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ORIGINAL ARTICLE

# De-escalated neoadjuvant therapy with nanoparticle albumin-bound paclitaxel and trastuzumab for low-risk pure HER2 breast cancer

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## Abstract

**Purpose** Neoadjuvant trastuzumab combined with anthracycline and taxane is now considered a standard regimen for human epidermal growth factor receptor 2 (HER2)-positive breast cancer. A less toxic, non-anthracycline regimen has been considered as a treatment option for patients with node-negative small tumors. Estrogen receptor-negative and HER2-positive (pure HER2) tumors are more likely to achieve a pathological complete response (pCR). This study evaluates the activity and safety of neoadjuvant nanoparticle albumin-bound paclitaxel (nab-PTX) plus trastuzumab for pure HER2 breast cancer in patients with low risk of relapse.

**Methods** We treated patients with tumors measuring ≤ 3 cm, node-negative, pure HER2 breast cancer using neoadjuvant nab-PTX 260 mg/m2 with trastuzumab every 3 weeks for four cycles. The primary endpoint was the pCR rate. The secondary endpoints included the clinical response rate, disease-free survival, pathologic response rate (defined as pCR or minimal residual invasive disease only in the breast), breast-conserving surgery conversion rate, safety, and disease-free survival. Depending on the pathological findings of surgical specimens, the administration of adjuvant anthracycline could be omitted.

**Results** Eighteen patients were enrolled. No patient required dose delays or reductions; none showed disease progression, and all patients underwent surgery as scheduled. Of the 18 patients, 66.7% achieved pCR, and the adjuvant anthracycline regimen was omitted for all patients. The incidence of severe adverse events was quite low.

**Conclusion** This less toxic, anthracycline-free regimen appears to be a significantly effective neoadjuvant therapy for patients with pure HER2 breast cancer at low relapse risk.

**Keywords** Human epidermal growth factor receptor 2 · Estrogen receptor negative · Neoadjuvant chemotherapy · Nanoparticle albumin-bound paclitaxel · Pathological complete response

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## Introduction

Overexpression of human epidermal growth factor receptor 2 (HER2), which occurs in 20% of all breast cancers, is a predictor of poor prognosis and a marker for response to chemotherapy and HER2-targeted therapies [1]. Neoadjuvant trastuzumab combined with anthracycline and taxane has been extensively investigated in clinical trials in the past few years [2, 3] and is now considered a standard regimen. However, co-administration of anthracyclines and trastuzumab sometimes leads to clinically noteworthy adverse effects, such as cardiac dysfunction [4].

Conversely, because patients with small tumors and node-negative cancers have an originally low risk of recurrence, physicians must be careful not to over-treat, finding the balance between therapeutic effect and toxicity. Recently, a single-arm, phase 2 trial found that adjuvant paclitaxel (PTX) with trastuzumab was effective in patients with node-negative, small (< 3 cm), HER2-positive breast cancer [5]. Based on this result, adjuvant therapy with this less toxic non-anthracycline regimen became one of the treatment option for the patients with low risk of relapse [6]. Additionally, preclinical and clinical studies have revealed that the combination of taxane and trastuzumab may be synergistic in terms of anti-tumor effects [7–9]. Nanoparticle albumin-bound (nab-) PTX is a solvent-free formulation of paclitaxel, and in a recent phase 3 trial showed that nab-paclitaxel in the neoadjuvant setting significantly increased (pathological complete response) pCR rates compared with solvent-based paclitaxel [10].

Among HER2-positive tumors, different responses to neoadjuvant therapy have been observed between patients in the estrogen receptor (ER)-positive (luminal-HER2) and ER-negative (pure HER2) subgroups. In particular, pure HER2 tumors are more likely to demonstrate a pCR and a positive relationship between pCR and favorable outcomes than luminal-HER2 tumors [11, 12]. We previously observed a higher pCR rate in pure HER2 (71%) than in luminal-HER2 tumors (36%) after treatment with neoadjuvant anthracycline followed by treatment with nab-PTX plus trastuzumab in a phase 2 study [13]. These observations indicate that these 2 types of tumors should be treated using different approaches.

