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Safety and Relative Dose Intensity of Dose-dense Doxorubicin and Cyclophosphamide Followed by Dose-dense Paclitaxel

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Abstract. *Background/Aim: Dose-dense doxorubicin and cyclophosphamide (ddAC) followed by dose-dense paclitaxel (ddP) (ddAC-P) has improved disease-free survival of patients with breast cancer. The aim of this study was to evaluate the safety and relative dose intensity (RDI) of ddAC-P administered together with pegfilgrastim. Patients and Methods: Between May 2015 and Aug 2017, 44 patients were retrospectively reviewed; they were administered 4 cycles of ddAC, followed by 4 cycles of ddP. Pegfilgrastim (3.6 mg) was administered in every cycle. Results: The mean RDIs for ddAC-P, ddAC, and ddP were 95.0%, 94.5%, and 93.3%, respectively. The prevalence of high RDIs (≥85%) for ddAC-P, ddAC, and ddP was 90.9%, 84.1%, and 88.6%, respectively. Seven of the 10 patients with low RDIs experienced grade 1 or 2 fever. Conclusion: DdAC-P administered together with pegfilgrastim (3.6 mg) appears to be feasible and maintains RDI in most of Japanese patients with breast cancer. Rapid evaluation and proper management of fever may prevent low RDI.*

Compared to conventional chemotherapy, dose-dense doxorubicin and cyclophosphamide (ddAC) followed by dose-dense paclitaxel (ddP) (ddAC-P) serves as a perioperative chemotherapy regimen that improves disease-free survival of patients with breast cancer (1). This treatment requires preventive granulocyte-colony stimulating factor (G-CSF) as the primary prophylaxis. G-CSF had no indication for patients with breast cancer as primary prophylaxis, and pegfilgrastim was not approved in Japan, until November 2014. At that time, pegfilgrastim was approved in Japan at a dose of 3.6 mg, according to data obtained from registration trials, included pharmacokinetics and dose-identification study in the country (2). The Pharmaceuticals and Medical Devices Agency indicated pegfilgrastim for patients with breast cancer as primary prophylaxis based on the results of the registration trials that evaluated docetaxel and cyclophosphamide or docetaxel, doxorubicin, and cyclophosphamide, but not ddAC-P (3, 4). This lack of safety data regarding the combined use of ddAC-P and pegfilgrastim at a dose of 3.6 mg has resulted in the inclusion of a cautionary sentence in the package inserts of pegfilgrastim in Japan.

To elucidate the feasibility of ddAC-P regimen in Japanese patients, a retrospective study was conducted to analyze the safety aspects and relative dose intensity (RDI) in patients with breast cancer receiving ddAC-P along with pegfilgrastim (3.6 mg). To the best of our knowledge, this is the first report on the feasibility of ddAC-P supported by pegfilgrastim at a dose of 3.6 mg in Japanese patients with breast cancer.

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Key Words: Dose-dense doxorubicin and cyclophosphamide, dose-dense paclitaxel, breast cancer, pegfilgrastim, perioperative chemotherapy.

Patients and Methods

Patients. Between May 2015 and Aug 2017, 44 patients with breast cancer who were administered 4 cycles of ddAC-P, doxorubicin (60 mg/m^2), and cyclophosphamide (600 mg/m^2) every 14 days, followed by 4 cycles of paclitaxel (175 mg/m^2) every 14 days were retrospectively reviewed. Pegfilgrastim (3.6 mg) was subcutaneously administered on day 3 of every ddAC-P cycle.

This study was approved by the Institutional Review Boards of Hyogo Cancer Center, and all the patients provided written informed consent.

Assessment. Adverse events were independently assessed by pharmacists using the Common Terminology Criteria for Adverse Events (version 4.0). In the neoadjuvant setting, the anti-tumor efficacy was evaluated by magnetic resonance imaging and

ultrasound after chemotherapy on the basis of the Response Evaluation Criteria in Solid Tumors (version 1.1).

We assessed the RDI of ddAC-P, ddAC, and ddP. RDI of ≥85% was defined as "high RDI," whereas that of <85% was defined as "low RDI." The prevalence of high RDI and the factors responsible for low RDI were also investigated.

