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Phase II Study of Nab-paclitaxel Plus Cyclophosphamide Plus Trastuzumab Neoadjuvant Chemotherapy in Early HER-2-positive Breast Cancer

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Phase II Study of Nab-paclitaxel Plus Cyclophosphamide Plus Trastuzumab Neoadjuvant Chemotherapy in Early HER-2-positive Breast Cancer

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Abstract. *Background/Aim: This phase II trial evaluated the efficacy and safety of neoadjuvant nab-paclitaxel plus cyclophosphamide (CPA) plus trastuzumab (AbraC-HER) in patients with early HER2-positive breast cancer. Patients and Methods: This was a single-arm, open-label, single-center prospective phase II study. The primary endpoint was pathological complete response rate (pCR rate). The secondary endpoints were clinical antitumor efficacy and the frequency and severity of adverse events. Results: Fifty-nine patients were enrolled in this study. pCR (ypT0/is ypN0) was achieved in 29 patients (49%). The overall response rate was 88.1% (52/59) in all patients. Dose reductions because of adverse events occurred in 3 patients (5.1%) and relative dose intensity was 98%. Compared to Abra-HER, AbraC-HER induced fewer adverse effects. Conclusion: Treatment with nab-paclitaxel plus CPA plus trastuzumab was tolerable and effective with a high pCR rate. This AbraC-HER neoadjuvant therapy may be a feasible new treatment option for patients with early HER2-positive breast cancer.*

Breast cancer incidence has been increasing year by year and is the leading cause of age-adjusted morbidity by cancer type in Japan (1, 2). Breast cancer is considered a systemic disease from a relatively early stage, and is therefore subject to systemic multidisciplinary treatment, including chemotherapy and endocrine therapy (3). The usefulness of preoperative chemotherapy (neoadjuvant chemotherapy: NAC) in breast cancer is based on several biological and clinical factors: 1) Early initiation of systemic therapy can decrease breast cancer mortality, 2) the effect of the drug can be evaluated clinically, and 3) reduction in tumor size can enable breast-conserving therapy (4). Because of its particularly effective treatment of HER2-positive breast cancer, NAC including anti-HER2 therapy is the standard care and currently recommended for HER2-positive breast cancer (5, 6).

Taxanes are among the most important components of adjuvant chemotherapy for early breast cancer (4-7). Nab-paclitaxel is a nanoparticle albumin-bound paclitaxel using a novel delivery mechanism that is solvent-free (8-12). In neoadjuvant setting, the phase III GeparSepto trial showed a significant increase in the pathological complete response (pCR) rate for nab-paclitaxel compared with solvent-based paclitaxel, especially in HER2-positive breast cancer (13, 14). In our previous phase II study, NAC with 260 mg/m^2 nab-paclitaxel and trastuzumab (Abra-HER) had similar efficacy compared with docetaxel and trastuzumab conventional therapy (15). However, grade 3 or higher peripheral neuropathy and hepatic dysfunction were observed in around 30% of cases with Abra-HER. Therefore, in this study, nab-paclitaxel was reduced from 260 mg/m^2 to 220 mg/m^2, and cyclophosphamide (CPA) was added in order to maintain efficacy while improving safety. CPA is one of the oldest drugs used in oncology; it is typically used as a component of combination regimens such as AC (doxorubicin and CPA), TC (docetaxel and CPA), and other combination therapies (16, 17). In this phase II trial, we evaluated nab-paclitaxel plus CPA plus trastuzumab (AbraC-HER) as a neoadjuvant treatment for early HER2-positive breast cancer in terms of both its efficacy (pCR rate) and safety.

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Key Words: nab-PTX, HER-2 positive breast cancer, cyclophosphamide, neoadjuvant chemotherapy.

Patients and Methods

Study design and patients. We conducted a single arm, open-label, single-center phase II trial to evaluate the efficacy of neoadjuvant nab-paclitaxel plus CPA plus trastuzumab (AbraC-HER) in patients with early HER2-positive breast cancer. The study was carried out at National Hospital Organization Takasaki General Medical Center, Japan. The study protocol was approved by the Ethics Committee (H27-46) of the National Hospital Organization Takasaki General Medical Center. Written consent was obtained from all patients for the use of their records and imaging in future studies.

