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Comparison of EQ-5D Scores among Anthracycline-Containing Regimens followed by Taxane and Taxane-Only Regimens for Node-Positive Breast Cancer Patients after Surgery: The N-SAS BC 02 Trial

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ABSTRACT

Objective: To examine health-related quality of life, we investigated the effect of adjuvant chemotherapy regimens on utility scores assessed by the EuroQoL-5D (EQ-5D) instrument in a randomized, controlled trial for breast cancer patients after surgery. We also investigated the relationship between Functional Assessment of Cancer Therapy (FACT) scale scores and EQ-5D utilities. **Methods:** Patients were randomly assigned to the following four chemotherapy regimens: four cycles of anthracycline followed by paclitaxel (ACP), four cycles of anthracycline-containing regimens followed by docetaxel (ACD), eight cycles of paclitaxel (PTX), and eight cycles of docetaxel (DTX). Of 1060 registered, the first 300 consecutive patients were included in the current utility study. Utility scores were assessed using the EQ-5D instrument at baseline; cycles 3, 5, and 7; 7 months; and 1 year. We also evaluated the correlation between these scores and FACT-G, -B, and -Taxane scores at each time point. **Results:** Utility scores were significantly lower in the DTX group than in the ACP and ACD groups. Mean utility scores in the DTX group were lowest at 7 months and tended to remain low for a long time. The combined anthracycline followed by taxane group had significantly higher utility scores that the taxane-alone group, with no significant difference depending on the type of taxane. Only the FACT-G social/family well-being subscale had no relationship with EQ-5D responses and utility scores. **Conclusions:** Although the regimens in this study were similar in that they included taxane, the mean utility scores and longitudinal patterns of utility scores were different among regimens.

Keywords: anthracycline, breast cancer, EuroQoL-5D, functional assessment of cancer therapy, health-related quality of life, taxane, utility.

Introduction

In Japan, the number of patient deaths due to breast cancer is increasing, whereas breast cancer mortality has generally decreased since the 1990s in Europe and the United States [1]. In 2007, the death toll from breast cancer in Japan was estimated at 12,000 persons per year, and the age-adjusted mortality was 11.9 per 100,000 persons, making breast cancer second to colorectal cancer as leading causes of death due to malignant neoplasms in women [2]. Decreasing deaths due to breast cancer is one of the most important women's public health issues.

For increasing numbers of women with breast cancer, adjuvant combination chemotherapies are being used to prevent microscopic metastasis. Many kinds of chemotherapy regimens have been developed in the past two or three decades. Anthracycline-based regimens (doxorubicin or epirubicin) have proved to be superior to CMF (cyclophosphamide, methotrexate, and fluorouracil) [1] and are primarily used as adjuvants to standard chemotherapy in breast cancer patients. Taxane (paclitaxel or docetaxel) [3,4], one of the most widely used anticancer drugs, is also being used in adjuvant breast cancer patients. Meta-analysis of 13 studies (N = 22,903) shows that taxanes, in combination or in sequence with anthracycline (AC)-based regimens, significantly improve disease-free survival (DFS) and overall survival of early breast cancer patients [5]. The pooled hazard ratios estimated by the meta-analysis were 0.83 (95% confidence interval [CI] 0.79–0.87) for DFS and 0.85 (95% CI 0.79–0.91) for overall survival . The efficacy, however, of taxane alone regimens without AC or cyclophosphamide is not known.

The National Surgical Adjuvant Study of Breast Cancer-02 (N-SAS BC 02) was conducted to compare two general protocols for treating node-positive breast cancer patients: 1) four cycles of AC-containing regimens followed by four cycles of taxane and 2) eight cycles of taxane. Because AC regimens have a risk of causing life-threatening cardiotoxicity [6], they are contraindicated in patients with abnormal cardiac function. If taxane regimens are not inferior to AC-based regimens, the use of taxane alone as an alternative chemotherapy might be increased.

Nevertheless, it is possible that administration of taxane will cause serious adverse events, such as peripheral neuropathy. It is

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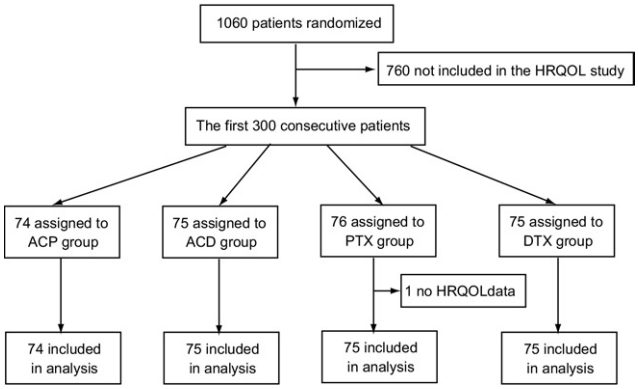

Fig. 1 – Study design and allocation of patients into treatment groups.

well-known that taxane-induced peripheral neuropathy occurs in proportion to the dose level and cumulative dose. Even if eight-cycle taxane regimens have a nearly identical efficacy as AC-based regimens, such adverse events may decrease health-related quality of life (HRQOL) or expected quality-adjusted life years (QALYs) [7]. To examine the HRQOL, we included measurement by the Functional Assessment of Cancer Therapy (FACT) scale [8,9] and EuroQoL-5D (EQ-5D) [10,11] as secondary end points in N-SAS BC 02 trial. EQ-5D scores are also intended for use in the economic evaluation of eight-cycle taxane regimens. In this article, we report on utility scores of early breast cancer patients measured by EQ-5D and the relationship between EQ-5D and FACT scale scores.

