**Original Article**

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# QOL Evaluation of Nab-Paclitaxel and Docetaxel for Early Breast Cancer

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**ABSTRACT**

**Objective:** A previous randomized phase II study showed that neoadjuvant nab-paclitaxel (nab-PTX) 100 mg/m$^2$) was effective and well-tolerated in patients with HER2-negative early-stage breast cancer, compared with docetaxel (DTX). We evaluated patient outcomes in terms of the Functional Assessment of Cancer Therapy-Breast (FACT-B), as a measure of health-related quality of life (HRQoL).

**Materials and Methods:** Stage I–III HER2-negative breast cancer patients from the previous study were included. They received either four cycles of nab-PTX (100 mg/m$^2$ days 1/8/15) every 4 weeks, or DTX (75 mg/m$^2$ day 1) every 3 weeks, both followed by four cycles of 5-fluorouracil/epirubicin/cyclophosphamide (FEC). Patients completed a health-related quality-of-life questionnaire at baseline, after one and four cycles of taxanes, before administration of FEC, and after administration of one and four cycles of FEC.

**Results:** Thirty-six eligible patients were enrolled. The baseline characteristics of the two groups were well balanced. FACT-B scores at baseline and after four cycles of taxanes were 115/108 (DTX/nab-PTX) and 99/92, respectively. There were no significant differences between DTX and nab-PTX for FACT-B, FACT-B-Trial Outcome Index (FACT-B-TOI) and FACT-General. FACT-B and FACT-B TOI scores tended to decrease after one cycle and after four cycles of chemotherapy which did not recover to the baseline scores through the end of chemotherapy in each group.

**Conclusion:** There were no significant safety differences between nab-PTX and DTX. HRQoL tended to decrease during taxane-based anticancer treatment, with no significant differences between the treatments. We suggest that the HRQoL questionnaire has limited ability to evaluate different chemotherapy schedules. Trial registration UMIN000009855. Nov 20, 2012 registered.

**Keywords:** Breast cancer therapy, side effect, quality of life, patient support system

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## Introduction

Remarkable progression in cancer chemotherapy has led to direct benefits for cancer patients. Numerous drugs and regimens have been studied in relation to breast cancer, including taxanes, which are key breast cancer chemotherapy agents, with confirmed antitumor and recurrence-inhibitory effects (1). However, taxanes are also commonly associated with side effects. The taxane docetaxel (DTX) can cause oedema, nausea, vomiting, and gastrointestinal symptoms, while paclitaxel (PTX) is associated with peripheral neuropathy, arthralgia, and myalgia. These adverse effects can significantly reduce a patient's quality of life (QoL). Furthermore, repeated adverse events may also force patients to stop their treatment, thus highlighting a major problem in the delivery of cancer chemotherapy. Moreover, previous studies suggested that the relative dose intensity of chemotherapy was related to the overall and relapse-free survival in patients with breast cancer (2).

Patients receiving cancer chemotherapy are monitored closely, not only in terms of the therapeutic effects, but also in terms of their QoL. Several studies have reported on the relationship between QoL and the evaluation of chemotherapy using the Common Terminology Criteria for Adverse Events (CTCAE). However, these studies showed that the evaluation of side effects reported by the medical staff did not necessarily coincide with those reported by the patients (3). For example, taxane-related peripheral neuropathy was reported differently by breast cancer patients and medical staff in the N-SAS BC 02 trial (4). Furthermore, in terms of palliative care, it has been suggested that medical staff might not be aware of serious concerns of patients with cognitive and psychological issues, and may also be unaware of the serious physical and social debilitating effects of chemotherapy. It is therefore critical to understand and evaluate the QoL in cancer patients.



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Nanoparticle albumin-bound PTX (nab-PTX) is a new, solvent-free, 130-nm albumin-bound PTX, developed to avoid the Cremophor vehicle used in solvent-based PTX. Nab-PTX can be suspended in physiological saline solution, making it possible to administer higher PTX doses than that in conventional solvents. Nab-PTX 100 mg/m$^2$ demonstrated superior activity to DTX in patients with metastatic breast cancer in a randomized phase II trial (CA024). The frequency of grade 3 adverse effects, such as significant fatigue and febrile neutropenia, were also lower in the nab-PTX-treated cohort, though there was no difference in the frequency of peripheral neuropathy (5). Nab-PTX is therefore expected to be effective for neoadjuvant chemotherapy, with a reduced adverse event profile. We conducted a randomized phase II trial to compare DTX with nab-PTX 100 mg/m$^2$ followed by 5-fluorouracil/epirubicin/cyclophosphamide (FEC) as neoadjuvant chemotherapy in breast cancer patients. The most common grade 3–4 adverse event was neutropenia. Peripheral sensory neuropathy was observed in any grade though no grade 3–4 peripheral sensory neuropathy was observed in either arm (6).