Women aged 20-80 years old with a histological diagnosis of HER2-positive breast cancer were considered eligible for the study. Eligibility required an Eastern Cooperative Oncology Group performance status (PS) (ECOG Scale) of 0 or 1, a body surface area >1.25 m^2, and HER2-positive stage I or higher, regardless of ER positivity or negativity. In addition, to be eligible, patients were required to be treatment-naïve, with no priory surgery, radiotherapy, chemotherapy, endocrine therapy, or immunotherapy for breast cancer, and to demonstrate intact major organ function according to laboratory test values within 14 days prior to enrollment; white blood cell count ≥4,000/mm^3, neutrophil count ≥2,000/mm^3, platelet count ≥100,000/mm^3, hemoglobin ≥9.0 g/dl, AST ≤2.5 times the upper limit of institutional normal, ALT ≤2.5 times the upper limit of institutional normal, total bilirubin ≤1.5 mg/dl, creatinine ≤1.5 mg/dl or less, and ejection fraction of 50% or more on echocardiography. The expected efficacy rate of the attempted combination therapy was 30%, the threshold efficacy rate was 15%, the one-sided alpha was 0.05, and the power was 80%. Using the statistical tools of the Southwest Oncology Group Statistical Center, the required number of patients was calculated to be 47. Therefore, the sample size was 47 eligible cases although we were able to enroll more.

Patients with the following confounders were excluded: 1) Patients with serious complications [*e.g.*, difficult-to-control diabetes mellitus, clinically problematic infectious diseases, cardiac diseases (unstable angina, myocardial infarction within 6 months), psychiatric symptoms]; 2) Patients with clear findings of interstitial pneumonia or pulmonary fibrosis on simple chest radiographs; 3) Patients with distant metastases, 4) Patients with a history of severe drug allergy; 5) Patients with simultaneous multiple cancers or multiple heterogeneous cancers with a disease-free interval of 5 years or less (not including intraepithelial or intramucosal carcinoma considered curable by local treatment); 6) Patients with inflammatory breast cancer; 7) Pregnant or possibly pregnant patient; and 8) Patients otherwise judged as inappropriate by the attending physician.

Treatment procedure. On the first day of treatment, nab-paclitaxel was administered at a dose of 220 mg/m^2, then CPA at a dose of 600 mg/m^2, and trastuzumab at 8 mg/kg (for all remaining cycles, the trastuzumab dose was 6 mg/kg). Three weeks later, the second cycle was administered. Four 3-week cycles were followed by surgery, performed 3 to 6 weeks later. Concomitant treatment that might affect the evaluation of the study (other antitumor agents, hormonal therapy, biochemical modulation, radiation and surgery, bisphosphonates, *etc*.) was prohibited during the treatment period. Symptomatic treatment of any adverse events was performed at the discretion of the treating physician, and information on the drugs used was recorded in the medical record. For all patients in this study, an anthracycline regimen was given postoperatively.

For the second and subsequent courses of treatment, the following criteria had to be met before administration of chemotherapy; white blood cell count ≥3,000/mm^3, neutrophil count ≥1,500/mm^3, platelet count ≥100,000/mm^3, hemoglobin ≥8.0 g/dl, total bilirubin ≤1.5 mg/dl, peripheral neuropathy ≤grade 1, other non-hematological toxicities (excluding alopecia, nausea and vomiting) ≤grade 1. Patients underwent laboratory testing on the scheduled administration day or no more than 1 day before. When the laboratory test results did not meet the dosing criteria for round 2, dosing was postponed for 1 week. If, one week later, the patients met the lab criteria, the planned dose was administered; otherwise, it was postponed for another week. If the patient fulfilled the lab criteria after two weeks of postponed and/or grade 3/4 adverse events were observed during the previous course, the dose of nab-paclitaxel may be reduced to 180 mg/m^2. Adverse events were defined as white blood cell count <1,000/mm^3, neutrophil count <500/mm^3, platelet count <50,000/mm^3, peripheral neuropathy ≥grade 3, and/or other non-hematological toxicity (excluding alopecia, nausea, and vomiting). Once the dose was reduced, it was not increased again, even if no toxicity was observed after the reduction. After dose reduction, discontinuation of treatment was allowed if reappearance of adverse events were observed.