Results

Patient characteristics. Patient characteristics are summarized in Table I. The median age of the patients was 51.5 years (age range=34-69 years). All patients belonged to Eastern Cooperative Oncology Group performance status (ECOG PS) 0 or 1. Stage IIA, IIB, and IIIA accounted for 77.3% of cases; 75% of cases were ER/PgR$^+$, HER2$^-$, and 25% were ER/PgR$^-$, HER2$^-$. The neoadjuvant setting was represented by 43.2% of the cases.

Hospitalization for monitoring. Treatment-related death was not observed. To be on the safe side, patients with adverse events were proactively hospitalized for effective monitoring. As a result of this policy, the recovery of five patients with adverse events was monitored by maintaining them as inpatients. Three patients with fever (grade 2 fever on day 15 of the 4th cycle of ddAC, grade 1 fever on day 15 of the 1st cycle of ddP, and grade 1 fever on day 16 of the 2nd cycle of ddP), one patient with dizziness (grade 2 on day 7 of the 4th cycle of ddAC), and one patient with pneumonitis (grade 3 on day 18 of the 4th cycle of ddAC) were hospitalized for approximately 1 week. Four of the five patients rapidly recovered after being treated only with hydration. None of them received intensive care, such as vasopressor therapy or respiratory management. One patient with pneumonitis received oxygen for 3 days and was discharged after 6 days of hospitalization.

Adverse events. Adverse events are summarized in Table II. The common (≥50%) non-hematological toxicities were peripheral neuropathy (90.5%) and arthritis/myalgia (79%). Most of these were grade 1 or 2, with only two patients experiencing grade 3 peripheral neuropathy. None of the patients experienced grade 3 or 4 arthritis/myalgia. Eight (18.2%) patients had fever, and all were either grade 1 or 2. The most common hematological toxicity was lymphopenia (52.3%). The patients neither experienced febrile neutropenia (FN) nor did they require blood transfusion. One patient (2.3%) on ddP developed grade 2 pneumonitis; we could not exclude *Pneumocystis jiroveci* pneumonia (PCP) owing to the presence of a ground-glass pattern on computed tomography (CT) images; hence, a treatment course of trimethoprim/sulfamethoxazole (TMP/SMX) (15 mg/kg) was initiated. However, serum β-D-glucan levels did not increase, and the patient recovered 7 days later in the absence of steroid treatment. One patient (2.3%) on ddAC developed grade 3 pneumonitis. We suspected PCP or interstitial lung disease (ILD) because of the ground-glass pattern observed on CT, and the patient recovered following a course of TMP/SMX without steroids. Bronchoscopy was not performed, which precluded a definitive diagnosis. Nevertheless, serum β-D-glucan levels did not increase, suggesting that ILD was more probable than PCP.

Treatment discontinuation, dose delay, and dose reduction. ddP was discontinued in cycle 1 in one patient (2.3%), because of strong anxiety after the development of grade 2 pneumonitis. Treatment delay occurred in 34.1% of ddAC-treated patients and in 31.8% of ddP-treated patients. The

Table I. *Patient characteristics*

Characteristic	n (%)
Age - years	
Median (range)	51.5 (34-69)
ECOG PS	
0	38 (86.4)
1	6 (13.6)
Stage	
IA, IB,	5 (11.4)
IIA, IIB, IIIA	34 (77.3)
IIIB, IIIC,	4 (9.0)
IV	1 (2.3)
Subtype	
ER/PgR$^+$, HER2$^-$	33 (75.0)
ER/PgR$^-$, HER2$^-$	11 (25.0)
Treatment setting	
Neoadjuvant	19 (43.2)
Adjuvant	25 (56.8)
Surgery	
Lumpectomy	11 (25.0)
Mastectomy	33 (75.0)

ECOG PS: Eastern Cooperative Oncology Group performance status.

Table II. *Adverse events (AE)*

AEs	n (%)			
	Grade 1	Grade 2	Grade 3	Grade 4
Fever	7 (15.9)	1 (2.3)	0	0
Febrile neutropenia	0	0	0	0
Pneumonitis	0	1 (2.3)	1 (2.3)	0
Lung infection	0	1 (2.3)	0	0
Nausea	-	-	1 (2.3)	0
Peripheral sensory neuropathy	22 (50.0)	16 (36.0)	2 (4.5)	0
Arthritis/Myalgia	15 (34.0)	20 (45.0)	0	0
Lymphopenia	-	-	22 (50.0)	1 (2.3)
Neutropenia	-	-	2 (4.5)	1 (2.3)

-: Not assessed.