In the current study, we further investigated the relationship between health-related QoL (HRQoL) and adverse events as an add-on to the previous randomized phase II trial.

## Materials and Methods

### Study Design

This study was conducted to evaluate adverse events and HRQoL, as an add-on to a multicentre phase II trial of neoadjuvant nab-PTX compared with DTX in patients with early-stage breast cancer. Thirty-six patients were enrolled at six centres from March 2012 to March 2014. This study was approved by the Showa University of Ethics Committee in March 2012.

### Patients

Patients with stage I–III human epidermal growth factor 2 (HER2)-negative early-stage breast cancer were included in this multicentre, randomized phase II trial. Eligible patients were ≥20 years old, with Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1, histologically confirmed invasive breast cancer with clinical stage T1c-3, N0/M0 or T1-3, N1/M0, and had received no treatment for their current breast cancer. All tumours were locally tested for oestrogen receptor, progesterone receptor, and HER2 status. All patients provided written informed consent before enrolment in this study.

### Treatment

All patients received treatment as outlined in Figure 1.

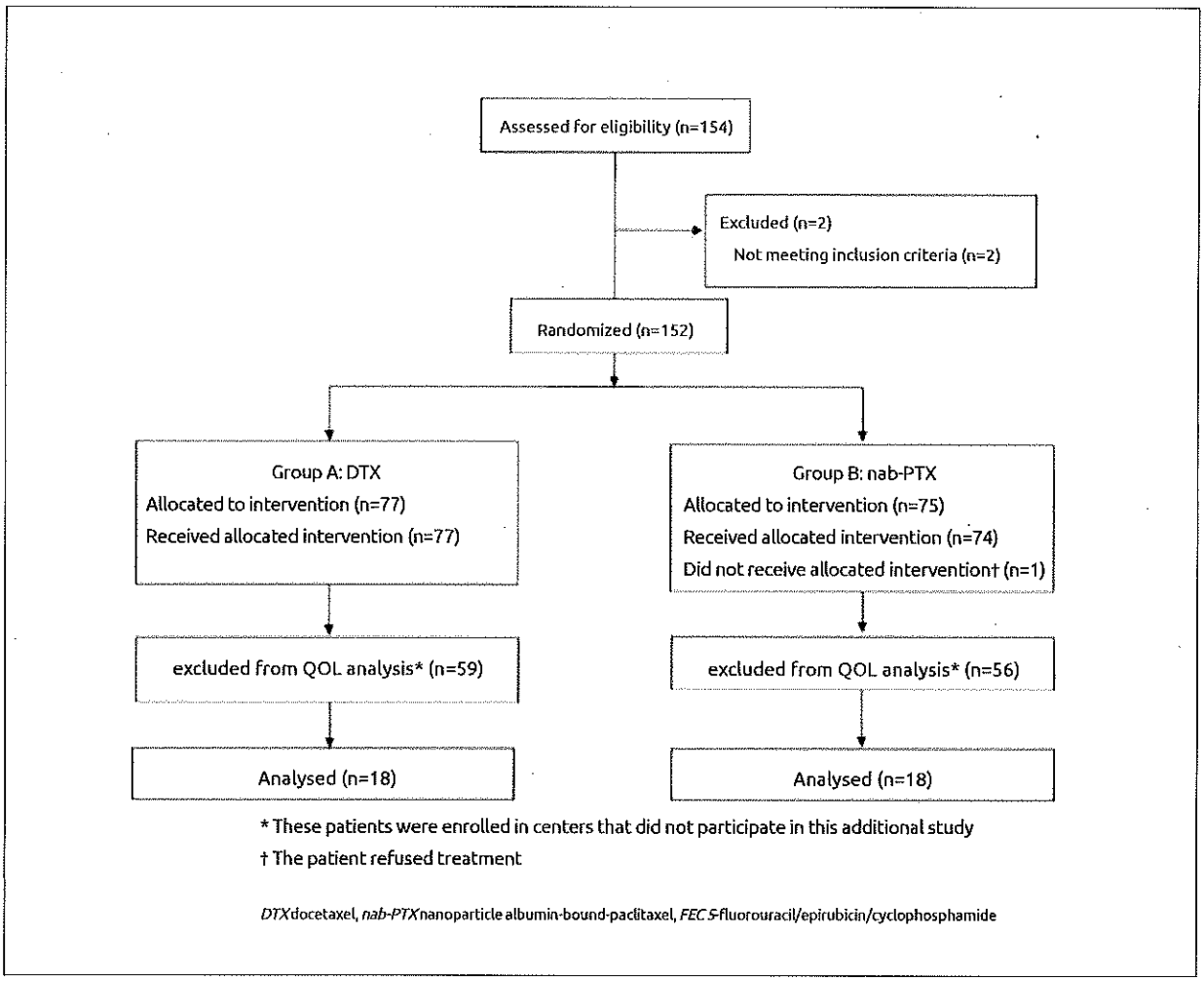


**Figure 1.** Consort diagram in this study

Table 1. Patient characteristics (n=36)

| Characteristic | Group A:DTX (n=18) Number of Patients (%) | Group B:nab-PTX (n=18) Number of Patients (%) | p |
|---|---|---|---|
| Median Age (Range) | 49 (41–67) | 51 (39–63) | 0.800 |
| ECOG PS 0 | 18 (100) | 18 (100) | 1.000 |
| T2/3 | 16 (89) | 16 (89) | 1.000 |
| N (+) | 6 (33) | 8 (44) | 0.494 |
| ER (+) | 14 (78) | 14 (78) | 1.000 |
| PgR (+) | 12 (78) | 9 (50) | 0.310 |
| TNBC | 4 (22) | 4 (22) | 1.000 |
| Ki67 ≥20% | 7 (39) | 12 (67) | 0.095 |