Assessments. The primary endpoint was pCR rate. The pCR status was defined as the absence of invasive cancer in the breast and lymph nodes (ypT0/ypTis, ypN0). The secondary endpoints were clinical antitumor efficacy, and frequency and severity of adverse events. Clinical antitumor efficacy was assessed based on the RECIST criteria for the evaluation of therapeutic efficacy in solid tumors. The Kaplan–Meier approach was used to estimate the median DFS value. The grade of adverse events was assessed with the NCI-Common Toxicity Criteria Ver. 4.0. The incidence of adverse events was calculated according to grade. Hematology and biochemistry assessments, physical examinations, and periodic measurements of vital signs were performed before the start of each treatment cycle.

Results

Patient characteristics. From January 2016 to March 2018, a total of 59 patients were enrolled in this study at National Hospital Organization Takasaki General Medical Center, Japan. The characteristics of patients are summarized in Table I. The median age was 58 years (range=32-74 years). All patients were female and PS 0 at the onset of treatment. In terms of TNM tumor stage, 18 patients were T1, 39 were T2, and 2 were T3. In terms of TNM node stage, 42 were N0, 14 were N1, and 3 were N2. In terms of HER2-positivity, 10 patients were immunohistochemistry (IHC)-2+/ISH-positive and 49 patients were IHC-3+. Twenty-five patients comprising the luminal-HER2 group were both hormonal receptor (HR)-positive (ER+ and/or PgR+) and HER2-positive, while 34 had HER2-enriched tumors.

Pathological tumor responses. Of the 59 patients, pCR (ypTo/is ypN0) was achieved in 29 patients (49%). pCR was observed in 6 patients (24.0%) of the luminal-HER2 group

Table I. *Demographics and characteristics of patients (n=59).*

Age median (range), (y.o.)	58 (32-74)
PS (n)	
0	59 (100%)
1	0 (0%)
T factor	
T1	18 (30.5%)
T2	39 (66.1%)
T3	2 (3.4%)
N factor	
N0	42 (71.2%)
N1	14 (23.7%)
N2	3 (5.1%)
Stage	
I	16 (27.1%)
II	38 (64.4%)
III	5 (8.5%)
Subtype	
Luminal-HER2	25 (42.4%)
HER2-enriched	34 (57.6%)
Ki-67, (n)	
<20%	2 (3.4%)
≥20%	47 (79.7%)
Unknown	10 (16.9%)

and 8 (47%) of the HER2-enriched group. The overall clinical response was complete response (CR) in 16 (27.1%), partial response (PR) in 36 (61.0%), stable disease (SD) in 7 (11.9%), and progressive disease (PD) in 0 (0%) patients. The overall response rate (ORR) was 88.1% (52/59) in all patients. In the luminal-HER2 group, the overall clinical response was CR in 4 (16.7%), PR in 17 (70.8%), and SD in 3 (12.5%), for an ORR of 87.5%. In the HER2-enriched group, the overall clinical response was CR in 12 (34.3%), PR in 19 (54.3%), and SD in 4 (11.4%), for an ORR of 88.6%. The overall median follow-up period was 31.2 months (range=9.5-50.9 months). Fifty months disease-free survival was 96.6%, with disease recurrence observed in only 2 patients (Figure 1).

Safety. All patients were assessed for toxicities during the treatment. The adverse events are shown in Table II. Regarding hematologic toxicity, leukopenia occurred in 25 patients (42.4%), neutropenia in 23 (39.0%), anemia in one (1.7%), and thrombocytopenia in one (1.7%). Grade 3/4 adverse events included leukopenia in 1 patient (1.7%) and neutropenia in 5 patients (8.5%). In terms of non-hematological toxicities, the most common adverse event was peripheral neuropathy. All patients had some peripheral neuropathy, with grade 3/4 events occurring in 5 patients (8.5%). Elevation of serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), or γ-GTP was observed in 20-32%, with grade 3/4 events presenting in 6 patients (10%). One patient had febrile neutropenia (1.7%). Dose reductions because of adverse events occurred in 3 patients (5.1%). Treatment was discontinued because of elevation of AST in one patient (1.7%). There was no treatment-related mortality. The relative dose intensity (RDI) in this treatment was 98%.

