for HER-2-positive metastatic breast cancer. Oncologist *13*: 515-525, 2008.

13 Seidman AD, Berry D, Cirrincione C *et al*: Randomized phase III trial of weekly compared with every-3-weeks paclitaxel for metastatic breast cancer, with trastuzumab for all HER-2 overexpressors and random assignment to trastuzumab or not in HER-2 nonoverexpressors: final results of Cancer and Leukemia Group B protocol 9840. J Clin Oncol *26*: 1642-1649, 2008.

14 Coudert BP, Largillier R, Arnould L *et al*: Multicenter phase II trial of neoadjuvant therapy with trastuzumab, docetaxel, and carboplatin for human epidermal growth factor-2 overexpressing stage II or III breast cancer: Results of the GETN (A)-1 trial. J Clin Oncol *25*: 2678-2684, 2007.

15 Limentani SA, Brufsky AM, Erban JK *et al*: Phase II study of neoadjuvant docetaxel, vinorelbine, and trastuzumab followed by surgery and adjuvant doxorubicin plus cyclophosphamide in women with human epidermal growth factor 2-overexpressing locally advanced breast cancer. J Clin Oncol *25*: 1232-1238, 2007.

16 Hannemann J, Oosterkamp HM, Bosch CAJ *et al*: Changes in gene expression associated with response to neoadjuvant chemotherapy in breast cancer. J Clin Oncol *23*: 3331-3342, 2005.

17 Gralow JR, Burstein HJ, Wood W *et al*: Preoperative therapy in invasive breast cancer: pathologic assessment and systemic therapy issue in operable disease. J Clin Oncol *26*: 814-819, 2008.

18 Miyoshi Y, Kurosumi M, Kurebayashi J *et al*: Low nuclear grade but not cell proliferation predictive of pathological complete response to docetaxel in human breast cancers. J Cancer Res Clin Oncol *134*: 561-567, 2008.

19 Colleoni M, Viale G, Zahrieh D *et al*: Chemotherapy is more effective in patients with breast cancer not expressing steroid hormone receptors: a study of preoperative treatment. Clin Cancer Res *10*: 6622-6628, 2004.

20 Bonadonna G, Valagussa P, Zucali R *et al*: Primary chemotherapy in surgically resectable breast cancer. CA Cancer J Clin *45*: 227-243, 1995.

21 Mazouni C, Kau SW, Frye D *et al*: Inclusion of taxanes, particularly weekly paclitaxel, in preoperative chemotherapy improves pathologic complete response rate in estrogen receptor-positive breast cancers. Ann Oncol *18*: 874-880, 2007.

22 Fisher B, Bryant J, Wolmark N *et al*: Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. J Clin Oncol *16*: 2672-2685, 1998.

23 Kuerer HM, Newman LA, Smith TL *et al*: Clinical course of breast cancer patients with complete pathologic primary tumor and axillary lymph node response to doxorubicin-based neoadjuvant chemotherapy. J Clin Oncol *17*: 460-469, 1999.

24 Bonadonna G, Valagussa P, Brambilla C *et al*: Primary chemotherapy in operable breast cancer: eight-year experience at the Milan Cancer Institute. J Clin Oncol *16*: 93-100, 1998.

25 Tewari M, Krishnamurthy A and Shukla HS: Predictive markers of response to neoadjuvant chemotherapy in breast cancer. Surg Oncol (in press).

26 Penault-Llorca F, Abrial C, Mouret-Reynier MA *et al*: Achieving higher pathological complete response rates in HER-2-positive patients with induction chemotherapy without trastuzumab in operable breast cancer. The Oncologist *12*: 390-396, 2007.

27 Rouzier R, Perou CM, Symmans WF *et al*: Breast cancer molecular subtypes respond differently to preoperative chemotherapy. Clin Cancer Res *11*: 5678-5685, 2005.

28 Buzdar AU, Valero V, Ibrahim NK *et al*: Neoadjuvant therapy with paclitaxel followed by 5-fluorouracil, epirubicin, and cyclophosphamide chemotherapy and concurrent trastuzumab in human epidermal growth factor receptor 2-positive operable breast cancer: An update of the initial randomized study population and data of additional patients treated with the same regimen. Clin Cancer Res *13*: 228-233, 2007.

29 von Minckwitz G, Blohmer J, Vogel P *et al*: *In vivo* chemosensitivity-adapted preoperative chemotherapy in patients with early-stage breast cancer: the Gepar-TRIO pilot study. Ann Oncol *16*: 56-63, 2005.

30 von Minckwitz G, Kümmel S, Vogel P *et al*: Intensified neoadjuvant chemotherapy in early-responding breast cancer: phase III randomized GeparTrio study. J Natl Cancer Inst *100*: 552-562, 2008.

31 Smith IC, Heys SD, Hutcheon AW *et al*: Neoadjuvant chemotherapy in breast cancer: significantly enhanced response with docetaxel. J Clin Oncol *20*: 1456-1466, 2002.

32 Fenton M, Ries L, Strenger RS *et al*: Frequent pathologic complete responses seen with neoadjuvant q4week carboplatin and weekly paclitaxel ±weekly trastuzumab in resectable and locally advanced breast cancer: a Brown University Oncology Group (BrUOG) study. Breast Cancer Res Treat *94(Suppl 1)*: 5054, 2005.

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