Neoadjuvant Paclitaxel for Operable Breast Cancer: Multicenter Phase II Trial with Clinical Outcomes

MORIHIKO KIMURA[1], MUNEAKI SANO[2], MINORU FUJIMORI[3], HIROSHI NAKAGOMI[4], TAKESHI NEGISHI[5], YASUHIRO YANAGITA[6] and NOBUAKI SATO[7]

[1]Department of Surgery, General Ota Hospital (previously Department of Breast Surgery, Gunma Cancer Center), Ota, Gunma;
[2]Niigata Breast Exam Center (previously Department of Surgery, Niigata Cancer Center Hospital), Niigata;
[3]Department of Surgery, Shinshu University School of Medicine, Matsumoto, Nagano;
[4]Department of Surgery, Yamanashi Prefectural Central Hospital, Kofu, Yamanashi;
[5]Department of Surgery, Isesaki Municipal Hospital, Isesaki, Gunma;
[6]Department of Breast Surgery, Gunma Cancer Center, Ota, Gunma;
[7]Department of Surgery, Niigata Cancer Center Hospital, Niigata, Japan

Abstract. *Aim: To determine the efficacy of preoperative weekly paclitaxel for patients with operable breast cancer tumors greater than 3 cm. Patients and Methods: Paclitaxel 80 mg/m^2 weekly x 3 times every 4 weeks for 3 cycles was administered to 53 patients. Twnty-two patients were stage II, 26 stage III, 5 stage IV. Median age (range) was 53 (24-73)years, and 32 patients were negative for estrogen receptor. Thirteen patients showed HER2 overexpression. Results: Eligible cases composed of 53 patients for evaluation of response. Seven patients had a clinical complete response and 29 patients had a partial response. The overall response rate was 67.9%, including three patients with a pathological complete response. In 18 patients with HER2 overexpression, a clinical complete response was observed in 5, a partial response was observed in 9, and stable disease was found in 4. No treatment, related to grade 3 neutropenia, was given for 1 patient (2%). Other hematological and non-hematological toxicity was found in only 1 patient with fatigue. Conclusion: Preoperative weekly paclitaxel induced a high clinical response rate with a high safety profile. HER2-overepressing tumors had a higher clinical response rate than non-HER2-overepxressing tumors (91% vs. 50%, respectively). Further studies are needed to determine whether an increase in the cycles of paclitaxel and/or adding anthracyclines may lead to higher pathological complete response and breast-conservation rates in the neoadjuvant setting.*

Correspondence to: Morihiko Kimura, Department of Surgery, General Ota Hospital, 29-5, Hachiman cho, Ota, Gunma 373-8585, Japan. Tel: +81276226631, Fax: +81276257498, e-mail: kimuraota@yahoo.co.jp

Key Words: Neoadjuvant chemotherapy, paclitaxel, breast cancer, HER2 overexpression.

A number of recent reports have described neoadjuvant chemotherapy for breast cancer as elevating the breast conservation rate and improving the prognoses of patients showing pathological complete response (pCR).

Among the first large-scale clinical trials on neoadjuvant chemotherapy were the National Surgical and Adjuvant Breast and Bowel Project (NSABP) trial B-18 and the European Organisation for Research and Treatment of Cancer (EORTC) trial 10902. The findings from these trials demonstrated that combined chemotherapy with anthracycline, whether employed preoperatively or postoperatively, resulted in similar disease-free survival (DFS) and overall survival (OS), while the breast conservation rate was higher in patients receiving neoadjuvant chemotherapy, and prognoses were better in these with pCR (1, 2). However, the pCR rate of 10% in those who received anthracycline therapy was far from satisfactory, which warranted the development of a better regimen to further improve the pCR.

The NSABP B-27 was one of the largest scale trials on neoadjuvant taxane-based chemotherapy (3). In the trial, sequential administration of docetaxel following an anthracycline-based chemotherapy (AC therapy) produced a pCR rate as high as 26.1%. The DFS and OS were also found to be better in patients with pCR than these without pCR. Based on this evidence, a combination of anthracycline and taxane is considered the current standard for neoadjuvant chemotherapy.

