Original Article

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Nab-Paclitaxel Followed by 5-Fluorouracil, Epirubicin and Cyclophosphamide in Neoadjuvant Chemotherapy for Resectable Breast Cancer: A Phase II Trial

Takanori Kin, Shoichiro Ohtani, Reina Maeda, Ayako Ueno, Miwa Fujihara, Yuri Takamatsu, Yukiko Kajiwara, Mitsuya Ito, Kensuke Kawasaki, Keisuke Abe, Yasuhiro Sakata, Koichi Hiraki

Abstract

Background: The aim of this phase II study was to evaluate combined nab-paclitaxel (nab-PTX) with sequential anthracycline-based therapy as a neoadjuvant chemotherapy.

Methods: We enrolled 41 patients with advanced breast cancer (stage IIA - IIC). All patients were to receive three-weekly nab-PTX (260 mg/m²) for four cycles followed by three-weekly 5-fluorouracil, epirubicin and cyclophosphamide (FEC) for four cycles. Trastuzumab administration was permitted in human epidermal growth factor receptor 2 (HER2)-positive patients.

Results: The overall pathological complete response (pCR) rate was 24% (10 of 41). In patients with luminal A, luminal B (HER2-), luminal B (HER2+), triple-negative and HER2, the pCR rates were 0% (0/2), 7% (1/14), 42% (3/7), 25% (4/16) and 100% (2/2), respectively. The most significant toxicities of nab-PTX were grade 2/3 peripheral sensory neuropathy (24%) and grade 3/4 neutropenia (26%). Febrile neutropenia was not observed in any patient. The most significant toxicities of FEC were grade 3/4 neutropenia (24%) and grade 3 febrile neutropenia (9%). One patient died of sepsis secondary to pneumonia during FEC treatment.

Conclusions: Neoadjuvant chemotherapy using nab-PTX with trastuzumab every 3 weeks followed by FEC was suitably tolerated and associated with a high pCR rate of 55% for patients with HER2-positive breast cancer.

Keywords: Breast cancer; Nab-paclitaxel; Neoadjuvant chemotherapy

Introduction

Neoadjuvant chemotherapy has become the standard treatment for advanced breast cancer, particularly anthracycline followed by taxane. Taxane regimens comprising three-weekly docetaxel or weekly paclitaxel are frequently administered [1]. Three-weekly docetaxel permits convenient dosing timings and reduced outpatient visit frequency compared with weekly paclitaxel; however, bone marrow suppression, including grade 4 neutropenia, is more frequently observed in patients administered three-weekly docetaxel compared with those administered weekly paclitaxel [2].

Nab-paclitaxel (nab-PTX) is a nanoparticle albumin-bound PTX. Because PTX has poor solubility in water, polyoxyethylene castor oil (Cremophor EL) and dehydrated ethanol are required. However, Cremophor EL is considered to be a cause of anaphylactoid reactions and delayed neuropathy [3-5], and dehydrated ethanol is difficult to administer in weak drinkers. Because nab-PTX does not contain Cremophor EL and dehydrated ethanol, the administration of steroids and antihistamines is not necessarily required as prophylaxis against anaphylactoid symptoms. Furthermore, excluding Cremophor EL decreases the administration time for nab-PTX compared with that for PTX. In addition, compared with PTX, nab-PTX reportedly has a higher tumor penetration and is associated with a significantly shorter recovery from grade 3 peripheral neuropathy [6].

