Phase III trial of doxorubicin plus cyclophosphamide (AC), docetaxel, and alternating AC and docetaxel as front-line chemotherapy for metastatic breast cancer: Japan Clinical Oncology Group trial (JCOG9802)


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Background: This randomized, multicenter, phase III trial compared doxorubicin plus cyclophosphamide (AC), single-agent docetaxel (D), and an alternating regimen of AC and docetaxel (AC–D) as first-line chemotherapy in metastatic breast cancer (MBC).

Patients and methods: Patients with MBC resistant to endocrine therapy were entered in a randomized study to receive either six cycles of AC (doxorubicin 40 mg/m² plus cyclophosphamide 500 mg/m²), D (60 mg/m²), or alternating treatment with AC–D (i.e. three cycles of AC and three cycles of D). Treatment was administered every 3 weeks.

Results: A total of 441 patients were entered in a randomized study. Response rates were 30% for AC, 41% for D, and 35% for AC–D. The median times to treatment failure (TTFs) were 6.4, 6.4, and 6.7 months (one-sided log-rank test, \( P = 0.13 \) for AC versus D, \( P = 0.14 \) for AC versus AC–D) and median overall survival (OS) was 22.6, 25.7, and 25.0 months (\( P = 0.09 \) for AC versus D, \( P = 0.13 \) for AC versus AC–D) in the AC, D, and AC–D, respectively.

Conclusion: There was no difference in the TTF among the three arms. However, there was a trend toward a better response and better OS in the D than in the AC.

Key words: cyclophosphamide, docetaxel, doxorubicin, metastatic breast cancer, phase III

introduction

Metastatic breast cancer (MBC) is unlikely to be cured by currently available treatment; however, systemic therapy can provide symptomatic relief and prolong survival [1]. Cytotoxic chemotherapy is generally the treatment option of choice in patients with hormone receptor-negative disease, patients whose disease has become resistant to hormonal therapy, and patients in whom impending organ failure necessitates rapid tumor shrinkage. Anthracycline monotherapy or combination therapy has been used as first-line treatment of MBC for over 30 years. Although anthracycline-based chemotherapy remains the standard treatment, several toxic effects can limit its usefulness in a palliative setting.

Docetaxel was introduced for the treatment of advanced breast cancer in the 1990s. Single-agent docetaxel is very active against advanced breast cancer. Four large randomized phase III trials have compared anthracycline-based regimens with docetaxel-based regimens as first-line treatment of MBC. Chan et al. [2] compared single-agent docetaxel with single-agent doxorubicin and reported higher response rates and a longer time to progression (TTP) with docetaxel, but no difference in survival. Nabholz et al. [3] compared doxorubicin plus docetaxel with doxorubicin plus cyclophosphamide (AC). The former had higher response rates and a longer TTP, but did not improve survival. Mackey et al. [4] compared a combination of docetaxel, doxorubicin, and cyclophosphamide (TAC) with 5-fluorouracil plus doxorubicin plus cyclophosphamide (FAC). TAC had a higher response rate, but there was no difference in either TTP or survival. To date, only one study, carried out by Bontenbal et al. [5], showed that doxorubicin plus docetaxel is superior to FAC in terms of response rate, TTP, and survival.
Because these trials failed to reach clear-cut conclusions, the optimal regimen for first-line chemotherapy in patients with MBC remains controversial.