We hypothesized that patients with a low risk of relapse per se will have an extremely favorable prognosis if they achieved pCR with a minimum neoadjuvant regimen of taxane plus trastuzumab even without further adjuvant chemotherapeutic drugs, such as anthracycline. Therefore, we conducted a phase 2 trial of neoadjuvant nab-PTX plus trastuzumab administered every 3 weeks for four cycles to evaluate its efficacy in terms of the pCR rate for small, node-negative, pure HER2 breast cancer.

## Patients and methods

This study was conducted in accordance with the Declaration of Helsinki and approved by the review board of each participating institution. Patients were required to give written informed consent. This study was registered with ClinicalTrials.gov, number NCT02598310 and University hospital Medical Information Network-Clinical Trials Registry, number UMIN000019616.

## Patients

This study is a multicenter, prospective, open-label, single-arm, phase 2 clinical trial. Eligible patients had node-negative invasive pure HER2 breast cancer with a tumor measuring ≤ 3 cm. All tumors were tested locally for ER, progesterone receptor (PgR), and HER2 expression. Tumors with < 10% positively stained tumor cells were classified as negative for ER and PgR. Being HER2-positive was defined as 3+ staining intensity by immunohistochemistry (IHC) or HER2 gene amplification by fluorescent in situ hybridization (FISH). A FISH ratio of > 2.0 was considered positive. The Eastern Cooperative Oncology Group performance status had to be < 2, and patients were required to have adequate organ function (aspartate aminotransferase, alanine aminotransferase, and bilirubin ≤ 1.5 × upper limit of normal; leukocytes ≥ 4000/μL; neutrophils ≥ 2000/μL; thrombocytes ≥ $10 \times 10^4$/μL; serum creatinine ≤ 1.5 mg/dL; and normal left ventricular ejection fraction). Cardiac function was monitored after commencement of the study but before surgery. Patients were excluded if they had a confirmed infection; serious concomitant illness such as severe cardiovascular disease, uncontrolled diabetes, malignant hypertension, or hemorrhagic disease; active concomitant malignancy; brain metastasis; peripheral neuropathy; history of edema with severe drug allergy; or previous long-term use of corticosteroids. Pregnant or lactating women were also excluded. Mammography, ultrasonography, magnetic resonance imaging (MRI), or computed tomography (CT) was used to assess the presence of tumors.

### Treatment

Each patient received four cycles of nab-PTX (260 mg/$m^2$) with trastuzumab (6 mg/kg; 8 mg/kg as a loading dose) every 3 weeks. Toxicities were evaluated using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0) throughout the treatment. Prophylaxis with colony-stimulating factor administration was not allowed. Each treatment could be withheld for a maximum of 3 weeks, only owing to severe toxicity. If the adverse

event did not improve, the planned treatment was discontinued and surgery was recommended. The dose of each chemotherapeutic agent could be reduced from the starting dose in case of febrile neutropenia, grade 3/4 thrombocytopenia, or grade 3/4 non-hematologic toxicities (except for nausea/vomiting or fatigue). Dose reduction was as follows: nab-PTX from 260 to 220 to 180 mg/m$^2$. Once the study treatment was discontinued because of disease progression or toxicity, it was not allowed to be resumed; however, trastuzumab was continued even if nab-PTX was delayed. No dose reduction of trastuzumab was allowed.

Patients underwent surgery 4–6 weeks after completing the treatment and clinical assessment of the tumor response. Depending on the pathological findings of the surgical specimen, administration of adjuvant anthracycline could be omitted at the local physician's discretion. All the patients who underwent breast-conserving surgery (BCS) or mastectomy with multiple lymph node metastases underwent radiotherapy. One year of adjuvant trastuzumab was then administered. Patients with 1–9% ER or PgR-positive tumors that were weakly hormone sensitive could be administered adjuvant endocrine therapy.