Focusing on paclitaxel, a taxane preparation, we have used this drug in the treatment of metastatic or recurrent cancer and achieved a high clinical response rate of 71% (4). We then evaluated paclitaxel monotherapy as neoadjuvant chemotherapy in 2001. There are few reports showing the beneficial effect of taxane alone in neoadjuvant chemotherapy. The knowledge of the effect of this drug alone should be instrumental in combination therapy. In this paper, we present the results of neoadjuvant paclitaxel-only (PTX) chemotherapy with long-term follow-up. This study may serve as a basic indicator for neoadjuvant combination chemotherapy with anthracycline and taxane.

Patients and Methods

Patients. The patients enrolled in this study had operable breast cancer, for which the primary lesion was histologically or cytologically confirmed breast cancer. In addition, these patients satisfied the following inclusion criteria: (i) primary breast tumor larger than 3 cm in diameter (clinical T2-4, N0-1, M0); (ii) ECOG performance status (PS) of 0-2; (iii) at least 20 years old and less than 75 years old; (iv) adequate hematologic, hepatic, renal, and cardiac functions (WBC count: ≥4,000/mm^3 or neutrophil count: ≥2,000/mm^3; platelet count: ≥100,000/mm^3; Hgb: ≥9 g/dL; aspartate aminotransferase (AST) and alanine aminotransferase (ALT): ≤1.5 times the upper normal limit; serum bilirubin: ≤1.5 mg/dL; serum creatinine: ≤1.5 mg/dL; ECG: within the normal range); and (v) the patient gave informed consent.

Patients were excluded from the study if they had any of the following: serious bone marrow disease; a history of drug allergic reactions; serious complications; fever, with suspicion of an infection; peripheral neuropathy; brain metastasis with symptoms; an active double-cancer; inflammatory breast cancer; male breast cancer; pregnancy, the possibility of a pregnancy, or currently breastfeeding; interstitial pneumonia; pulmonary fibrosis; edema; pleural effusion or pericardial fluid retention requiring treatment; diabetes requiring insulin therapy; a requirement for treatment with a steroid; severe psychosis; psychiatric disorder; or any other condition for which the investigator judged the patient unsuited for inclusion in the study.

Study methods. Fifty-six patients with operable breast cancer satisfied the inclusion criteria and were centrally enrolled in the study by facsimile transmission during the period from May 2001 through February 2003. Patients were treated with weekly PTX at 80 mg/m^2 *i.v.* over 1 hour on days 1, 8, and 15 followed by a 2-week interval without administration. The course was repeated three times prior to surgical resection.

Premedications consisted of dexamethasone 20 mg *i.v.*, diphenhydramine 50 mg *po,* and an H2-blocker (ranitidine 50 mg, or famotidine 20 mg) *i.v.*, administered 30 to 60 minutes before the PTX infusion. If patients did not experience any manifestation of hypersensitivity or allergic reaction after the first infusion, dexamethasone was dose-reduced during the next infusion.

Therapy was held pending recovery of absolute neutrophil count to 1,500 cells/mm^3, platelets more than 75,000/mm^3. PTX was dose-reduced in decrements of 10 mg/m^2 in the event of grade 4 hematological toxicity or grade 3 non-hematological toxicity (except alopecia). Patients were scheduled to undergo surgery 2 to 4 weeks after the three cycles. Surgery was performed earlier in cases of obvious progression or prolonged toxicity.