Discussion

The efficacy of nab-paclitaxel in metastatic breast cancer is well established (9-12). Recently, several studies have reported nab-paclitaxel use in a neoadjuvant setting in early breast cancer patients (11-15, 18-22). The phase III neoadjuvant trial GeparSepto showed a significant increase in the pCR rate for nab-paclitaxel compared with solvent-based paclitaxel, especially in HER2-positive breast cancer (13, 14). In that trial, patients were treated for 12 weeks with a weekly dose of nab-paclitaxel. In the neoadjuvant ETNA study, nab-paclitaxel 125 mg/m^2 for 3 out of 4 weeks did not show pCR-based efficacy compared with solvent-based paclitaxel 90 mg/m^2 on the same schedule (22). In terms of frequency of administration and patient visits, a 3-week regimen may be superior to a weekly regimen. In our previous phase II study, a once-every-3-week regimen of NAC with nab-paclitaxel 260 mg/m^2 and trastuzumab (Abra-HER) had similar efficacy compared with docetaxel and trastuzumab therapy (15). Nab-paclitaxel was developed to reduce the toxicity of taxane; however, grade 3 or higher peripheral neuropathy and hepatic dysfunction were observed in around 30% of patients in our Abra-HER study. Thus, in the current phase II study, we reduced nab-paclitaxel from 260 mg/m^2 to 220 mg/m^2 and added CPA, aiming for better safety with maintained efficacy. A previous adjuvant study of nab-paclitaxel plus CPA plus trastuzumab revealed that this combination therapy was feasible and well tolerated in patients with HER2-positive breast cancer; however, patients in this study were treated weekly (18). In the present study, we conducted a phase II study that evaluated the neoadjuvant therapy of nab-paclitaxel plus CPA plus trastuzumab (AbraC-HER) given once every 3 weeks in terms of its feasibility (pCR rate) and safety.

The pCR rate is considered a potential surrogate marker of response to neoadjuvant therapy and overall survival (5, 6). The present study's pCR rate was 49% in all patients, 24% in the luminal-HER2 group and 62% in the HER2-enriched group. Most preoperative regimens contain an anthracycline regimen, but we opted to hold anthracycline until the postoperative period. In our previous phase II Abra-HER study, the observed pCR was 35% in all patients, 21% in the luminal-HER2 group and 50% in the HER2-enriched group (15): essentially the same efficacy as that in the present study. Given the improved safety, our results suggest that triweekly nab-paclitaxel plus CPA plus trastuzumab

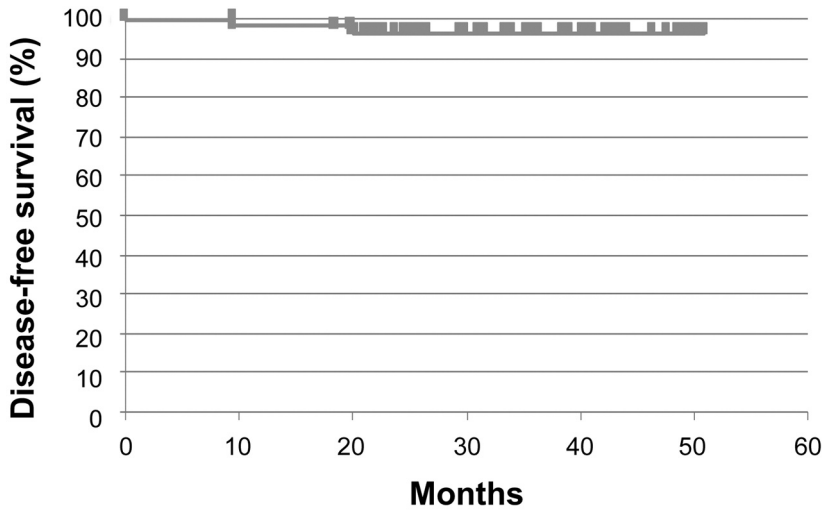

Figure 1. *Kaplan–Meier estimates of the disease-free survival. The overall median follow-up period was 31.2 months (range=9.5-50.9 months). Disease-free survival was 96.6%, with disease recurrence observed in only 2 patients.*

(AbraC-HER) is an effective neoadjuvant treatment option for early HER-2 positive breast cancer.