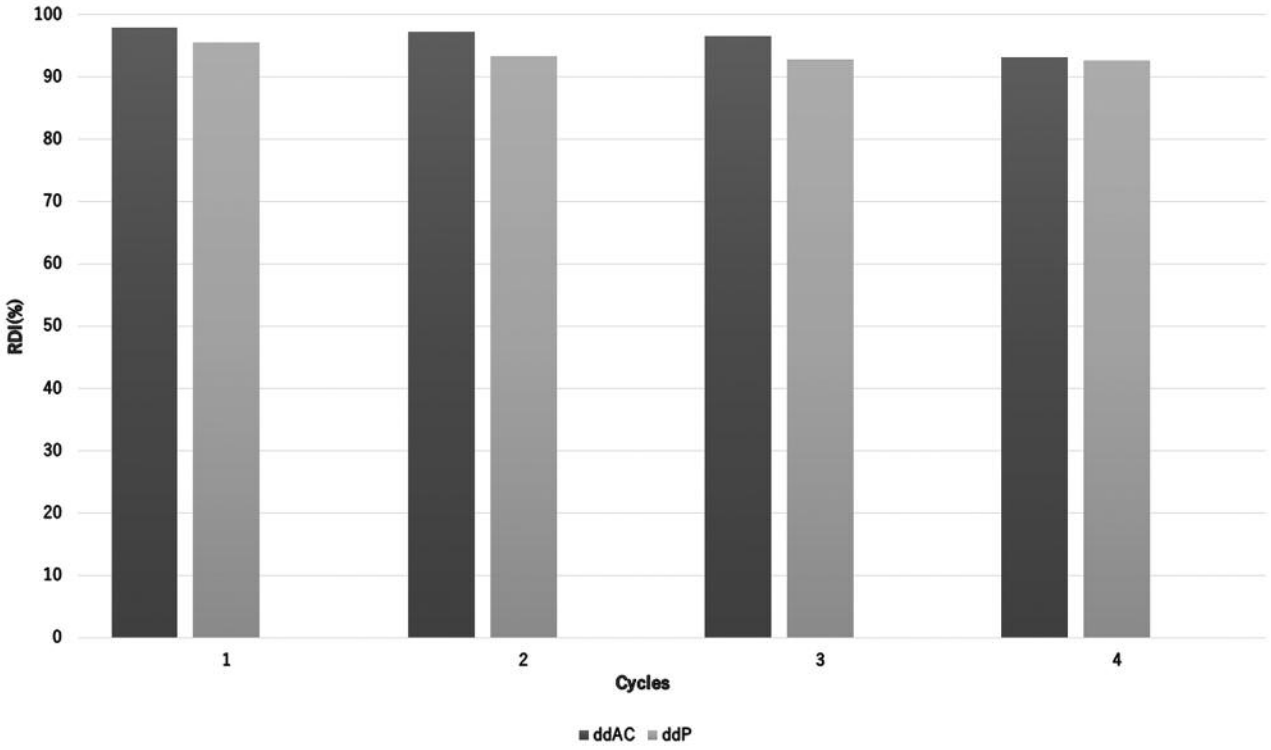

Figure 1. *The mean percent relative dose intensity (RDI) per treatment cycle. Black bars represent ddAC and gray bars represent ddP. The mean RDI of cycles 1-4 were 98%, 97.2%, 96.6%, and 93.2% for ddAC, and 95.6%, 93.3%, 92.9%, and 92.6% for ddP, respectively.*

major reasons for delaying ddAC therapy were holiday (33.3%, 5/15), grade 1/2 fever in cycles 1, 3, and 4 (33.3%, 5/15), and grade 1/2 upper respiratory infection (13.3%, 2/15) in cycles 1 and 2. The prime factors for delaying ddP treatment were holiday (35.7%, 5/14) and grade 1 fever in cycles 1 and 2 (28.6%, 4/14).

Although no dose reduction occurred in the ddAC-treated patients, it was required in 22.7% (n=10) of the ddP-treated patients. The major contributing factors were grade 2/3 peripheral sensory neuropathy (80%) during cycle 2 (1/8), cycle 3 (3/8), and cycle 4 (4/8). Additionally, dose reduction was required in one patient for grade 2 myalgia.