The primary efficacy assessment endpoint was clinical response rate, while the secondary endpoints were pathological complete response (pCR), compliance, safety and survival. Evaluation of the clinical effect was performed in accordance with the Response Evaluation Criteria in Solid Tumors (RECIST)(5). Evaluation of the pathological response was performed in accordance with the "General Rules for Clinical and Pathological Recording of Breast Cancer" (in *Guidelines for Treatment of Breast Cancer,* 13th Edition; edited by the Japanese Breast Cancer Society)(6). Measurement of measurable lesions and evaluation of evaluable lesions were performed objectively on the basis of image findings using X-rays, CT scans, MRI and extracorporeal measurements. The same methods were used for completing the measurements and evaluations in the same patient. The safety of the chemotherapy was assessed on the basis of the Japanese Clinical Oncology Group (JCOG) version of the NCI-Common Toxicity Criteria (7).

Analyzed parameters and statistical treatment of data. The background factors, analyzed for eligible patients, were age, performance status (PS), estrogen receptor (ER) and progesteron receptor status (PgR) (assessed by an immunohistochemistory (IHC) technique). The HER2 status was assessed by IHC on formalin-fixed paraffin-embedded tissue. The intensity of membrane staining was evaluated according to the following criteria set forth by the DAKO HercepTest (rabbit antihuman HER2/neu polyclonal antibody; DAKO Corporation, Tokyo Japan): score 0, no or up to 10% membrane staining; score 1+, partial and/or faint membrane staining present in more than 10% of tumor cells; score 2+, weak to moderate complete membrane staining present in more than 10% of tumor cells; and score 3+, strong complete membrane staining present in more than 10% of tumor cells. Score 0 and 1+ were considered normal, while scores 2+ and 3+ were considered as HER2 overexpression. Tumor response was evaluated after each cycle and the categories employed were complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD).

Multivariate analysis of patient background factors to identify any that influence the therapeutic effect was carried out by means of logistic regression analysis. Survival was calculated by the Kaplan-Meier method.

Results

Patients background factors. Although 56 patients were enrolled in the study during the period from May 2001 through March 2003, 3 patients were considered ineligible because of inflammatory breast cancer (one patient) and treatment refusal (two patients). The age range of the patients was 24-73 years, with a median age of 53 years. At the time of the start of this study, the ER status was positive in 21 patients. The HER2 status was negative in 13 patients, 1+ in 10, 2+ in 5, 3+ in 13 and unknown in 12. The menopausal status was pre-menopausal in 21 patients (Table I). The cumulative completion rate was 86.8% and the dose was not reduced for any patient.

Table I. *Patient characteristics.*

Characteristic	No. of patients (%)
Age (years)	
Median (range)	53 (24-73)
Clinical tumor status	
T2	18 (34)
T3	26 (49)
T4	9 (17)
Clinical nodal status	
N0	17 (32)
N1	28 (53)
N2	7 (13)
N3	1 (2)
Stage	
IIA	12 (23)
IIB	10 (19)
IIIA	18 (34)
IIIB	8 (15)
IV	5 (9)
Menopausal status	
Pre	22 (42)
Post	31 (58)
Estrogen receptor	
Negative	32 (60)
Positive	21 (40)
HER2/neu status (HercepTest)	
0	13 (25)
1+	10 (19)
2+	5 (9)
3+	13 (25)
Unknown	12 (23)

Table II. *Tumor response of paclitaxel (clinical and pathological response).*

Clinical response (RECIST)						
N	CR	PR	SD	PD	ORR	95% CI*
53	7	29	16	1	67.9%	55.4-80.5
Pathological response**						
N	G3	G2	G1b	G1a	G0	pCR***
53	3	14	10	20	6	5.7%

*95% CI: 95% confidence interval; **Pathological response: Evaluation of the pathological response was performed in accordance with the "General Rules for Clinical and Pathological Recording of Breast Cancer", the 13th edition; edited by the Japanese Breast Cancer Society; ***pCR: pathological CR was Grade 3 only.