A phase II study for advanced or recurrent breast cancer comparing three-weekly nab-PTX (300 mg/m²) with three-weekly docetaxel (100 mg/m²) reported an equal or higher response rate (46% vs. 37%) and a significantly lower incidence of grade 4 febrile neutropenia (5% vs. 75%, P < 0.001) for nab-PTX compared with docetaxel [7]. A phase III study for advanced or recurrent breast cancer comparing three-weekly nab-PTX (260 mg/m²) with three-weekly PTX (175 mg/m²) reported a significantly higher response rate (33% vs. 18%, P = 0.001) for nab-PTX [8]. Therefore, neoadjuvant chemotherapy using nab-PTX has greater safety and efficacy compared with docetaxel.
Recently, the use of nab-PTX with immune checkpoint inhibitors such as pembrolizumab or atezolizumab has been suggested [9]. Because steroid premedication to prevent allergic reaction is not required when using nab-PTX, immunosuppression can be avoided. Nab-PTX has attracted a great deal of attention and this study may become the reference data for following study. The aim of this phase II study was to evaluate combined nab-PTX with sequential anthracycline-based therapy as a neoadjuvant chemotherapy. Though the efficacy of nab-PTX followed by 5-fluorouracil, epirubicin and cyclophosphamide (FEC) in neoadjuvant chemotherapy for all subtypes’ breast cancer was revealed by the randomized phase III trial, it was only performed for German [10]. In Japan, limited to published data, there are only three trials but two trials only targeted to human epidermal growth factor receptor 2 (HER2)-positive or HER2-negative breast cancer [11, 12], and one trial added cyclophosphamide to nab-PTX [13]. There are no published data of nab-PTX followed by FEC for all subtypes in Japanese. The primary endpoint of our trial is pathological complete response (pCR) and this is the only one to confirm the reproducibility of randomized phase III trial in Japan.

Patients and Methods

This was a single-center, single-arm, phase II clinical trial. The study protocol was approved by our institutional review boards (29-143) and has been registered with the University Hospital Medical Information Network Center (UMIN 000009733). This study was conducted in compliance with the ethical standards of the responsible institution on human subjects as well as with the Helsinki Declaration.

Patient eligibility

Patients aged 20 - 70 years with an Eastern Cooperative Oncology Group performance status of 0 - 1 were enrolled. All patients were histologically diagnosed with operable breast cancer (clinical T1-3, N0-2, M0) that was previously untreated. Estrogen receptor (ER) and progesterone receptor (PgR) positivity and HER2 status were confirmed. ER and PgR positivity were defined as ≥1% positively stained tumor cells. Hormone receptor positivity was defined as the expression of ER and/or PgR. HER2 positivity was defined as 3+ staining intensity using immunohistochemistry or gene amplification using fluorescence in situ hybridization. A ratio > 2.2 was considered to indicate HER2 positivity. Patients were excluded if they had severe heart failure, significant comorbidity (e.g., uncontrolled diabetes, hypertension, renal failure, hepatic failure and confirmed infection), any other concomitant malignancy, peripheral neuropathy, synchronous or metachronous bilateral breast cancer, or were pregnant and lactating.

Treatment

All patients were administered three-weekly nab-PTX (260 mg/m²) for four cycles followed by three-weekly FEC (5-fluorouracil, 500 mg/m²; epirubicin, 100 mg/m²; cyclophosphamide, 500 mg/m²) for four cycles. Trastuzumab administration was permitted in HER2-positive patients, with 8 mg/kg given as a loading dose followed by 6 mg/kg tri-weekly up to 1 year postoperatively. Dose reductions from baseline dose (nab-PTX, from 260 to 220 or 180 mg/m²; FEC, 100 to 75 or 60 mg/m² of epirubicin) were required for grade 3 to 4 thrombocytopenia, febrile neutropenia for greater than 3 days, or grade 3 to 4 non-hematologic toxicity (except for nausea, vomiting, peripheral neuropathy, alopecia and fatigue). The reduced dose was decided by toxicity severity. Toxicities were evaluated using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE, version 4.0) throughout the treatment. Surgery was performed within 28 - 42 days of the last day of chemotherapy. All patients who underwent breast conserving surgery or mastectomy with large breast tumors or multiple lymph node metastases received radiation therapy. Hormone therapy was permitted in cases of hormone receptor-positive breast tumors.

Endpoints

The primary endpoint was pCR, defined as no histologic evidence of residual invasive tumor in breast and axillary lymph nodes. Secondary endpoints that were assessed comprised breast conserving surgery (BCS) rate, response rate (RR), safety, disease-free survival (DFS) and overall survival (OS), as well as pCR rate, RR and BCS rate of each subtype. Clinical tumor response was assessed using the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1) by computed tomography (CT), magnetic resonance imaging (MRI), ultrasonography, or physical examination. Patients were evaluated for complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD).