In addition, there are few reliable data on utility scores of breast cancer patients in Japan. Unfortunately, it is rare for longitudinal HRQOL or utility scores to be collected in Japanese prospective clinical trials. We planned to prospectively evaluate utility scores during treatment as well as 1 year post-treatment in breast cancer patients receiving four different types of taxane-containing adjuvant chemotherapy.

Methods

Patients

The N-SAS BC 02 trial included the following eligibility criteria: age 18 to 70 years, node-positive disease, no metastasis (stages I-IIIA), no previous hormone or chemotherapy, and an Eastern Cooperative Oncology Group performance status of 0–1 [12]. Patients who were both estrogen receptor and progesterone receptor positive were excluded. The study protocol of N-SAS BC 02, however, was amended to permit the enrollment of both hormone-positive patients from June 2003. Written informed consent was required from all patients before study enrollment, and the study was approved by the institutional review boards of the participating centers.

Study design and treatment protocols

Based on the 2 × 2 factorial design, the 1060 eligible patients were randomly assigned to receive one of the following four regimens: a) four cycles of AC-containing regimens (doxorubicin 60 mg/m^2 or epirubicin 75 mg/m^2 + cyclophosphamide 600 mg/m^2 every 3 weeks × 4) followed by paclitaxel (175 mg/m^2 every 3 weeks × 4) (ACP group), b) four cycles of AC followed by docetaxel (75 mg/m^2 every 3 weeks × 4) (ACD group), c) eight cycles of paclitaxel (175 mg/m^2 every 3 weeks × 8) (PTX group) , and d) eight cycles of docetaxel (75 mg/m^2 every 3 weeks × 8) (DTX group).

Table 1 – Baseline characteristics of patients shown as number (percentage of group).

Characteristic	ACP (n = 74)	ACD (n = 75)	PTX (n = 75)	DTX (n = 75)	Total (N = 299)
Age in years					
<40	4 (5.4)	8 (10.7)	13 (17.3)	10 (13.3)	35 (11.7)
40 to <50	16 (21.6)	14 (18.7)	15 (20.0)	25 (33.3)	70 (23.4)
50 to <60	41 (55.4)	38 (50.7)	32 (42.7)	28 (37.3)	139 (46.5)
>60	13 (17.6)	15 (20.0)	15 (20.0)	12 (16.0)	55 (18.4)
Age in years, median	54	53	53	51	53
Performance status					
0	64 (86.5)	63 (84.0)	65 (86.7)	62 (82.7)	254 (84.9)
1	5 (6.8)	9 (12.0)	8 (10.7)	7 (9.3)	29 (9.7)
Unknown	5 (6.8)	3 (4.0)	2 (2.7)	6 (8.0)	16 (5.4)
Tumor size, cm					
<3	41 (55.4)	42 (56.0)	43 (57.3)	43 (57.3)	169 (56.5)
≥3	33 (44.6)	33 (44.0)	32 (42.7)	32 (42.7)	130 (43.5)
No. of positive lymph nodes					
1–3	41 (55.4)	41 (54.7)	41 (54.7)	41 (54.7)	164 (54.8)
4-9	18 (24.3)	20 (26.7)	21 (28.0)	21 (28.0)	80 (26.8)
>10	15 (20.3)	14 (18.7)	13 (17.3)	13 (17.3)	55 (18.4)
Surgery					
Conserving	31 (41.9)	30 (40.0)	32 (42.7)	31 (41.3)	124 (41.5)
Mastectomy	41 (55.4)	45 (60.0)	42 (56.0)	44 (58.7)	172 (57.5)
Other	2 (2.7)	0 (0.0)	1 (1.3)	0 (0.0)	3 (1.0)
Hormone receptor					
Positive	29 (39.2)	31 (41.3)	28 (37.3)	29 (38.7)	117 (39.1)
Negative	45 (60.8)	44 (58.7)	47 (62.7)	46 (61.3)	182 (60.9)
HER2 receptor					
Positive	17 (23.0)	20 (26.7)	19 (25.3)	18 (24.0)	74 (24.7)
Negative	36 (48.6)	31 (41.3)	33 (44.0)	31 (41.3)	131 (43.8)
Unknown	21 (28.4)	24 (32.0)	23 (30.7)	26 (34.7)	94 (31.4)