Table III. *Clinical effect and HER2 / hormone status.*

	N	CR+PR	NC+PD	
HER2 (3+)	13	12 (92%)	1 (8%)	
HER2 (0-2+)	28	14 (50%)	14 (50%)	$p=0.011$
Unknown	12	10 (83%)	2 (17%)	(χ^2-test)
Any positive*	25	18 (72%)	7 (28%)	
Triple negative**	15	7 (47%)	8 (53%)	$p=0.084$
Unknown	13	11 (85%)	2 (15%)	(χ^2-test)

*Any positive: ER, PgR or HER2 positive; **triple negative: ER, PgR and HER2 are all negative (HER2: 0-2+).

Table IV. *Results of multivariate analysis of patient background factors for the correlation with the clinical effect of paclitaxel.*

Factor	Variable	Walter χ^2	*p*-value
T	0 / 1 / 2 / 3 / 4	0.323	0.8509
N	0 / 1 / 2 / 3	0.067	0.9955
ER	– / +	0.254	0.6146
HER2	– / + / unknown	7.342	0.0255
Menopausal status	pre / post	6.312	0.0120

Response rate. Table II shows the data on the clinical responses of the 53 eligible patients. Seven patients achieved CR and 29 patients PR, while 14 patients were assessed with SD and 1 patient with PD. The response rate was 67.9% (95% confidence interval (CI): 55.4 80.5). The pathological response was assessed as grade 3 in 3 patients and grade 2 in 14, grade 1b in 10, grade 1a in 20 and grade 0 in 6. The pathological CR rate was 5.7%.

The response rate in regard to the HER2 status as assessed by immunohistochemisty was examined. Thirteen patients were HER2 positive and 28 patients were negative. In HER2-positive patients, CR+PR was observed in 12 (92%). On the other hand, in HER2-negative patients, CR+PR was observed 14 (50%). Paclitaxel therapy for HER2-positive patients was effective. Moreover, 25 patients were positive for either ER, or PgR, or HER2, and 15 patients demonstrated a triple negative status (13 patients were unknown). Paclitaxel therapy was effective in seven patients (46.7%) of the triple negative patients (Table III).

Patient background factors influencing clinical effect. Table IV presents the results of the multivariate analysis (by logistic regression analysis) to identify potential responders by detecting patient background factors that influenced the patients' response to paclitaxel chemotherapy. The data for all 53 patients revealed that paclitaxel chemotherapy was clearly associated with HER2 and menopausal status. That is, the response rate was significantly higher in pre-menopausal patients compared with post-menopausal patients, in HER2-positive patients compared with negative patients. The site of

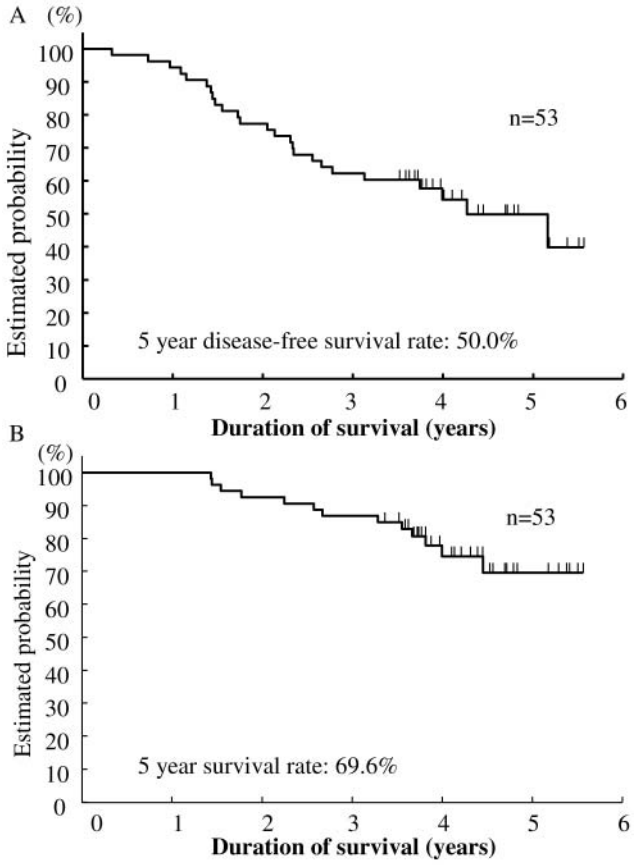

Figure 1. *A, Disease-free survival and B, overall survival after the start of treatment with paclitaxel.*