Statistical analysis

The pCR rate is different by HER2 positivity. The proportion of HER2 positivity will relate to the overall pCR rate. In this study, the threshold for HER2-negative cases was set to 10% and the expected value to 20%, and the threshold for HER2-positive cases was set to 20% and the expected value to 45%. The calculation was performed under the condition of α error (one side) of 5% and detection power of 90%. Considering that HER2-negative is about 80% of the total cases, the threshold of this pCR rate is 18% and the expected value is 40%, and considering the slightly unqualified cases, the target number of cases to accumulate in this study is 35.

Results

Patient characteristics

From February 2013 to February 2017, we enrolled 41 patients.
with advanced breast cancer (stage IIA - IIIC) without prior treatment regardless of hormone receptor or HER2 status (Table 1). A total of nine of 41 enrolled patients (22%) had HER2-positive tumors, and 32 of 41 patients (78%) had HER2-negative tumors, with a median age of 55 years (range 35 - 70 years) and 53 years (range 37 - 62 years), respectively. Hormone re-

### Table 1. Patients Characteristics

| Characteristics                          | Nab-PTX (n = 32) | Nab-PTX + trastuzumab (n = 9) |
|------------------------------------------|------------------|-------------------------------|
| Median age (range)                       | 55 (35 - 70)     | 53 (37 - 62)                  |
| Performance status = 0                   | 32 (100)         | 9 (100)                       |
| Menopausal status                        |                  |                               |
| Pre-menopausal                           | 14 (43)          | 5 (56)                        |
| Post-menopausal                          | 18 (57)          | 4 (44)                        |
| Clinical tumor stage                     |                  |                               |
| T1                                       | 0                | 1 (10)                        |
| T2                                       | 28 (88)          | 5 (56)                        |
| T3                                       | 2 (6)            | 3 (34)                        |
| T4                                       | 2 (6)            | 0                             |
| Clinical nodal stage                     |                  |                               |
| N0                                       | 13 (40)          | 1 (10)                        |
| N1                                       | 11 (34)          | 4 (44)                        |
| N2                                       | 4 (13)           | 2 (23)                        |
| N3                                       | 4 (13)           | 2 (23)                        |
| Clinical stage                           |                  |                               |
| IIA                                      | 11 (34)          | 1 (10)                        |
| IIB                                      | 13 (40)          | 3 (34)                        |
| IIIA                                     | 3 (10)           | 3 (34)                        |
| IIIB                                     | 1 (3)            | 0                             |
| IIIC                                     | 4 (13)           | 2 (23)                        |
| Grade                                    |                  |                               |
| I                                        | 8 (25)           | 0                             |
| II                                       | 8 (25)           | 3 (34)                        |
| III                                      | 16 (50)          | 6 (66)                        |
| ER status                                |                  |                               |
| Positive                                 | 17 (53)          | 7 (77)                        |
| Negative                                 | 15 (47)          | 2 (23)                        |
| PgR status                               |                  |                               |
| Positive                                 | 13 (40)          | 6 (66)                        |
| Negative                                 | 19 (60)          | 3 (34)                        |
| Subtype                                  |                  |                               |
| Luminal A                                | 2 (6)            | 0                             |
| Luminal B                                | 14 (44)          | 0                             |
| Luminal HER2                              | 0                | 7 (77)                        |
| HER2                                     | 0                | 2 (23)                        |
| Triple-negative                           | 16 (50)          | 0                             |

Data presented as n (%). Nab-PTX: nab-paclitaxel; ER: estrogen receptor; PgR: progesterone receptor; HER2: human epidermal growth factor receptor 2.
respectively. For HER2-positive breast cancer, the pCR rate (0 of 2), 7% (1/14), 42% (3/7), 25% (4/16) and 100% (2/2), negative and HER2+ (positivity was 3+), the pCR rate was 0%.

In patients with luminal A, luminal B, luminal HER2+, triple-negative status. In the HER2-negative group, the major- way to have a triple-negative status. In the HER2-negative group, the majority of patients (24/32 patients, 75%) had stage II breast cancer.