Alternating chemotherapy is an approach designed to produce maximal antitumor activity by alternating non-cross-resistant regimens of chemotherapy [6]. Alternating chemotherapy has been suggested to be effective in Hodgkin’s disease and small-cell lung cancer [7, 8]. In breast cancer, the use of alternating chemotherapy remains controversial because a previous study showed that alternating doxorubicin and CMF (cyclophosphamide, methotrexate, and 5-fluorouracil) produced no clinical benefit [9]. To clarify the clinical benefits of single-agent docetaxel and an alternating regimen including doxorubicin and docetaxel, we carried out a randomized clinical trial in which patients were randomly assigned to receive a conventional regimen of AC, docetaxel alone (D), or an alternating regimen of AC and docetaxel (AC–D) as first-line chemotherapy for MBC. The dose of docetaxel was 60 mg/m², based on the results of a Japanese phase II trial [10]. Because this study was designed to evaluate the clinical benefits of first-line treatment independently of the effects of second-line crossover treatment, we designated the time to treatment failure (TTF) as the primary end point.

patients and methods

eligibility criteria

Patients were eligible if they had histologically proven MBC that was resistant to hormonal therapy, such as disease that was estrogen receptor negative, failed to respond to hormonal therapy, or relapsed within 6 months after adjuvant hormonal therapy. Patients who had received adjuvant chemotherapy were eligible, except for those who had recurrence within 6 months after the end of anthracycline-based adjuvant chemotherapy. Patients who had previously received anthracyclines for the treatment of MBC and those who had previously received taxanes were excluded. Eligible patients had to have lesions that could be measured or assessed, an age between 20 and 75 years, an Eastern Cooperative Oncology Group performance status of zero to three, and the following laboratory values: white cell count ≥4000/μl or absolute neutrophil count ≥2000/μl, platelets ≥100 000/μl, aspartate aminotransferase and alanine aminotransferase ≤1.5× the upper limit of normal or ≤560 IU/l, total bilirubin concentration ≤1.5 mg/dl, creatinine clearance ≤1.5 mg/dl, and a normal electrocardiogram or minimum abnormalities requiring no treatment. Patients with any of the following conditions were excluded from the study: pregnancy; malignant pleural effusion, ascites, or pericardial effusion that required emergency treatment; active infections; synchronous or metachronous (within 5 years) malignancy other than carcinoma in situ, previous stem-cell transplantation; brain metastasis requiring emergency treatment; a history of receiving >250 mg/m² of anthracyclines; cardiac disease of New York Heart Association class II or higher; a history of drug hypersensitivity; interstitial pneumonitis or pulmonary fibrosis; positive surface antigen of hepatitis B virus (HBsAg); positive hepatitis C virus (HCV) (deleted by amendment on 29 May 2002); and treatment with antipsychotic medication. All patients gave informed consent before enrollment. The study protocol was approved by the institutional review boards at the participating institutions.

treatment schedule

The treatment scheme is shown in Figure 1. Patients were randomly assigned to receive doxorubicin 40 mg/m² plus cyclophosphamide 500 mg/m² (AC) every 3 weeks for six cycles; docetaxel 60 mg/m² (D), administered by i.v. infusion over the course of 1 h every 3 weeks for six cycles; or AC and D in the same doses, administered alternately every 3 weeks for a total three cycles of AC and three cycles of D (alternating AC–D).

Dexamethasone was given in an i.v. dose of 8 mg 1 h before docetaxel and in an oral dose of 4 mg 12, 24, 36, and 48 h after infusion. Antiemetics were used at the investigator’s discretion. On treatment failure or disease progression, patients were crossed over to alternative agents.
progression during or after treatment, patients were crossed over from AC to D or from D to AC. The alternating AC–D regimen was restarted at the time of disease progression in patients who had completed six cycles of first-line AC–D.

Treatment was delayed for up to 3 weeks in the event of toxicity, but was restarted when laboratory values returned to the following values: white cell count $\geq$10000/μl or absolute neutrophil count $\geq$1500/μl, platelet count $\geq$100 000/μl, aspartate aminotransferase and alanine aminotransferase $<1.5\times$ the upper limit of normal or $\leq$50 IU/l, and creatinine clearance $\geq$1.5 mg/dl. Dose reduction (40–30 mg/m$^2$ doxorubicin and 500–400 mg/m$^2$ cyclophosphamide for AC and 60–50 mg/m$^2$ for D) was implemented when febrile neutropenia, grade 4 thrombocytopenia, or grade 3 non-hematologic toxicity (except nausea and vomiting) occurred. Treatment was terminated in the event of any grade 4 non-hematologic toxicity. Doses that were reduced because of toxicity could not be reincreased. Granulocyte colony-stimulating factor (filgrastim or lenograstim) could be used if the absolute neutrophil count fell to $<500/\mu$l or if febrile neutropenia developed.

