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Efficacy and feasibility of dose-dense neoadjuvant chemotherapy versus conventional neoadjuvant chemotherapy in patients with HER2-negative breast cancer: A single-center retrospective study

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Background: Dose-dense chemotherapy (DDCT) is a standard treatment for patients with high-risk breast cancer. Although there are numerous reports regarding DDCT, it is unclear whether sequential DDCT is effective or feasible as preoperative treatment for Japanese patients. We evaluated the efficacy and safety of neoadjuvant DDCT for patients with human epidermal growth factor receptor 2 (HER2)-negative breast cancer.
Methods: This retrospective study evaluated 39 patients with breast cancer, who were preoperatively treated with anthracycline-containing regimens and taxanes. According to the chemotherapy regimens patients were divided into the DDCT group (dd-group) and the conventional chemotherapy (CCT) group (q3w-group). The efficacy of neoadjuvant chemotherapy was evaluated based on the pathological complete response (pCR) rate. Adverse events were evaluated according to the Common Terminology Criteria for Adverse Events version 5.0.
Results: There were no apparent differences in tumor stage, histopathological subtype, or surgical procedure. There was not significant difference in the pCR rate (dd-group, 17.6%; q3w-group, 22.7%). Three-year disease-free survival rates were similar in two groups. The rates of dose reduction, delay of treatment, and discontinuation of treatment in the two groups did not differ to a statistically significant extent. There were no significant differences in the adverse events of the two groups.
Conclusion: The pCR rate for DDCT was similar to that of CCT. DDCT may be feasible for Japanese breast cancer patients.

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Key words: Dose-dense chemotherapy, Breast cancer, Neoadjuvant, Feasibility

Introduction

Dose-dense chemotherapy (DDCT) is a standard treatment for patients with high-risk breast cancer, as several randomized controlled studies have revealed that its survival benefit is superior to that of conventional chemotherapy (CCT) [1-3]. In recent years, the Gruppo Italiano Mammella 2 (GIM2) study found that DDCT using epirubicin plus cyclophosphamide (EC) followed by paclitaxel (PTX) was superior to standard treatment [3]. This treatment requires preventive granulocyte-colony stimulating factor as primary prophylaxis. In Japan, pegfilgrastim was approved for patients with breast cancer as primary prophylaxis based on the results of the registration trials in November 2014.

Although there are numerous reports regarding DDCT, it is unclear whether sequential DDCT is effective or feasible as a preoperative treatment for Japanese patients. Therefore, this study aimed to verify the efficacy and feasibility of neoadjuvant

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DDCT among Japanese patients with human epidermal growth factor receptor 2 (HER2)-negative breast cancer.

Patients and Methods

Between April 2014 and December 2021, 39 patients with HER2-negative breast cancer, who were preoperatively treated with anthracycline-containing regimens and taxanes, were retrospectively analyzed. This study was approved by the Institutional Review Boards of Nagasaki Harbor Medical Center (NIRB No. R02-019), and all patients provided their written informed consent.

According to chemotherapy regimens patients were divided into two groups. The DDCT group (dd-group) received four cycles of epirubicin (90 mg/m^2) and cyclophosphamide (600 mg/m^2) every two weeks, followed by four cycles of paclitaxel (PTX) (175 mg/m^2) every two weeks. The CCT group (q3w-group) received four cycles of fluorouracil (500 mg/m^2), epirubicin (100 mg/m^2) and cyclophosphamide (500 mg/m^2) every three weeks, or epirubicin (90 mg/m^2) and cyclophosphamide (600 mg/m^2) every three weeks, followed by four cycles of docetaxel (DTX) (75 mg/m^2) every three weeks. Patients in the dd-group had primary pegfilgrastim (3.6 mg) prophylaxis subcutaneously on days 2-3 of each cycle.

The efficacy of neoadjuvant chemotherapy was evaluated based on the pathological complete response (pCR) rate. We defined pCR as the absence of residual invasive cancer in surgical pathologic specimens (ypT0/ypTis and ypN0) after neoadjuvant chemotherapy. Adverse events were evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE version 5.0).

All statistical analyses in this study were performed using the EZR software package, version 1.55 (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [4]. The Mann–Whitney U test was used to compare the continuous data between the two groups. Fisher's exact test was used for the univariate analysis of ordered variables. *P values of* < 0.05 were considered statistically significant.