ECOG PS: ECOG Performance Status; ER:estrogen receptor; PgR: progesterone receptor; TNBC: triple-negative breast cancer

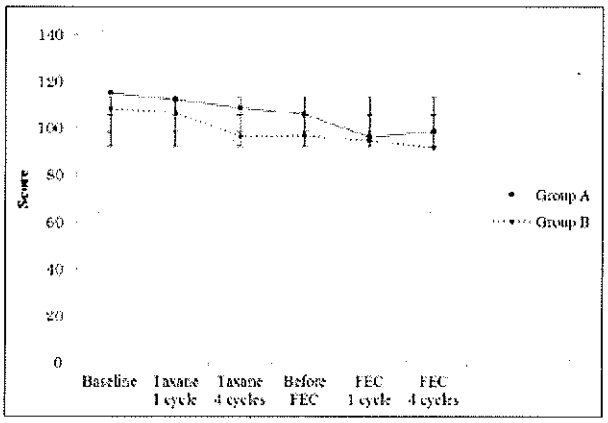


**Figure 2.** FACT-B

Patients received either four cycles of DTX (75 mg/m² on day 1; group A) (Taxotere®: Sanofi K.K.) every 3 weeks, or four cycles of nab-PTX (100 mg/m² on days 1, 8, and 15; group B) (Abraxane®: TAIHO Pharmaceutical Co., Ltd) every 4 weeks, followed by four cycles of FE100C (5-fluorouracil 500 mg/m², epirubicin 100 mg/m², cyclophosphamide 500 mg/m² every 3 weeks) (Fluorouracil®:Kyowa Hakko Kirin Co. Ltd. Farmorubicin®: Pfizer Japan Inc. Endoxan®: SHIONOGI & Co. Ltd.) in both groups.

### End Points and Statistical Analysis

The primary endpoint was the occurrence of grade 3 or 4 adverse events, and the secondary endpoints were QoL and adverse events of all grades. Toxicity was evaluated in all patients who received at least one dose of study therapy and was graded according to the National Cancer Institute CTCAE version 4.0. QoL was evaluated using the Functional Assessment of Cancer Therapy-Breast (FACT-B), FACT-B-Trial Outcome Index (FACT-B-TOI), and FACT-General (FACT-G). QoL was assessed at six timepoints: at baseline, after administration of one and four cycles of taxanes, before administration of FE100C, and after one and four cycles of FE100C. FACT-B is a 36-item HRQoL questionnaire comprising the FACT-G generic cancer instrument and FACT-B-TOI. FACT-G evaluates HRQoL across four domains: physical well-being, social/family well-being, emotional well-being, and functional well-being. FACT-B-TOI evaluates HRQoL across three domains: physical well-being, functional well-being, and breast cancer subscale. Respondents rate each item on a four-point scale from 0 ('not at all') to 4 ('very much'), with higher scores representing better HRQoL scores.