### Endpoints

The primary endpoint was pCR rate, defined as no histological evidence of residual invasive tumor cells in the breast and axillary lymph nodes (ypT0/Tis and ypN0). A case of ypT0/is with tumor cells remaining in lymph nodes (ypN+) was also documented (considered as non-pCR in this study). All surgical specimens were microscopically examined by the pathologists at each institution.

Secondary endpoints included pathological response rate, clinical response rate, BCS conversion rate, safety, and disease-free survival. Pathological response was defined as pCR or minimal residual invasive disease only in the breast. The clinical tumor response was assessed using the Response Evaluation Criteria in Solid Tumors guidelines by physical examination, ultrasound, and MRI/CT. Patients with complete or partial response were considered responders. The BCS conversion rate was defined as the percentage of cases in which BCS was performed as the final surgical procedure among cases that were not identified as unsuitable for breast conservation at baseline. Disease-free survival was defined as the time from entry in the study to the first of recurrence or relapse, a new primary cancer, or death.

We also investigated the relationship between pathologic response and baseline serum HER2 level or changes in serum HER2 level during the study treatment. Serum samples were obtained before and after treatment. The serum HER2 levels were measured using a commercially available chemiluminescence immunoassay. The baseline serum HER2 level was analyzed as a dichotomous variable (high, $> 15.2$ ng/mL; low, $\leq 15.2$ ng/mL).

### Statistical analysis

Our previous study on neoadjuvant anthracycline followed by nab-PTX plus trastuzumab for HER2-positive breast cancer reported a pCR rate of 49% (95% CI 35–63%) [13]. Therefore, a sample of 28 patients was required according to binomial distribution, with a one-sided threshold pCR rate of 35%, an expected pCR rate of 55%, an α error of 10%, and a β error of 20%. Consequently, the accrual of 30 patients was planned to produce a minimum of 28 evaluable patients.

## Results

### Patient population

This study was terminated without the expected number owing to slow accrual. From November 2015 to October 2018, 18 patients from 11 Japanese institutions were enrolled. All of them could be evaluated for efficacy and safety analysis. The patient characteristics are summarized in Table 1. The median age was 62 years (range, 38–70), and most patients (78%) had stage I cancer. IHC analysis results revealed 14 patients (78%) with HER2 3+ cancer.

### Treatment administration and study completion

There was neither a delay nor dose reduction in the study treatment. No patient showed disease progression, and all underwent surgery as scheduled.

#### Clinical and pathological assessments

pCR was observed in 12 of 18 patients (66.7%) (95% CI 43.7–83.7%). Of these patients, 8 (66.7%) had no residual tumor cells (ypT0 and ypN0). One patient without pCR had tumor cells remaining in one sentinel lymph node (ypT1, ypN+). A pathological response was observed in 14 patients (77.8%) (Table 2). Overall, all patients provided a clinical response, with a complete response in 8 patients. Of the patients with pCR, 8 (66.7%) had a complete clinical response after the study treatment. Overall, BCS was performed for 14 (78%) patients, and the BCS conversion rate was 50% (2/4). Adjuvant anthracycline was administered to all patients without pCR and to no patient with pCR. In addition, we performed radiotherapy in all patients who underwent BCS. Survival outcomes will be reported separately. An exploratory analysis of the relationship between the level of serum HER2 and treatment effects in 15 patients (paired serum samples were missing for 3 patients) showed

**Table 1** Patient characteristics

| Characteristic | No. of patients ($N=18$) |
|---|---|
| Median age, years (range) | 62 (38–70) |
| Performance status | |
| 0 | 18 (100%) |
| 1 | 0 (0%) |
| Menopausal status | |
| Premenopausal | 4 (22%) |
| Postmenopausal | 14 (78%) |
| Median tumor size, cm (range) | 1.7 (1.0–2.9) |
| Clinical stage | |
| I | 14 (78%) |
| IIA | 4 (22%) |
| ER status | |
| 0% | 17 (94%) |
| 1–9% | 1 (6%) |
| PgR status | |
| 0% | 17 (94%) |
| 1–9% | 1 (6%) |
| HER2 status (IHC) | |
| 3+ | 14 (78%) |
| 2+ | 4 (22%) |
| Base line serum HER2, ng/mL[a] | |
| Median (range) | 15.3 (10.1–21.1) |
| > 15.2 | 9 (53%) |
| ≤ 15.2 | 8 (47%) |