Study completion

In total, 34 patients completed the protocol (83%); dose reductions were required in six patients (14%) during FEC treatment but in no patients during nab-PTX treatment. Relative dose intensity of nab-PTX was 100% and FEC was 75%. Overall, discontinuation was recorded for seven patients (17%) because of hepatic dysfunction (one patient), sensory peripheral neuropathy (two patients) and progression of breast cancer during nab-PTX treatment (three patients). One patient died of sepsis secondary to pneumonia during the first time FEC treatment. She was healthy and had no medical history. Though FEC was administered after four cycles of nab-PTX, the day 8 after one cycle of FEC treatment, there was no hematologic or non-hematologic adverse events. The day 15, she died of sepsis secondary to pneumonia during the first time FEC treatment. She was healthy and had no medical history.

Adverse events

The most significant toxicities associated with nab-PTX were grade 2/3 peripheral sensory neuropathy (24%), grade 2 joint pain (17%) and grade 3/4 neutropenia (26%; Table 3). Febrile neutropenia was not observed in any patient. The most significant toxicities associated with FEC were grade 2/3 nausea (31%), grade 2/3 anorexia (31%), grade 3/4 neutropenia (24%) and grade 3 febrile neutropenia (9%). A 70-year-old woman died of sepsis secondary to pneumonia during the first time FEC treatment. She was healthy and had no medical history. Though FEC was administered after four cycles of nab-PTX, the day 8 after one cycle of FEC treatment, there was no hematologic or non-hematologic adverse events. The day 15, she was found at home in cardiopulmonary arrest. The family did not want pathological dissection.

Increased survival has been reported in patients who underwent neoadjuvant chemotherapy for breast cancer and achieved pCR [14, 15]. Accordingly, the pCR rate is considered a useful prognostic factor. In the GeparSepto trial, a randomized phase III trial comparing nab-PTX with solvent-based PTX as neoadjuvant chemotherapy, the overall pCR rate was significantly higher for nab-PTX (42.7%; 95% confidence interval (CI), 38.8 - 46.7 vs. 34.5%; 95% CI, 30.7 - 38.3) [10]. In contrast, the ETNA trial, a randomized phase III trial studying HER2-negative breast cancer, was unable to demonstrate an improved pCR rate with nab-PTX compared with solvent-based PTX (22.5% vs. 18.6%) [16]. A systematic review and meta-analysis of nab-PTX as neoadjuvant chemotherapy reported an overall pCR rate of 32% (95% CI: 25-38%), with pCR rates for hormone receptor-positive, triple-negative and HER2-positive breast cancer of 14% (95% CI: 11-17%), 41% (95% CI: 38-45%) and 54% (95% CI: 43-66%), respectively [17]. In the present study, the overall pCR rate was 24%, which is similar or lower than rates reported in previous trials. Particularly, the pCR rate for HER2-positive breast cancer was very high (55%). Several neoadjuvant studies have reported the pCR rate of nab-PTX with trastuzumab for HER2-positive breast cancer to be 48-62% [10, 11, 13]. Generally, higher pCR rates are observed in patients with ER-negative breast cancers, although the underlying causes are unclear. Accordingly, higher pCR rates in triple-negative breast cancers have also been observed; however, this finding was not replicated in our study (pCR = 25% for triple-negative breast cancer). The relatively small sample size of the present study may have contributed to the lower pCR rate observed for triple-negative breast cancer.

Our findings demonstrate reasonable tolerability profiles, which are comparable to those reported previously. A total of 83% patients completed the protocol, with dose reduction re-

**Table 2. Response**

| Clinical response | N (%) |
|-------------------|-------|
| Overall RR        | 37/41 (90) |
| cCR               | 4/41 (9) |
| cPR               | 33/41 (81) |
| HER2-positive     | 9/9 (100) |
| cCR               | 2/9 (22) |
| cPR               | 7/9 (78) |

| Pathological response | N (%) |
|-----------------------|-------|
| Overall pCR rate      | 10/41 (24) |
| Luminal A             | 0/2 (0) |
| Luminal B             | 1/14 (7) |
| Luminal HER2          | 3/7 (42) |
| Triple-negative       | 4/16 (25) |
| HER2                  | 2/2 (100) |