RDI. The mean percent of RDIs per treatment cycle are shown in Figure 1. The mean values for ddAC-P, ddAC, and ddP were 95.0%, 94.5%, and 93.3%, respectively. The percentage of prevalence of high RDI (≥85%) for ddAC-P, ddAC, and ddP was 90.9%, 84.1%, and 88.6%, respectively. Low RDI was observed in 10 patients owing to grade 1 or 2 fever (7/10; Table III).

The risk factors that may account for the low RDI were also investigated. The proportion of elderly patients (>65 years) with low RDI *vs*. high RDI for ddAC were 28.6% (2/7) *vs*. 8.1% (3/37) (odds ratio 4.7, p=0.15; Fisher's exact test). Although the difference was not significant, the trend suggests that elderly patients may be at risk of low RDI. Eight patients developed grade 1 or 2 fever. Seven of the eight patients (87.5%) with fever suffered from low RDI.

Table III. *Adverse events (AE) associated with low RDI*

AEs	n (%)
Fever (grade 1, 2)	7 (70.0)
Pneumonitis (grade 3)	1 (10.0)
Other†	2 (20.0)

†Other AEs were herpes zoster and symptoms that resembled encephalitis.

Treatment efficacy. Among the 19 patients who received ddAC-P as neoadjuvant chemotherapy, the clinical complete response (cCR) rate and clinical partial response (cPR) rates were 15.8% (n=3) and 68.4% (n=13), respectively. In the neoadjuvant setting, the rate of lumpectomy was 21.1% (n=4).

The median duration of follow-up was 17.8 months, and all patients survived without recurrence.

Discussion

This is the first study that evaluated the safety aspects and the RDI of ddAC-P supported by pegfilgrastim (3.6 mg). No mortality or FN occurred in the study patients; Intensive care unit (ICU) admission was also not required. This safety profile (no treatment-related death, no ICU admission, and no FN) is comparable with that reported in previous studies. Previous studies regarding ddAC-P (or ddEC-P) include CALGB9741, Gruppo Italiano Mammla 2 (GIM2), and SWOG0221 (1, 5, 6). All these investigations employed pegfilgrastim (6.0 mg) or daily filgrastim. Mizuno *et al*. and Morita *et al*. have studied ddAC (or ddEC) using pegfilgrastim (6.0 mg); ddP was not included in both the studies (7, 8).

The mean RDI was >90% for ddAC-P, ddAC, and ddP; this result is consistent with the RDI reported in the GIM2 study (5). Almost 90% patients achieved high RDI, which is also comparable with that reported in previous studies on ddAC or ddEC (5, 7, 8).

Furthermore, our data suggest that the primary reason for low RDI was grade 1 or 2 fever, and no other risk factors were detected. Grade 1/2 and grade 3/4 fever were observed in 18% and 0% of patients in our study; this result is not higher than that obtained in the previous GIM 2 study (26% and <1%). There were no other risk factors, such as age, and complications in patients experienced fever. PCP has been reported in patients with breast cancer receiving ddAC; hence, careful examinations and observations were ensured in case of fever as it may cause low RDI (9, 10).

In a previous study of a ddAC-P regimen (CALGB9741), blood transfusion and hospitalization for FN were observed in 3% and 2% of cases, respectively (1). Treatment-related death was observed in 0.4% of patients on ddAC and in 0.3% of those on ddP in the SWOG S0221 trial (6). However, FN and treatment-related deaths were not observed in our study, and blood transfusions were not required. These toxicity data indicated that low-dose pegfilgrastim (3.6 mg) is not associated with increased toxicity in Japanese patients.

Limitations of our study include the small sample size and its retrospective nature. Therefore, a phase 2 study on ddAC-P has already been initiated to provide more information (West Japan Oncology Group; WJOG 9016B).

In conclusion, ddAC-P plus pegfilgrastim (3.6 mg) is a feasible therapeutic strategy that maintains RDI in Japanese patients with breast cancer. Fever was the most common adverse event associated with low RDI. Management of this complication is therefore critical in maintaining the RDI.

Conflicts of Interest

The Authors have no conflicts of interest.

Authors' Contributions

M. Nishimura, K. Matsumoto, and S. Takao wrote the manuscript. M. Arase and S. Watanabe assessed the adverse events.

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