Results

The patient characteristics are shown in Table 1. There were seventeen breast cancer patients in dd-group between August 2018 and Jun 2021, and in twenty-two patients in q3w-group between January 2015 and November 2017. In q3w-group, seventeen (77.3%) patients of FEC followed by DTX and five (22.7%) patients of EC followed by DTX were enrolled. All of the patients were female, and the median age

Table 1. Patient Characteristics

Characteristics	dd-group (n=17) n (%)	q3w-group (n=22) n (%)	*p*-value
The date of starting chemotherapy	Aug. 2018 - Jun. 2021	Jan. 2015 - Nov. 2017	-
Chemotherapy regime			-
dd EC - dd PTX	17 (100)	-	
q3w FEC - q3w DTX	-	17 (77.3)	
q3w EC - q3w DTX	-	5 (22.7)	
Age - years			0.34
Median (range)	55 (39-69)	58.5 (31-70)	
Stage			1
IA, IB	1 (5.9)	2 (9.1)	
IIA, IIB	13 (76.5)	17 (77.3)	
IIIA, IIIB, IIIC	3 (17.6)	3 (13.6)	
Subtype			0.74
Luminal	12 (70.6)	14 (63.6)	
Triple-negative	5 (29.4)	8 (36.4)	
Surgery			0.34
Breast conserving surgery	7 (41.2)	13 (59.1)	
Mastectomy	10 (58.8)	9 (40.9)	
Axillary procedure			0.73
Sentinel lymph node biopsy	6 (35.3)	6 (27.3)	
Axillary lymph node dissection	11 (64.7)	16 (72.7)	

dd-group, dose-dense chemotherapy group; q3w-group, conventional chemotherapy group.

of the patients in the dd-group and q3w-group was 55 (39-69) years and 58.5 (31-70) years, respectively. There were no apparent differences in tumor stage, histopathological subtype, or surgical procedure.

The pCR rates are shown in Table 2. The pCR rate was 17.6% in the dd-group and 22.7% in the q3w-group. Furthermore, there was no apparent difference in the pCR rate between the histological subtypes. Three-year disease-free survival rates were 91.7% in dd-group and 90.9% in q3w-group (p=0.84) (Figure 1).

The rates of dose reduction, delay of treatment, and discontinuation of treatment in the two groups did not differ to a statistically significant extent (Table 3). Although no discontinuation occurred in the dd-group patients, it was required in 9.1% (2/22) of the q3w-group patients. The reasons for discontinuation were febrile neutropenia (grade 3 on day 12 of the 3rd cycle of DTX) and pneumonitis (grade 1 on day 8 of the 2nd cycle of DTX). Treatment delay occurred in 11.8% of the dd-group patients and 13.6% of the q3w-group patients. The reasons for delaying treatment in the dd-group were febrile neutropenia (grade 3 on day 10 of the 1st cycle of PTX) and hospital closure due to a COVID-19 cluster. The reason for the delay of treatment in the q3w-group was grade 3 neutropenia. Dose reduction was required in one patient (5.9%) of the dd-group due to grade 3 neutropenia, and in four patients (18.2%) of the q3w-group due to grade 3 fatigue (n=3), grade 3 neutropenia (n=1), and ischemic colitis (n=1). There was no treatment-related death.

The non-hematological adverse events are summarized in Figure 2. The non-hematological adverse events of the dd-group and q3w-group did not differ to a statistically significant extent. Most were grade 1 or 2 and were tolerable with supportive care. The hematological adverse events are shown in Figure 3. Furthermore, the hematological adverse

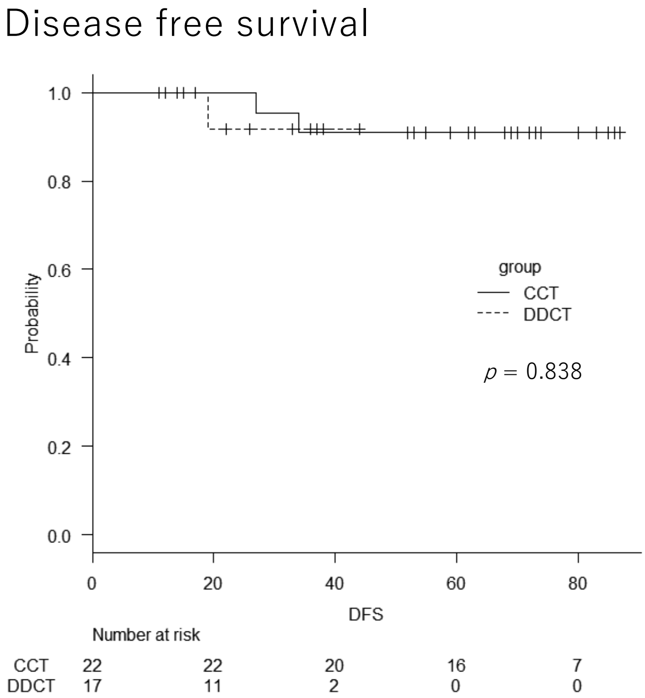

Figure 1. Disease-free survival analyses according to the treatment groups.