The HRQoL analysis included 36 of 152 patients who were randomly assigned to receive neoadjuvant chemotherapy and who filled out the HRQoL form. We analysed the intent-to-treat population.

All statistical analyses were performed using JMP® version 9.0.3 (SAS Institute, Cary, NC, USA).

## Results

### Patient Characteristics

Thirty-six eligible patients were enrolled in this study between March 2012 and March 2014 (Table 1). The baseline characteristics were well balanced between the two groups.

### Toxicity

Toxicity data are shown in Table 2. The most common grade 3–4 adverse event was neutropenia, which occurred in 44% and 33% of patients in the DTX and nab-PTX groups, respectively. There were no significant differences in haematological adverse events between the groups. Grade 1–2 non-haematological adverse events included myalgia (DTX 44%, nab-PTX 39%), arthralgia (DTX 33%, nab-PTX 33%), and peripheral sensory neuropathy (DTX 56%, nab-PTX 83%). No grade 3–4 myalgia, arthralgia, or peripheral sensory neuropathy was observed in either group.

### QoL

The time courses of the mean QoL scores assessed using FACT-B, FACT-B TOI, and FACT-G are shown in Figure 2-4. The FACT-B scores at baseline in the DTX and nab-PTX groups were 115 and 108, respectively, and these decreased to 109 and 97 after four cycles of taxanes, and 99 and 92 after four cycles of FE100C, respectively. The FACT-B-TOI scores at baseline in the DTX and nab-PTX groups were 76 and 72, respectively, and these decreased to 66 and 61 after four cycles of taxanes and to 60 and 55 after four cycles of FE100C, respectively. The equivalent FACT-G scores were 86 and 80 at baseline, 85 and 73 after four cycles of taxanes, and 77 and 71 after four cycles of FE100C. The baseline scores in the DTX group were slightly higher than those in the nab-PTX in each evaluation. However, the changes of HRQoL were similar in both groups, with no significant differences.

Table 2. Most common treatment-related adverse events

| Adverse Event | Group A:DTX (n=18) All grade/Grade 3 or 4; n (%) | Group B:nab-PTX (n=18) All grade/Grade 3 or 4; n (%) | P |
|---|---|---|---|
| Neutropenia | 12 (67)/8 (44) | 16 (89)/6 (33) | 0.109 [a]/0.494 [a] |
| Leucopenia | 13 (72)/3 (17) | 13 (72)/4 (22) | 1.000 [a]/0.674 [a] |
| Peripheral sensory neuropathy | 10 (56)/0 (0) | 15 (83)/0 (0) | 0.070 [a]/- |
| Myalgia | 8 (44)/0 (0) | 7 (39)/0 (0) | 0.735 [a]/- |
| Arthralgia | 6 (33)/0 (0) | 6 (33)/0 (0) | 1.000 [a]/- |
| Fatigue | 53 (69)/0 (0) | 47 (64)/0 (0) | 1.000 [a]/- |
| Alopecia | 16 (89)/- | 14 (82)/- | 0.371 [a]/- |
| Diarrhea | 4 (22)/0 (0) | 3(18)/0 (0) | 0.674 [a]/- |
| Vomiting | 1 (5)/0 (0) | 1 (6)/0 (0) | 1.000 [a]/- |
| Nausea | 8 (44)/0 (0) | 11 (65)/0 (0) | 0.317 [a]/- |
| Anorexia | 6 (33)/0 (0) | 5 (29)/0 (0) | 0.717 [a]/- |
| Stomatitis | 7 (39)/0 (0) | 5 (29)/0 (0) | 0.480 [a]/- |
| Pigmentation | 3 (17)/0 (0) | 7 (41)/0 (0) | 0.137 [a]/- |

