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RESEARCH ARTICLE

Efficacy and Safety of Neoadjuvant Chemotherapy with Dose De-Escalation Tri-Weekly Nanoparticle Albumin-Bound Paclitaxel and FEC for Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer

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Abstract

Introduction: Neoadjuvant chemotherapy (NAC) is widely used for human epidermal growth factor receptor 2-positive ($HER2^+$) breast cancer. The standard NAC regimen for $HER2^+$ breast cancer is an anthracycline, followed by taxane in combination with anti-HER2 drugs. However, the risk of toxicities such as cardiac dysfunction and peripheral neuropathy occasionally requires dose reduction. Nanoparticle albumin-bound paclitaxel (nab-PTX) is a new taxane used in NAC. The aim of this study was to examine the effects of tri-weekly low-dose nab-PTX with anti-HER2 drugs followed by fluorouracil, epirubicin, and cyclophosphamide (FEC) as NAC in patients with $HER2^+$ breast cancer.

Methods: Patients with operable primary $HER2^+$ breast cancer in clinical stages I–III were enrolled in this study. The NAC regimen included four courses of nab-PTX (220 mg/m^2) concurrently with trastuzumab (6 mg/kg) tri-weekly, followed by four courses of FEC75 (5-fluorouracil: 500 mg/m^2, epirubicin: 75 mg/m^2, and cyclophosphamide: 500 mg/m^2). Pathological responses, adverse events, and follow-up data at 36 months were evaluated.

Results: Among the 20 patients enrolled, 15 completed the treatment protocol. The pathological complete response (pCR) rates were 60.0% overall and 85.7% in hormone receptor-negative/$HER2^+$ patients. At 36 months, one secondary malignancy was observed. The most frequent adverse event was peripheral sensory neuropathy (25/42, 59.5%), which persisted in four (16%) patients at 36-month follow-up.

Conclusions: NAC with low-dose tri-weekly nab-PTX followed by FEC demonstrated favorable pCR and disease-free survival. Peripheral sensory neuropathy remains a concerning long-term adverse effect in some patients, even after reducing the nab-PTX dosage.

Keywords: albumin-bound paclitaxel, human epidermal growth factor receptor 2, neoadjuvant chemotherapy, breast cancer, peripheral neuropathy

Introduction

Neoadjuvant chemotherapy (NAC) is the standard treatment for early and locally advanced breast cancer because it enables less extensive surgery and provides information on treatment effects. Currently, the standard treatment for breast cancer is NAC consisting of an anthracycline and taxane-based regimens. The most frequently used drugs are the solvent-based paclitaxel (sb-PTX) and

docetaxel[1]; however, their adverse effects (e.g., peripheral neuropathy and allergic reactions) are associated with the vehicles such as polyethylated castor oil and ethanol which are used in the formulation of these drugs that limits their long-term efficacy. Nanoparticle albumin-bound PTX (nab-PTX) is a solvent-free, 130 nm particle form of PTX bound to albumin, which was developed to avoid such adverse effects. Although nab-PTX has been utilized as a NAC in breast cancer, toxicities such as peripheral neuropathy are still observed, necessitating dose reduction to complete the treatment.[2] In addition, the long-term adverse events of nab-PTX have not been widely examined, and thus further research is required.

In 2014, we conducted a single-institution phase II clinical study (nab-PTX220 study) with reduced doses of tri-weekly q3w nab-PTX and FEC (5-fluorouracil: 500 mg/m^2, epirubicin: 75 mg/m^2, and cyclophosphamide: 500 mg/m^2) to assess the efficacy and safety of dose-reduced nab-PTX as an NAC. Herein, we report these results, along with the long-term outcomes, including the adverse effects.

Material and methods

Nab-PTX220 study design

Women aged ≥20 years with histologically confirmed breast cancer were included in this study. The inclusion criteria were as follows: Eastern Cooperative Oncology Group performance status of 0–1; clinical stage T1c-3, N0/M0 or T1-3, N1/M0; adequate bone marrow, liver, and kidney function; estrogen receptor (ER), progesterone receptor (PgR) and human epidermal growth factor receptor-2 (HER2) expression status confirmed using core needle biopsy specimens; curative surgery were performed following neoadjuvant treatment. Primary lesion and lymph nodes were detected using ultrasonography, computed tomography, or magnetic resonance imaging. No history of therapy, including chemotherapy, radiotherapy, hormonal therapy, and immunotherapy and malignancy. The written informed consent were obtained from all the participants. The HER2 was defined as positive according to an immunohistochemical HER2 protein staining score of 3+ in >10% of tumor cells, or HER2 gene was regarded as amplified when the HER2/chromosome enumeration probe 17 (CEP17) ratio was >2.0 in a dual-probe assay by fluorescence *in situ* hybridization. ER and PgR were considered as positive when immunohistochemical staining showed at least 1% positivity. Cancer was considered as hormone receptor (HR)-positive when either ER or PgR was positive.