Table 2. Treatment Response

	dd-group (n=17) n (%)	q3w-group (n=22) n (%)	*p*-value
Total (n=39)			1
Non-pCR	14 (82.4)	17 (77.3)	
pCR	3 (17.6)	5 (22.7)	
Luminal (n=26)			0.58
Non-pCR	10 (83.3)	13 (92.9)	
pCR	2 (16.7)	1 (7.1)	
Triple-negative (n=13)			0.56
Non-pCR	4 (80)	4 (50)	
pCR	1 (20)	4 (50)	

dd-group, dose-dense chemotherapy group; q3w-group, conventional chemotherapy group.

Table 3. Treatment Completion

	dd-group (n=17) n (%)	q3w-group (n=22) n (%)	*p*-value
Discontinuation	-	2 (9.1)	0.50
Delay of treatment	2 (11.8)	3 (13.6)	1
Dose reduction	1 (5.9)	4 (18.2)	0.36

dd-group, dose-dense chemotherapy group; q3w-group, conventional chemotherapy group.

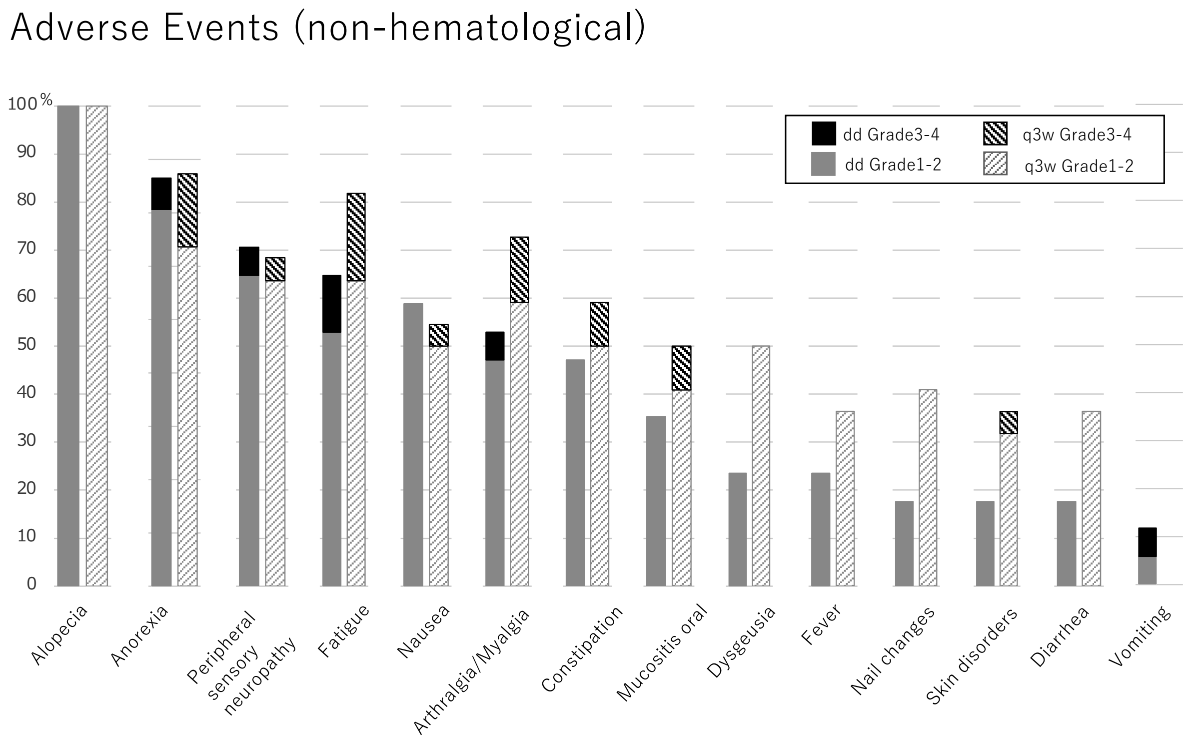

Figure 2. Non-hematological adverse events. There were no significant differences between the dd-group and q3w-group.