[a] $\chi^2$ test

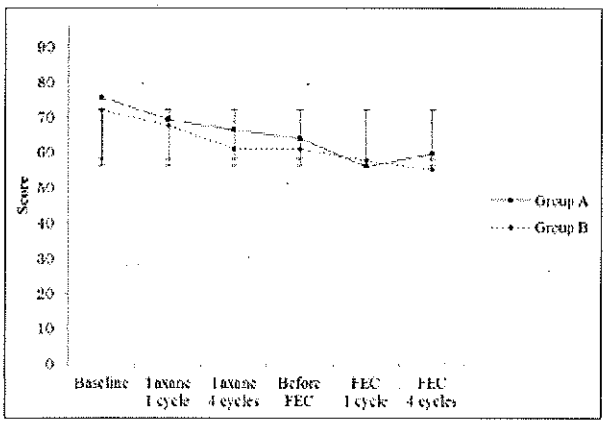


**Figure 3.** FACT-B TOI

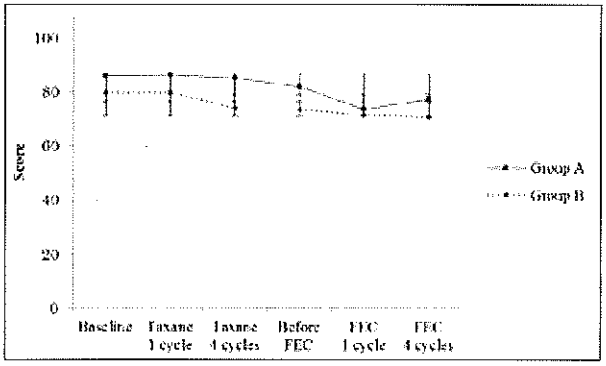


**Figure 4.** FACT-G

The FACT-B and FACT-B TOI scores tended to decrease after one cycle and after four cycles of chemotherapy which did not recover to the baseline scores through the end of chemotherapy in each group.

## Discussion and Conclusion

The present study demonstrated that the frequencies and severity of taxane-related adverse events, such as febrile neutropenia, myalgia, arthralgia, alopecia, and fatigue, were similar in breast cancer patients taking DTX or nab-PTX. Furthermore, HRQoL tended to decrease during treatment with either taxane. Better management of taxane-related adverse events is therefore required.

Patient-reported outcomes (PROs), in which patients evaluate the therapeutic effects of treatments without the aid of a doctor, have recently been considered as an important new drug-evaluation criterion in clinical trials (7). However, despite the use of PRO evaluation criteria, the criteria used in clinical trials are not necessarily consistent with those used during normal medical practice. Furthermore, there are many different methods for evaluating QoL, and no suitable evaluation methods have currently been established for inclusion in clinical trials. The QoL evaluation FACT-B was used in the present study and is frequently used for breast cancer patients in Japan. However, FACT-B has some restrictions, including the fact that the questionnaires ask about "very recent symptoms (about the last 7 days)", and it may therefore not be able to collect information on side effects occurring immediately after chemotherapy administration (7, 8).

In this study, we administered nab-PTX once a week and DTX every 3 weeks, and the effects of DTX on QoL immediately after administration were therefore not evaluated. Developing a more reliable, valid, and high-quality QoL evaluation method is therefore considered to be a future challenge. In addition, the present study only enrolled 36 patients, and further studies with more patients will be needed to validate these results. Various 'patient-support systems' have been developed in some countries to monitor patient side effects and conditions, and a self-recording system for PROs using a tablet computer is currently being developed (8). The STAR and Moovcare systems have also been reported to prevent severe adverse events and improve patient QoL (9, 10).

We previously and independently developed a patient-support system (11) and used it in eight cases registered in the current study, allowing medical staff to confirm data on outpatient-recorded side effects quantitatively. This demonstrated that this system could be used effectively to monitor patient QoL. We therefore suggest that it is necessary to consider introducing a patient-support system to allow accurate QoL assessments to be made.

The STAR and Moovcare systems were recently reported to contribute to improved overall survival (9). Patient-support systems are therefore expected to be introduced in the future to reduce the burden of patient medical expenses, and improve patient QoL and prognosis.

In conclusion, there was no significant difference in safety profiles between DTX and nab-PTX in patients with early-stage breast cancer, and HRQoL tended to decrease similarly during anticancer treatment with either taxane. We suggest that the ability of the HRQoL questionnaire to evaluate different schedules of chemotherapy is limited, and further studies are needed to establish better evaluation methods in the future.

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**Ethics Committee Approval:** Ethics committee approval was received for this study from the ethics committee of Showa University.

**Informed Consent:** Written informed consent was obtained from patients who participated in this study.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept - H.O., S.N., T.K.; Design - H.O., S.N., T.K.; Supervision - S.N.; Resources - H.O.; Materials - H.O., S.N., S.A.T., T.S., T.K., S.H., Y.K.; Data Collection and/or Processing - H.O., S.N., S.A.T., T.S., T.K., S.H., Y.K.; Analysis and/or Interpretation – H.O.; Literature Search - H.O.; Writing Manuscript – H.O.; Critical Review - H.O., S.N., S.A.T., T.S., T.K., S.H., Y.K.

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**Conflict of Interest:** The authors have no conflicts of interest to declare.

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