The patients were administered four cycles of nab-PTX (220 mg/m^2 q3w), followed by four cycles of q3w FEC without using prophylactic granulocyte colony-stimulating factor. For anti-HER2 treatment, q3w trastuzumab at 6 mg/kg (8 mg/kg as the loading dose) was administered concurrently with nab-PTX for four cycles. In addition, 13 cycles of trastuzumab were administered following the surgery. Toxicities were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. The protocol treatment was discontinued upon observation of any adverse events such as grade 4 non-hematologic toxicity, progression of the primary tumor, or lymph node metastasis. Adjuvant systemic or radiation therapy was administered as needed. This study was approved by the institutional review board of the Jikei University School of Medicine [25-305(7440)].

Assessment

The primary endpoint of the nab-PTX220 study was the pathological complete response (pCR) rate, which is defined as the absence of histological evidence of residual invasive tumor cells in the breast and axillary lymph nodes (ypT0/TisypN0). The secondary endpoint was toxicity.

Follow-up

All patients were followed up for at least 36 months; those who completed the treatment protocol and underwent surgery (n = 15) were analyzed for long-term follow-up. Relapse-free survival (RFS) was calculated as the time interval (in months) between the date of enrollment and the first observation of tumor recurrence (metastatic recurrence, local, or regional relapse), death, or last follow-up. Disease-free survival (DFS) was calculated as the time interval (in months) between the date of enrollment and the first observation of tumor recurrence (metastatic

recurrence and local or regional relapse), any second malignancy, death, or last follow-up. Overall survival (OS) was calculated as the time interval between the date of enrollment and death or last follow-up. This part was approved separately as observational study by the institutional review board of the Jikei University School of Medicine [32-484(10577)].

Statistical analysis

The pCR rates of previous neoadjuvant trials with anthracycline/taxane were 31.3%–65.2%.[3, 4] We estimated the required sample size of 17 by setting an efficacy of 60%, threshold efficacy of 35%, power of 80%, and the alpha value of 0.1% (one-sided) using the binomial test. All analyses were performed using SPSS statistical software version 24.0 (SPSS, Inc., Chicago, IL, USA), and the significance level for a two-sided test was set at 0.05. RFS and OS were assessed using Kaplan–Meier estimates, and sub-groups were analyzed using the log-rank test.

Results

Patient characteristics

Twenty patients were enrolled in this study. The patient and tumor characteristics are presented in Table 1.

Table 1. Patient and tumor characteristics

Characteristic	N (%)
Number of patients	20 (100.0)
Median age (range), years	61.5 (36–77)
PS	
0	13 (65.0)
1	7 (35.0)
cT	
1	2 (10.0)
2	15 (75.0)
3	3 (15.0)
cN	
0	8 (40.0)
1	9 (45.0)
2	3 (15.0)
Stage	
I	1 (5.0)
II	15 (75.0)
III	4 (20.0)
Histology	
Invasive ductal carcinoma	20 (100.0)
ER	
Negative (<1%)	8 (40.0)
Positive (≥1%)	12 (60.0)
PgR	
Negative (<1%)	12 (60.0)
Positive (≥1%)	8 (40.0)
Subtype	
HR^+	9 (45.0)
HR^-	11 (55.0)

PS, performance status; cT, clinical T stage; cN, clinical N stage; ER, estrogen receptor; PgR, progesterone receptor; HR, hormone receptor

The median age was 61.5 (36–77) years. Most patients had stage II or III disease, 60.0% of patients had clinically positive nodes at the initiation of chemotherapy, and 45% were HR^+. Regarding histology, all patients presented with invasive ductal carcinoma.

Outcomes

During the study, four patients discontinued the treatment protocol (patient decision, n = 3; liver dysfunction, n = 1). In total, 16 patients completed the protocol treatment, one of whom violated the protocol (use of prophylactic granulocyte colony-stimulating factor). Therefore, we assessed all patients who underwent surgery (n = 20) as the intention-to-treat group and those who completed the protocol (n = 15) as the completed protocol treatment group (Fig. 1).