*IHC* immunohistochemistry

[a]The number of patients was 17

**Table 2** Pathological response ($N=18$)

| | |
|---|---|
| pCR (ypT0/is and ypN0) | 12/18 (66.7%) |
| Pathological response | 14/18 (77.8%) |

*pCR* pathological complete response

no correlation between baseline serum HER2 or changes in serum HER2 levels and pathologic response.

## Safety profile

The incidence of treatment-related adverse events is summarized in Table 3. Overall, the incidence of severe adverse events was quite low in the patients included in this study. Observed grade 3 adverse events included neutropenia (6%), liver enzyme elevation (11%), and allergic reaction to infusion of trastuzumab (6%). Notably, sensory peripheral neuropathy was observed in a substantial number of patients (88%), but there were no severe events. Myalgia and arthralgia were frequent. There was no patient with > 10% decline in left ventricular ejection fraction from baseline to the end of planned therapy or unexpected serious adverse events.

**Table 3** Most common treatment-related adverse events

| Adverse event | No. of patients ($N=18$) | | | |
|---|---|---|---|---|
| | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
| Hematologic | | | | |
| Leucopenia | 2 (11%) | 2 (11%) | 0 | 0 |
| Neutropenia | 1 (6%) | 0 | 1 (6%) | 0 |
| Febrile neutropenia | – | – | 0 | 0 |
| Anemia | 3 (17%) | 0 | 0 | 0 |
| Thrombocytopenia | 1 (6%) | 0 | 0 | 0 |
| Alanine aminotransferase | 5 (28%) | 1 (6%) | 2 (11%) | 0 |
| Aspartate aminotransferase | 5 (28%) | 1 (6%) | 0 | 0 |
| Non-hematologic | | | | |
| Allergic reaction | 5 (28%) | 0 | 1 (6%) | 0 |
| Pyrexia | 3 (17%) | 0 | 0 | 0 |
| Fatigue | 3 (17%) | 1 (6%) | 0 | – |
| Nausea | 1 (6%) | 1 (6%) | 0 | – |
| Anorexia | 3 (17%) | 1 (6%) | 0 | 0 |
| Stomatitis | 1 (6%) | 0 | 0 | 0 |
| Myalgia | 7 (39%) | 2 (11%) | 0 | – |
| Arthralgia | 6 (33%) | 3 (17%) | 0 | – |
| Sensory neuropathy | 8 (44%) | 8 (44%) | 0 | 0 |

## Discussion

In this study on the efficacy of nab-PTX plus trastuzumab for treating smaller and node-negative pure HER2 breast cancer, we observed a 66.7% pCR rate after four cycles of nab-PTX plus trastuzumab administered every 3 weeks. All the patients omitted the adjuvant anthracycline regimen, and the incidence of severe adverse events was quite low.

The present standard neoadjuvant chemotherapeutic strategy for treating HER2-positive breast cancer is administration of anthracycline and taxane plus trastuzumab [14]. The 66.7% pCR rate observed in this study is not inferior to that reported in previous studies (up to 77.6%); the patients in the previous studies were also administered anthracycline [15]. With respect to the long-term adverse effects of anthracycline with trastuzumab (e.g., cardiac disfunction), anthracycline-free regimens may be necessary and sufficient for treating patients with profiles similar to that of this study. Indeed, no patient with pCR in this study was administered adjuvant anthracycline. De-escalation of further chemotherapy in patients with pCR after a less toxic regimen should be a promising area of future research for treating patients at low risk of relapse.