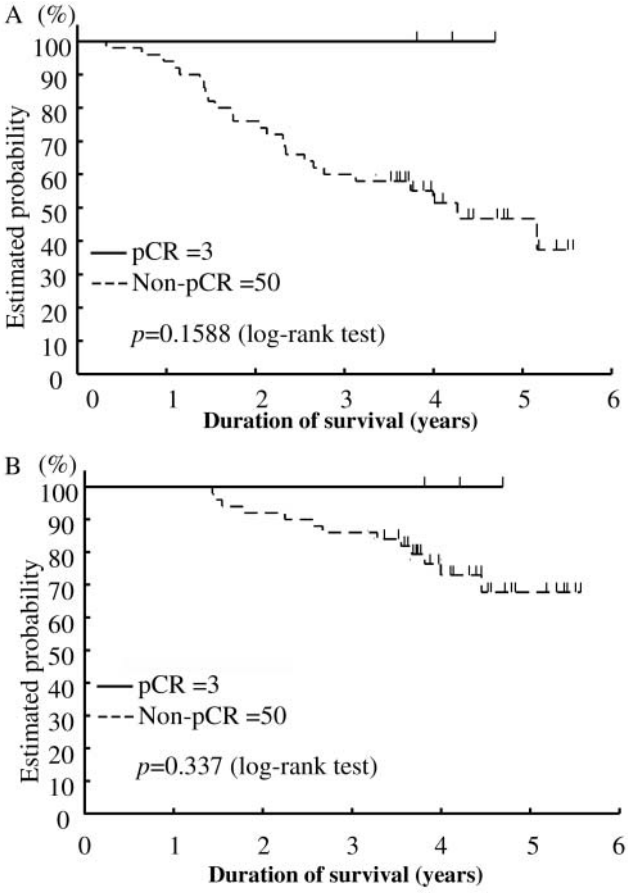

Figure 2. *A, Disease-free survival and B, overall survival by pathological effects after the start of treatment with paclitaxel.*

metastasis and the PS were not statistical significant background factors in patients with recurrent breast cancer.

Survival. Disease-free survival and overall survival curves of patients treated with paclitaxel therapy are shown in Figure 1. Five-year disease-free survival and the five-year survival rate were 50.0% and 69.6%, respectively (median follow-up time: 3.9 years).

Toxicity. Table V shows the data on toxicity recorded during the study. The most frequently occurring hematological toxicities were leukopenia and granulocytopenia, which showed incidences of grade 3 or 4 toxicity of 2% and 5%, respectively. No patients needed the granulocyte colony-stimulating factor (G-CSF). In addition, dose reduction was not necessary for any of the patients. As non-hematological toxicities, one patient experienced grade 3 fatigue. Other high-incidence non-hematologic toxicities that occurred were hair loss, peripheral neuropathy and myalgia/arthralgia, all of which were grade 2 or lower in severity. Accordingly, this combination chemotherapy was carried out safely (Table V).

Table V. *Toxicity+ (n=53).*

	Grade (%)					3≤
	0	1	2	3	4	
Leukocytopenia	51	27	20	2	0	2
Granulocytopenia	60	29	7	5	0	5
Anemia	71	19	10	0	0	0
Thrombocytopenia	100	0	0	0	0	0
AST	95	5	0	0	0	0
ALT	89	9	2	0	0	0
Alopecia	76	17	77	–	–	
Peripheral neuropathy	59	41	0	0	0	0
Myalgia/arthralgia	86	14	0	0	0	0
Fatigue	90	4	4	2	0	2
Malaise	86	10	4	0	0	0
Skin	92	6	2	0	0	0
Edema	98	2	0	0	0	0
Heartburn	98	2	0	0	0	0
Tumor pain	98	2	0	0	0	0

+NCI-CTC ver. 2
AST: aspartate aminotransferase, ALT: alanine aminotransferase.

