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

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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/m² weekly x 3 times every 4 weeks for 3 cycles was administered to 53 patients. Twenty-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-overexpressing tumors had a higher clinical response rate than non-HER2-overexpressing 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.

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 those 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 those without pCR. Based on this evidence, a combination of anthracycline and taxane is considered the current standard for neoadjuvant chemotherapy.

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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/mm³ or neutrophil count: ≥2,000/mm³; platelet count: ≥100,000/mm³; 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 an active double-cancer; inflammatory breast cancer; male breast infection; peripheral neuropathy; brain metastasis with symptoms; and (vi) the patient was unsuited for the 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 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).

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 1). The cumulative completion rate was 86.8% and the dose was not reduced for any patient.
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 immunohistochemistry 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 in 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
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).

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade (%)</th>
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<tbody>
<tr>
<td></td>
<td>0</td>
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<tr>
<td>Leukocytopenia</td>
<td>51</td>
</tr>
<tr>
<td>Granulocytopenia</td>
<td>60</td>
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<tr>
<td>Anemia</td>
<td>71</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>100</td>
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<tr>
<td>AST</td>
<td>95</td>
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<tr>
<td>ALT</td>
<td>89</td>
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<tr>
<td>Alopecia</td>
<td>76</td>
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<tr>
<td>Peripheral neuropathy</td>
<td>59</td>
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<tr>
<td>Myalgia/arthralgia</td>
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<tr>
<td>Fatigue</td>
<td>90</td>
</tr>
<tr>
<td>Malaise</td>
<td>86</td>
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<tr>
<td>Skin</td>
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<tr>
<td>Edema</td>
<td>98</td>
</tr>
<tr>
<td>Heartburn</td>
<td>98</td>
</tr>
<tr>
<td>Tumor pain</td>
<td>98</td>
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</tbody>
</table>

\(^*\)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 paclitaxel was significantly higher than in those on the standard every-three-week regimen. In a comparative study on neoadjuvant chemotherapy, 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/m² 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