RR: response rate; cCR: clinical complete response; cPR: clinical partial response; pCR: pathological complete response; HER2: human epidermal growth factor receptor 2.
quired in only 14% of patients during FEC treatment but in no patients during nab-PTX treatment. In the nab-PTX group, the majority of hematologic adverse events were neutropenia, with no cases of febrile neutropenia observed. The most significant non-hematological adverse event was peripheral sensory neuropathy, which resulted in two patients discontinuing the trial. In the present trial, the nab-PTX dose was three-weekly 260 mg/m² for four cycles. Although no previous trials have compared weekly and three-weekly nab-PTX treatment outcomes, a phase III trial comparing three-weekly nab-PTX with three-weekly solvent-based paclitaxel for metastatic breast cancer treatment demonstrated superior RR and progression-free survival (PFS) for three-weekly nab-PTX [8]. A study reported that weekly administration of solvent-based PTX for neoadjuvant chemotherapy may be more effective and tolerable than administration every 3 weeks [18]. Therefore, weekly nab-PTX may be superior to three-weekly nab-PTX. Some phase III trials (GeparSepto, ETNA) of neoadjuvant chemotherapy evaluated weekly nab-PTX; however, peripheral sensory neuropathy was more frequent in patients receiving nab-PTX compared with those receiving solvent-based PTX (53% and 62%, respectively, in the ETNA trial; and 66% and 86%, respectively, in the GeparSepto trial). Further, grade 3 or higher was observed in 1% and 4% of patients receiving PTX and nab-PTX, respectively, in the ETNA trial and 3% and 11% of patients, respectively, in the GeparSepto trial. Thus, peripheral sensory neuropathy appears to be a significant adverse event associated with the use of nab-PTX, which may impact on patient quality of life. The administration of nab-PTX for neoadjuvant chemotherapy may be tolerable because of the limited number of cycles required and the sensitivity for chemotherapy because of no treatment history of chemotherapy.

The present study has two limitations. First, it was a single-arm phase II trial with a relatively small sample size; therefore, a randomized controlled trial with a larger sample size is necessary to confirm our findings. Second, the study duration was relatively short, leading to unclear outcomes. Long-term follow-up is required to evaluate patient prognosis.

**Conclusions**

The present study is a prospective single-arm, phase II clinical trial. Though the primary endpoint was pCR for all subtypes, overall pCR rate was 24% and it did not meet (expected value is 40%). But neoadjuvant chemotherapy using nab-PTX with trastuzumab every three weeks followed by FEC was suitably tolerated and associated with a high pCR rate of 55% for patients with HER2-positive breast cancer. We think it may be a good option of neoadjuvant chemotherapy for HER2-positive breast cancer.

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冲突利益

作者没有利益冲突需要声明。

知情同意

我们从所有参与本研究的患者那里获得了书面知情同意。该研究方案由我们机构的人类研究委员会批准。我们参与了这项研究。研究方案由我们的研究机构的伦理委员会批准。

作者贡献

Takanori Kin: 设计和研究，数据分析和解释。Shoichiro Ohnami: 设计和研究，数据分析和解释，数据收集。Reina Maeda: 数据分析和解释。Miwa Fujihara: 数据分析和解释。Yuri Takamatsu: 数据分析和解释，数据收集和解释。Keisuke Abe: 设计和研究，数据分析和解释。Yasuhiko Sakata: 设计和研究，数据分析和解释。Takanori Kin: 设计和研究，数据分析和解释。Yasuhiko Sakata: 设计和研究，数据分析和解释。Yukiko Kajiwara: 数据分析。Mitsuya Ito: 数据分析和解释。Yuki Takamatsu: 数据分析。Reina Maeda: 数据分析和解释。Mitsuya Ito: 数据分析和解释。Keisuke Abe: 设计和研究，数据分析和解释。Yasuhiko Sakata: 设计和研究，数据分析和解释。Keisuke Abe: 设计和研究，数据分析和解释。

数据可用性

任何关于支持数据可用性的查询都应直接联系相应的作者。

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