Discussion

Paclitaxel is a key drug for breast cancer with a great deal of evidence of its effectiveness for treatment of metastatic, recurrent, and early-stage operable breast cancer.

In a comparative study on neoadjuvant chemotherapy, Buzdar *et al.* compared a paclitaxel-only regimen with FAC (fluoropyrimidine, anthracycline, cyclophosphamide) therapy containing anthracycline (8). The results of the study indicated that paclitaxel monotherapy produced a clinical response comparable to those observed with FAC therapy. The results also demonstrated sufficiently tolerable toxicity. Concomitant or sequential use of paclitaxel with anthracycline was later studied (9-12). Green *et al.* conducted a study on sequential administration in an FAC therapy to compare weekly dosing and every-three-week dosing of paclitaxel. The pCR rate was 28.2% in those who received treatment weekly, which was significantly higher than in those on the standard every-three-week regimen.

Frequent administration of paclitaxel in small doses based on the Norton-Simon hypothesis (13, 14) was examined and demonstrated to be clinically effective (15, 16). As we reported earlier, the dose-dense regimen of administering paclitaxel weekly appears more effective and thus more potent in reducing toxicity compared with a weekly dosing (4).

Paclitaxel works well with trastuzumab (17-19) and according to the report from Buzdar *et al.* on neoadjuvant chemotherapy in patients with early operable breast cancer, an outstandingly high pCR rate of 65.2% was achieved when four cycles of paclitaxel 225 mg/m^2 was administered followed by four cycles of FEC (fluoropyrimidine, epirubicin, cyclophosphamide) therapy together with trastuzumab (20).

In our study on neoadjuvant weekly paclitaxel chemotherapy for early operable breast cancer, the pCR rate was 5.7%, while the clinical response rate was 67.9%. HER2-positive patients responded better than HER2-negative patients, with a clinical response rate of 92% (12/13) and 50% (14/28), respectively (p=0.011). Multivariate analyses revealed that the HER2 status and menopause were independent predictive factors for efficacy. HER2 amplification or overexpression is correlated with poor prognoses, such as shorter survival (21-24), while there are increasing reports suggesting that it may serve as an important factor in predicting the effects of chemotherapy and hormone therapy (25-27). Under these circumstances, paclitaxel appears to play a part in the improvement of outcomes in HER2-positive breast cancer patients. The use of a weekly dosing schedule resulted in good compliance, with 86.8% of patients completing the study. At present, with an aim to further improve the pCR, numerous studies are under way to examine the neoadjuvant combination chemotherapy of paclitaxel with anthracycline, or with trastuzumab for HER2-positive breast cancer. The paclitaxel-only regimen in our present study produced an unsatisfactory pCR rate of 5.8%, however most of these patients postoperatively received adjuvant therapy (anthracycline-based, 45.3%; taxanes, 37.7%; other, 9.4%; no chemotherapy, 7.5%), and those who achieved pCR, as described in our previous reports, were free from relapse and had better prognoses compared with non-pCR patients (Figure 2).

In the current efforts of seeking better neoadjuvant chemotherapy with a high pCR-producing regimen, the clinical results of long-term follow-up of a weekly paclitaxel, which is a key drug in our chemotherapy, may be a highly significant indicator for determining the anticancer effect and toxicity of paclitaxel alone when considering combined use with other agents.

References

1 Wolmark N, Wang J, Mamounas E, Bryant J and Fisher B: Preoperative Chemotherapy in Patients With Operable Breast Cancer: Nine-Year Results From National Surgical Adjuvant Breast and Bowel Project B-18. J Natl Cancer Inst Monographs *30*: 96-102, 2001.