The importance of de-escalated therapy is limited to not only the domain of cytotoxic chemotherapies but also HER2

target therapies. Administering adjuvant trastuzumab for 1 year is considered the standard treatment for patients with HER2-positive breast cancer [16–18]. However, short-term trastuzumab therapy would be an attractive option and has been investigated in several clinical trials with conflicting results [19]. Patients with profiles similar to those of the cohort of this study might be good candidates for abbreviated trastuzumab therapy because patients with a low tumor burden have more favorable outcomes. Identification of a patient profile (such as pCR) suitable for de-escalated therapy is a topic for future studies.

Several studies have observed higher pCR rates with escalated therapy via dual-HER2 blockade using the combination of trastuzumab and pertuzumab/lapatinib [20, 21]. Markedly higher pCR rates (58.8–90.5%) were observed for pure HER2 breast cancer after treatment with chemotherapy and dual-HER2 blockade [22, 23]. However, although pCR is a favorable prognostic factor for individual patients, improvement in pCR via an experimental therapy is not a substitute for improved outcomes at the trial level [11]. The association between pCR and better prognosis has been consistent even in the patients treated by dual-HER 2 blockades; regardless of the strength of treatment, patients who achieve pCR are reported to have a better prognosis than those who do not achieve pCR [24, 25]. Therefore, therapeutic strategies that achieve pCR using efficient and effective therapy with fewer adverse effects and lower cost are advantageous. Identification of robust biomarkers that predict response to HER2-directed therapies to determine which patients can benefit from de-escalation strategies are still needed. On the other hand, optimization by inclusion of effective therapy for patients without pCR should also be addressed. More recently, a promising data from phase 3 study showed that adjuvant trastuzumab emtansine significantly reduced the risk of disease recurrence or death than trastuzumab alone for patients without pCR after neoadjuvant therapy [26].

In the present study, the frequency of severe adverse effects was very low. As expected, peripheral neuropathy was the most common adverse event, although no patient experienced grade 3/4 without prophylaxis for peripheral neuropathy. The incidence of grade 3/4 neuropathy was lower than that observed in our previous study (9%) [13]. This difference may be explained in part by differences in patient cohorts between the 2 studies. Specifically, patients in the present cohort were treatment naïve before nab-PTX administration, whereas those in the previous cohort had been treated with anthracycline before conducting the study. At present, nab-PTX is approved in Japan only for use in every-third-week regimens for breast cancer treatment, which is not common in Western countries. We performed this study using this approved dose interval. There are no available clinical data on direct comparison of tri-weekly and weekly neoadjuvant treatments of nab-PTX in combination with HER2 target agents. Although the tri-weekly regimen is more convenient for patients because of the lower number of visits, the incidence of any grade of neuropathy tends to be more frequent than in the weekly regimen [27]. However, in this study, we observed neither dose reduction nor discontinuation of study treatment owing to adverse events, including peripheral neuropathy.

A limitation of this study was the relatively small sample size; therefore, the results should be interpreted with caution. Originally, as many patients with small tumors who met eligible criteria of this study does not need mastectomy, they are less likely to benefit from BCS due to tumor shrinkage effect by neoadjuvant therapy. It is conceivable that there were a certain number of patients who selected primary surgery rather than neoadjuvant therapy of this study. Nevertheless, to our knowledge, this is the first study available on this topic. Further clinical investigation in a suitably large cohort is needed to substantiate our findings.

In conclusion, neoadjuvant nab-PTX plus trastuzumab for small and node-negative pure HER2 breast cancer was considerably effective and well tolerated. Minimizing chemotherapy is both reasonable and feasible, especially for lower-risk patients. Achieving pCR via neoadjuvant therapy might distinguish patients who are good candidates for lower intensity subsequent therapy.

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## Compliance with Ethical Standards

**Conflict of interest** The authors declare no conflicts of interest associated with this manuscript.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Informed consent** Informed consent was obtained from all individual participants included in the study.

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