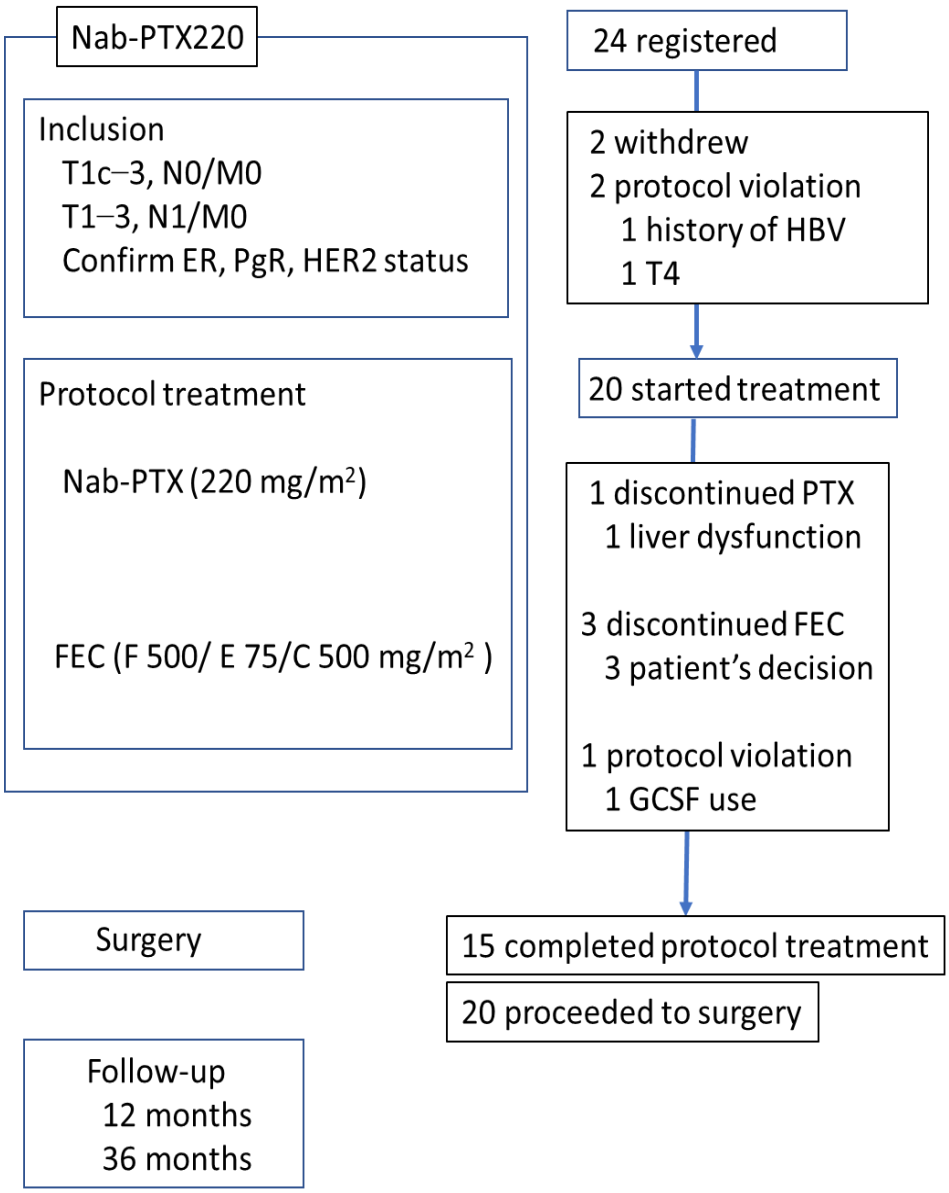

Figure 1. Study flow chart. ER, estrogen receptor; PgR, progesterone receptor; HER2, human epidermal growth factor receptor 2; HBV, hepatitis B virus infection; PTX, paclitaxel; Nab-PTX, nanoparticle albumin-bound paclitaxel; FEC, fluorouracil, epirubicin, and cyclophosphamide; GCSF, granulocyte colony-stimulating factor.

Operative procedures and pathological responses among patients who underwent surgery following completion of the treatment protocol are presented in Table 2.

Table 2. Surgical procedure and pathological response

	CPT N (%)	ITT N (%)
Total number of patients	15 (100.0)	20 (100.0)
Procedure (breast)		
Bp	9 (65.0)	13 (65.0)
Bt	6 (35.0)	7 (35.0)
Procedure (lymph node)		
SN	9 (60.0)	12 (60.0)
Ax	6 (40.0)	8 (40.0)
Pathological response		
ypT0ypN0	5 (33.3)	6 (30.0)
ypTisypN0	4 (26.7)	5 (25.0)
Other	6 (40.0)	9 (45.0)
Pathological response among N1 patients		
ypN+	2 (22.2)	3 (25.0)
ypN0	7 (77.8)	9 (75.0)

CPT, completed protocol treatment; ITT, intention-to-treat; Bp, partial mastectomy; Bt, total mastectomy; SN, sentinel lymph node biopsy; Ax, axillary lymph node dissection

In total, 60.0% of the patients achieved pCR, with 37.5% of HR^+ patients and 85.7% of HR^- patients achieving pCR (Table 3).