AbraC-HER was well tolerated in this trial. We compared adverse events to those in the previous Abra-HER trial, which used a nab-paclitaxel dose of 260 mg/m^2 (15). The most common toxicity was peripheral neuropathy, which was observed in all cases of both the Abra-HER and the AbraC-HER trials. Grade 3 or higher peripheral neuropathy was significantly improved, however, from 26% of patients in the Abra-HER study to 8% in the present AbraC-HER study (p=0.022). Grade 3/4 AST elevation was significantly improved from 15% of patients in the Abra-HER study to 3% in AbraC-HER (p=0.046). Grade 3/4 ALT elevation and γGTP elevation were also significantly improved from 30% to 10% (p=0.016) and 30% to 10% (p=0.016), respectively. Compared to Abra-HER, AbraC-HER induced fewer adverse effects. The hematological adverse events, including leukopenia, neutropenia, anemia, and thrombocytopenia, were not significantly different from those in the Abra-HER study. Dose reductions occurred in 5 patients (5 with hepatic dysfunction) in the Abra-HER study but only 2 patients (1 with peripheral neuropathy and 1 with hepatic dysfunction) in the present AbraC-HER study. Dose postponement occurred in 7 cases in the Abra-HER study (6 cases of hepatic dysfunction and 1 case of fever up) but only 3 cases in the present study (3 cases of hepatic dysfunction). The relative dose intensity (RDI) was 93% in the Abra-HER study and 98% in this AbraC-HER study, indicating higher treatment completion rate for AbraC-HER than Abra-HER. Less-toxic treatments should be chosen as long as the treatment is guaranteed to be effective. In light of these results, we suggest that the combination neoadjuvant therapy of nab-paclitaxel plus CPA plus trastuzumab (AbraC-HER) is a feasible and tolerable regimen in terms of both efficacy and safety.

Table II. *Common any-grade adverse events and grade 3/4 adverse events.*

Adverse events, (n)	All Grade	Grade 3/4
Leukopenia	25 (42.3%)	1 (1.7%)
Neutropenia	23 (39.0%)	5 (8.5%)
Anemia	1 (1.7%)	0
Platelet count decreased	1 (1.7%)	0
FN	1 (1.7%)	1 (1.7%)
Periferal neuropathy	59 (100%)	5 (8.5%)
Elevated AST	12 (20.3%)	2 (3.4%)
Elevated ALT	19 (32.2%)	6 (10.2%)
Elevated γGTP	15 (25.9%)	6 (10.2%)
Rash	14 (23.7%)	0

This study has potential limitations, the major one being the small number of cases (n=59) and the involvement of a single center. However, this is the first prospective clinical trial to evaluate the efficacy and feasibility of nab-paclitaxel plus CPA plus trastuzumab as NAC for early HER2-positive breast cancer. The combination of docetaxel with pertuzumab and trastuzumab as neoadjuvant treatment for HER2-positive breast cancer was examined in the APHINITY study and showed a significantly prolonged disease-free survival and overall survival compared with the placebo arm (docetaxel with placebo and trastuzumab). We could not include pertuzumab in the present investigation

because it had not yet been approved in Japan. Additional research on larger numbers of patients is needed to explore the addition of pertuzumab to nab-paclitaxel plus CPA plus trastuzumab to confirm and compare the effects and safety profiles of AbraC-HER with and without pertuzumab.

Conclusion

Treatment with tri-weekly nab-paclitaxel plus CPA plus trastuzumab was tolerable and showed efficacy with a high pCR rate. This AbraC-HER neoadjuvant therapy may be a feasible new treatment option for patients with early HER2-positive breast cancer. As the present study is a small. Open-label, single center trial with no formal hypothesis testing, further study is warranted to confirm the safety and efficacy of AbraC-HER.

Conflicts of Interest

The Authors declare that they have no competing interests in relation to this study.

Authors' Contributions

TF and MO analysed data and wrote the initial draft of the manuscript. MO, TF, YN, and DT collected data and were involved in the initial study conception and design. TF, YK and KS interpreted the results and were involved in drafting the work and revising it critically for important intellectual content. TF approved the final version to be published. All Authors have read and approved the final manuscript.

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