2 van der Hage JA, van de Velde CJ, Julien JP, Tubiana-Hulin M, Vandervelden C and Duchateau L: Preoperative Chemotherapy in Primary Operable Breast Cancer: Results From the European Organization for Research and Treatment of Cancer Trial 10902. J Clin Oncol *19*: 4224-4237, 2001.

3 Bear HD, Anderson S, Smith RE, Geyer CE Jr, Mamounas EP, Fisher B, Brown AM, Robidoux A, Margolese R, Kahlenberg MS, Paik S, Soran A, Wickerham DL and Wolmark N: Sequential Preoperative or Postoperative Docetaxel Added to Preoperative Doxorubicin Plus Cyclophosphamide for Operable Breast Cancer: National Surgical Adjuvant Breast and Bowel Project Protocol B-27. J Clin Oncol *24*: 2019-2027, 2006.

4 Kimura M, Koida T and Yanagita Y: Weekly administration of paclitaxel for advanced or metastatic breast cancer short-course premedications for outpatients. Jpn J Cancer Chemother *27*: 1703-1708, 2000.

5 Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC and Gwyther SG: New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst *92*: 205-216, 2000.

6 The Japanese Breast Cancer Society edited: General Rules for Clinical and Pathological Recording of Breast Cancer" (in Guidelines for Treatment of Breast Cancer, 13th Edition; edited by the Japanese Breast Cancer Society. KANEHARA&CO., LTD. 1998.

7 Japanese translation of common terminology criteria for adverse events (CTCAE), and instructions and guidelines. Int J Clin Oncol *9(Suppl 3)*: 1-82, 2004.

8 Buzdar AU, Singletary SE, Theriault RL, Booser DJ, Valero V, Ibrahim N, Smith TL, Asmar L, Frye D, Manuel N, Kau SW, McNeese M, Strom E, Hunt K, Ames F and Hortobagyi GN: Prospective evaluation of paclitaxel *versus* combination chemotherapy with fluorouracil, doxorubicin, and cyclophosphamide as neoadjuvant therapy in patients with operable breast cancer. J Clin Oncol *11*: 3412-3417, 1999.

9 Diéras V, Fumoleau P, Romieu G, Tubiana-Hulin M, Namer M, Mauriac L, Guastalla JP, Pujade-Lauraine E, Kerbrat P, Maillart P, Pénault-Llorca F, Buyse M and Pouillart P: Randomized parallel study of doxorubicin plus paclitaxel and doxorubicin plus cyclophosphamide as neoadjuvant treatment of patients with breast cancer. J Clin Oncol *22*: 4958-4965, 2004.

10 Bauerfeind G, Nestle-Kraemling C, Kahlert S, Muck B, Bastert G, Wagner U, Bothmann G, Brumm C, Schulz K-D and Untch M: Surgical management of patients following preoperative chemotherapy for primary breast cancer; results from a prospective randomised AGO protocol with dose dense paclitaxel and epirubicin chemotherapy [abstract 84]. Proc Am Soc Clin Oncol *22*, 2003.

11 Gianni L, Baselga J, Eiermann W, Guillem Porta V, Semiglazov V, Lluch A, Zambetti M, Sabadell D, Raab G, Llombart Cussac A, Bozhok A, Martinez-Agulló A, Greco M, Byakhov M, Lopez Lopez JJ, Mansutti M, Valagussa P and Bonadonna G: European Cooperative Trial in Operable Breast Cancer Study Group.: Feasibility and tolerability of sequential doxorubicin/paclitaxel followed by cyclophosphamide, methotrexate, and fluorouracil and its effects on tumor response as preoperative therapy. Clinical Cancer Res *11*: 8715-8721, 2005.

12 Green MC, Buzdar AU, Smith T, Ibrahim NK, Valero V, Rosales MF, Cristofanilli M, Booser DJ, Pusztai L, Rivera E, Theriault RL, Carter C, Frye D, Hunt KK, Symmans WF, Strom EA, Sahin AA, Sikov W and Hortobagyi GN: Weekly paclitaxel improves pathologic complete remission in operable breast cancer when compared with paclitaxel once every 3 weeks. J Clin Oncol *23*: 5983-5992, 2005.