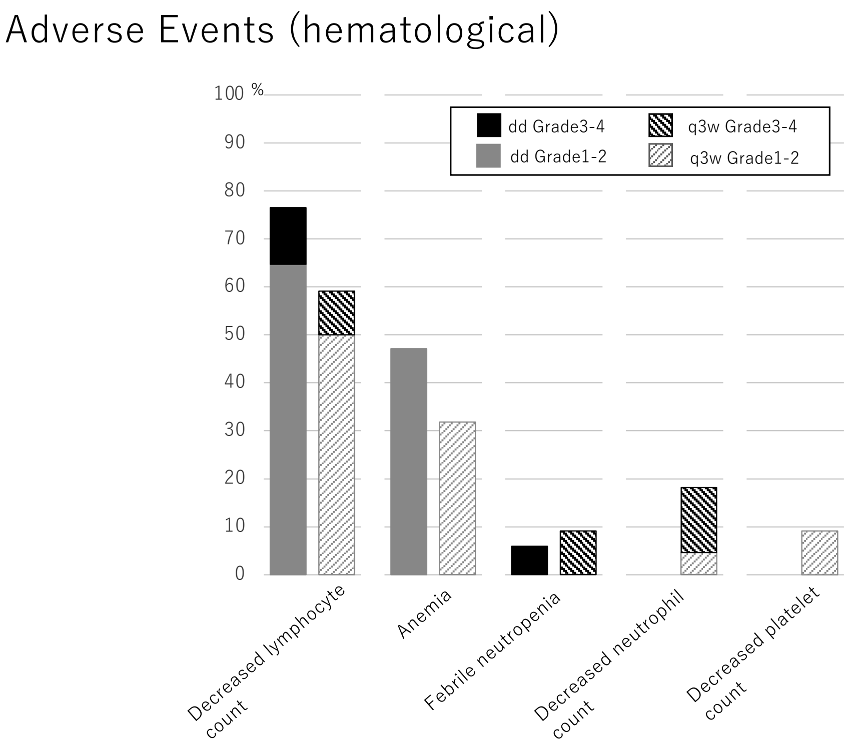

Figure 3. Hematological adverse events. There were no significant differences between the dd-group and q3w-group.

events of the two groups did not differ to a statistically significant extent. The most common hematological toxicity was lymphopenia in both groups.

Discussion

DDCT can shorten the interval between doses, therefore allowing tumor cells to be exposed to cytotoxic drugs more frequently. For breast cancer patients with a high tumor burden or locally advanced tumors that preclude surgical resection, DDCT can shorten the total treatment time and patients can undergo surgery after DDCT. Additionally, a higher pCR rate may result in more patients having the opportunity for breast tissue preservation and an improved quality of life.

This study investigated the efficacy and feasibility of neoadjuvant DDCT and for Japanese patients with breast cancer, and the results indicate that DDCT had similar efficacy to CCT. Furthermore, the rate of adverse effects and treatment completion were similar between DDCT and CCT.

A recent meta-analysis showed that patients receiving DDCT had a higher pCR rate in comparison to patients receiving standard chemotherapy [5]. Especially, patients with low hormone receptor expression levels or with TN breast cancer obtained a significantly higher pCR rate when they received DDCT [6-12]. However, DDCT did not provide a superior pCR rate relative to conventional treatment in the present study. There was also no apparent difference in the pCR rate between the histological subtypes in this study.

In the GIM2 study, the DDCT arm had a completion rate of 90% and an RDI of 98% [3]. In comparison, in Japan, CCT (fluorouracil, epirubicin, and cyclophosphamide → docetaxel) has a completion rate of 95–97% and approximately 11.3% of patients require dose reduction [6,7]. However, in the present study, only a few patients required dose reduction, which suggests that the feasibility of DDCT is not inferior to CCT. This is probably a consequence of the required use of granulocyte colony-stimulating factor in these groups, which decreases the incidence of leukopenia and febrile neutropenia [13]. Its use can also prevent dose reductions and delays but is associated with increased treatment costs [13, 14]. Other toxicities in this study were considered relatively minor and tolerable, although the DDCT was associated with higher rates of patients with a decreased lymphocyte counts and anemia in comparison to CCT.

The present study was associated with several limitations. First, it was a retrospective, single-institution study with a small sample size; thus, the generalizability of the findings is limited. Second, because of not randomized-controlled study, this was not directly compared neoadjuvant DDCT with neoadjuvant CCT. In the neoadjuvant setting, studies have used pCR as a surrogate endpoint, and the long-term results have been inconsistent [15]. Therefore, the comparison of efficacy was not conclusive.

In conclusion, the results of the present study suggest that DDCT was similar to the efficacy of CCT and generally feasible among patients with HER2-negative breast cancer.

Conflicts of Interest

The authors declare no conflicts of interest in association with the present study.

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