Table 3. Tumor subtype and pathological response

Subtype	ypT+ or N+	ypTisN0	ypT0N0	% pCR	*P*
HR^+	5	1	2	37.5	0.06
HR^-	1	3	3	85.7	

pCR,pathological complete response; HR, hormone receptor

At 36 months following study enrollment, there was only one secondary malignancy in a patient who developed acute myeloid leukemia at 30 months after enrollment. The patient was treated with chemotherapy and hematopoietic stem cell transplantation and was disease-free with pCR at 60 months of follow-up. There were two locoregional recurrences at a median follow-up of 61.5 months, one secondary malignancy, no systemic recurrence, and no death from any disease. Therefore, at the 61.6-month follow-up point, RFS, DFS, and OS were 90%, 85%, and 100%, respectively. Achieving the pCR or HR status did not affect the RFS of DFS.

Toxicity

Overall, 95.0% (19/20) of patients experienced at least one adverse effect. The toxicity profiles are listed in Table 4.

Table 4. Toxicity

Adverse event	All grades, N (%)	Grade 3,N (%)
Arthralgia/myalgia	13 (65.0)	
Peripheral neuropathy	11 (55.0)	1 (5.0)
Constipation	6 (30.0)	
Fatigue	5 (25.0)	
Nausea/vomiting	4 (20.0)	
Mucositis	4 (20.0)	
Skin rash	3 (15.0)	
Neutropenic fever	2 (10.0)	2 (10.0)
Anorexia	2 (10.0)	
Dose reduction	4 (20.0)	
Treatment postponement	5 (25.0)	
Treatment discontinuation	4 (20.0)	

The most frequent adverse event was peripheral sensory neuropathy (PSN) (11/20, 55.0%), including grade-3 neuropathy in one patient (5.0%). Among patients who experienced PSN, 18.2% (2/11) complained of numbness and/or paresthesia in the foot following a median time of 61.5 (37–86) months of follow-up. Two patients had Grade 3 neutropenic fever during the FEC treatment.

Discussion

The aim of this study was to examine the effects of q3w low-dose nab-PTX (220 mg/m^2) followed by FEC75 (5-fluorouracil: 500 mg/m^2, epirubicin: 75 mg/m^2, and cyclophosphamide: 500 mg/m^2) as a neoadjuvant treatment for HER2$^+$ breast cancer. The results revealed an overall pCR rate of 60.0% and excellent 3-year RFS and DFS.

Various studies have demonstrated the efficacy of nab-PTX in metastatic or advanced breast cancer.[5–8] In the metastatic setting, q3w nab-PTX (260 mg/m^2) showed a superior response than sb-PTX 175 mg/m^2.[7] In addition, a randomized phase II study in which patients with previously untreated metastatic breast cancer were administered nab-PTX 300 mg/m^2 q3w, 100 mg/m^2 weekly, 150 mg/m^2 weekly, or docetaxel 100 mg/m^2 q3w, weekly nab-PTX at 150 mg/m^2 demonstrated superior efficacy and safety over docetaxel.[10] Subsequently, the nab-PTX dose, and schedule in neoadjuvant settings have been evaluated in several studies. In studies on nab-PTX combined with anthracycline therapy, the pCR rate for breast cancer including all subtypes (HR$^+$/HER2$^+$, HR$^-$/HER2$^+$, HR$^+$HER2$^-$, HR$^+$HER2$^-$) has been 20%–40%.[11–15] In most studies, the dose of nab-PTX used has been 260 mg/m^2 q3w or 125 mg/m^2 weekly. The pCR rates varied according to the HR and HER2 status, with a high pCR rate (60%–75%) observed in HER2$^+$ patients, particularly in HR$^-$/HER2$^+$ patients.[11,12,16] Initially, we used nab-PTX 260mg/m^2 q3w, however, as many patients were required nab-PTX dose reduction to 220mg, which is recommended usage as one step dose reduction in reference to the product document, we intended to proceed this study. We found a pCR rate of 85.7% in HR$^-$/HER2$^+$ patients, which is comparable to that in previous studies, although we used a low dose of q3w nab-PTX (220 mg/m^2) and FEC75.