13 Norton L and Simon R: The Norton-Simon Hypothesis Revisited. Cancer Treat Reports *70*: 163-169, 1986.

14 Norton L: Evolving Concepts in the Systemic Drug Therapy of Breast Cancer. Semin Oncol *24*: S10-3-S10-10, 1997.

15 Seidman AD, Hudis CA, Albanell J, Tong W, Tepler I, Currie V, Moynahan ME, Theodoulou M, Gollub M, Baselga J and Norton L: Dose-dense therapy with weekly 1-hour paclitaxel infusions in the treatment of metastatic breast cancer. J Clin Oncol *16*: 3353-3361, 1998.

16 Perez EA, Vogel CL, Irwin DH, Kirshner JJ and Patel R: Multicenter phase II trial of weekly paclitaxel in women with metastatic breast cancer. J Clin Oncol *19*: 4216-4223, 2001.

17 Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, Fleming T, Eiermann W, Wolter J, Pegram M, Baselga J and Norton L: Use of Chemotherapy plus a Monoclonal Antibody against HER2 for Metastatic Breast Cancer That Overexpresses HER2. N Engl J Med *344*: 783-792, 2001.

18 Baselga J, Norton L, Albanell J, Kim YM and Mendelsohn J: Recombinant humanized anti-HER2 antibody (Herceptin) enhances the antitumor activity of paclitaxel and doxorubicin against HER2/neu overexpressing human breast cancer xenografts. Cancer Res *58*: 2825-2831, 1998.

19 Merlin JL, Barberi-Heyob M and Bachmann N: *In vitro* comparative evaluation of trastuzumab (Herceptin®) combined with paclitaxel (Taxol®) or docetaxel (Taxotere®) in HER2-expressing human breast cancer cell lines. Ann Oncol *13*: 1743-1748, 2002.

20 Buzdar AU, Ibrahim NK, Francis D, Booser DJ, Thomas ES, Theriault RL, Pusztai L, Green MC, Arun BK, Giordano SH, Cristofanilli M, Frye DK, Smith TL, Hunt KK, Singletary SE, Sahin AA, Ewer MS, Buchholz TA, Berry D and Hortobagyi GN: 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.

21 Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A and McGuire WL: Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. Science *235*: 177-182, 1987.

22 Slamon DJ, Godolphin W, Jones LA, Holt JA, Wong SG, Keith DE, Levin WJ, Stuart SG, Udove J and Ullrich A: Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer. Science *244*: 707-712, 1989.

23 BA Gusterson, RD Gelber, A Goldhirsch, KN Price, J Save-Soderborgh, R Anbazhagan, J Styles, CM Rudenstam, R Golouh and R Reed: Prognostic importance of c-erbB-2 expression in breast cancer. J Clin Oncol *10*: 1049-1056, 1992.

24 Press MF, Bernstein L, Thomas PA, Meisner LF, Zhou JY, Ma Y, Hung G, Robinson RA, Harris C, El-Naggar A, Slamon DJ, Phillips RN, Ross JS, Wolman SR and Flom KJ: HER-2/neu gene amplification characterized by fluorescence in situ hybridization: poor prognosis in node-negative breast carcinomas. J Clin Oncol *15*: 2894-2904, 1997.

25 Piccart MJ, Di Leo A and Hamilton A: HER2: a 'predictive factor' ready to use in the daily management of breast cancer patients? Eur J Cancer *36*: 1755-1761, 2000.

26 Lohrisch C and Piccart M: HER2/neu as a predictive factor in breast cancer. Clin Breast Cancer *2*: 129-135, 2001.

27 Piccart M, Lohrisch C, Di Leo A and Larsimont D: The predictive value of HER2 in breast cancer. Oncology *61(S2)*: 73-82, 2001.

Received November 15, 2007
Revised January 25, 2008
Accepted February 15, 2008