The GeparSepto trial was performed to compare the effectiveness of weekly nab-PTX 150 mg/m^2 (reduced to 125 mg/m^2 following study amendment) with weekly sb-PTX 80 mg/m^2 followed by EC demonstrated that patients treated with nab-PTX had a significantly better DFS than patients treated with sb-PTX.[17] In this trial, a significantly higher pCR rate was associated with a significantly improved invasive DFS, and the estimated 36-month DFS was 91.8% in the HR$^-$/HER2$^+$ subgroup. We observed comparable results with 36-month RFS, DFS, and OS of 90%, 85%, and 100%, respectively. There was no survival difference depending on the HR status or pCR status, possibly because of our small number of patients.

Other studies utilized more aggressive therapeutic regimens for more aggressive tumors. The

addition of pertuzumab to trastuzumab in combination chemotherapy significantly improved the survival of patients with high-risk $HER2^+$ breast cancer.[18] The study which compared dose-dense chemotherapy (either AC or FEC) with standard chemotherapy in conjunction with paclitaxel and trastuzumab showed little benefit in patients with $HER2^+$ breast cancer.[19]

However, dose de-escalation therapy has also been suggested as a means of reducing adverse events. Hence, dose de-escalation therapies were explored to reduce the adverse effects of chemotherapy. Cardiac toxicity is the most serious adverse event following anthracycline and anti-HER2 treatment. The risk of anthracycline-induced cardiotoxicity is dose-dependent and increases with the cumulative dose. To avoid cardiac toxicity, several studies have utilized FEC75,[3, 20] which was also applied in our study. In addition, anthracycline-free regimens have been tested for the treatment of selected low-risk tumors. In the neoadjuvant setting, a Japanese trial that included patients with low-risk $HR^-/HER2^+$ tumors reported a pCR rate of 66.7% using an anthracycline-free regimen of nab-PTX 260 mg/m^2 with q3w trastuzumab for four cycles.[21]

Most studies have reported acceptable toxicity profiles in terms of adverse events associated with nab-PTX.[7,15] However, according to the drug use survey for nab-PTX conducted in Japan based on the criteria for approval during 2010–2011, numerous adverse events were observed. In this survey, 934 patients were evaluated to determine the safety profiles of a q3w nab-PTX dose of 260 mg/m^2, with adverse events observed in 92.8% of patients, the most common of which were myelosuppression and PSN.[22] Both these adverse events occurred frequently following the second course of treatment and were the primary reason for discontinuation. In terms of treatment schedule, grade-3 or higher adverse events were more frequently observed with weekly administration[15] and higher drug doses.[5,11,14] In the GeparSepto trial, long-term follow-up of treatment-related PSN led to a significant decrease in the median time to resolve PSN following nab-PTX 125 mg/m^2 as compared to nab-PTX 150 mg/m^2. Nab-PTX combination therapy with other agents such as bevacizumab or atezolizumab resulted in a higher rate of discontinuation or reduction.[23,24] In our study, despite the low-dose administration of nab-PTX, 55.0% of patients reported PSN, and 18.5% continued to be symptomatic at 36 months following chemotherapy. Most studies have reported PSN as reversible, whereas in our study, even low-dose PTX caused prolonged PSN. Although this analysis was conducted as a phase II study, the results reflected real-world data.

De-escalation treatment has also been assessed to reduce adverse events resulting from nab-PTX. In the metastatic setting, a randomized phase II trial in Japan was performed to compare three different doses of q3w nab-PTX (260 vs. 220 vs. 180 mg/m^2) in patients with $HER2^-$ metastatic breast cancer; the results showed that the optimal treatment dose was 180 mg/m^2.[25] However, to date, no study of de-escalation nab-PTX has been conducted in the neoadjuvant setting. In our study, the pCR rates were 37.5% ($HR^+/HER2^+$) and 85.7% ($HR^-/HER2^+$) with concurrent administration of nab-PTX 220 mg/m^2 and trastuzumab, respectively, which is comparable or even better than those reported in other studies using the standard dose of anthracycline and nab-PTX. Because of the expected improved outcomes, low-dose nab-PTX can be considered an effective chemotherapeutic agent.

Our study had some limitations. First, this was a single-institution study with a limited number of patients. Hence, there was likely some bias. On the basis of our results, more number of patients need to be assessed. Second, PSN was diagnosed based on subjective assessment by patients and physicians. The extent of toxicity was assessed using the CTCAE criteria; however, the toxicity estimation may have changed according to each assessor.

In conclusion, NAC with low-dose q3w nab-PTX followed by FEC demonstrated favorable pCR rates and DFS, particularly in patients with $HR^-/HER2^+$ breast cancer. PSN remains a concerning long-term adverse effect in some patients, even after reducing the nab-PTX administration dose.

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