**assessments**

Prestudy evaluations included a complete medical history, physical examination, complete blood cell counts, serum chemical analysis, tumor markers (carcinoembryonic antigen and CA15–3), chest radiography and/or computed tomography (CT), bone scintigraphy (and if positive, bone radiography), and abdominal CT or ultrasonography. All lesions that could be measured or assessed were evaluated at least twice, during first- and second-line chemotherapy, respectively. Response was classified according to the criteria of the Japanese Research Society for Breast Cancer, which are similar to the World Health Organization criteria. Objective responses were confirmed by central review at regular group meetings. Toxic effects were evaluated according to the JCOG Toxicity Criteria [11]. These criteria were based on the National Cancer Institute—Common Toxicity Criteria. As a pilot study to evaluate the feasibility of treatment, quality of life (QoL) was assessed during first-line chemotherapy for the first 50 patients randomly assigned to each arm, using the Functional Assessment of Cancer Therapy-Breast (FACT-B) questionnaire. QoL was assessed at baseline and 6 and 18 weeks after treatment had begun.

**statistical considerations**

The primary end point of this trial was the TTF. The secondary end points were overall survival (OS), progression-free survival (PFS), response rate, and adverse events. TTF was calculated from the date of randomization to the date of first documentation of discontinuation of first-line chemotherapy, disease progression, or death from any cause. Data on patients who were alive without treatment failure were censored on the date on which they were last known to be alive. PFS was calculated from the date of randomization to the date of the first documentation of disease progression or death from any cause. Data on patients who were alive without progression were censored on the date on which they were last known to be alive. OS was calculated from the date of randomization to the date of death from any cause. Data on patients who were alive were censored at the time of the last follow-up visit.

Our hypothesis was that D or alternating AC–D would prolong TTF as compared with AC. We assumed that the median TTF in the AC arm would be 7 months and that D or alternating AC–D would improve the TTF by 3.5 months. To adjust for multiplicity associated with two-pair comparisons of AC versus D and AC versus alternating AC–D, the planned sample size was 147 patients for each treatment arm, with a one-sided alpha of 0.025, a power of 0.9, an accrual of 3 years, and a follow-up of 1 year. The target number of patients was thus 450. Interim analysis was planned when 300 patients had been randomly assigned treatment. Multiplicity by multiple look was adjusted with the use of the O’Brien–Fleming alpha-spending function. The intention-to-treat (ITT) population was defined as all patients who were randomly assigned treatment. TTF, PFS, and OS were analyzed for the ITT population and compared among the treatment arms by the log-rank test. Response and safety analyses were carried out for assessable patients. As a pilot study, QoL was assessed in the initially enrolled 150 patients to evaluate the feasibility of treatment. Scores were calculated according to the scoring guidelines for FACT-B, and changes from baseline scores were compared between the treatment arms by unpaired Student’s t-tests. All analyses were carried out with SAS software, version 8.2 (SAS Institute, Cary, NC).

**results**

**patient characteristics**

From January 1999 to May 2003, a total of 441 patients were enrolled at 29 institutions. We extended the accrual time from 3 to 4 years because enrollment was slower than expected. In May 2003, we stopped enrollment on reaching a sufficient number of events for analysis. Twenty-four patients were ineligible: 16 lacked a sufficient interval from the completion of previous treatment; one had breast sarcoma; five had positive or unknown test results for HBsAg or HCV; one had previously received an anthracycline for MBC; and one had double cancer. Of the 441 patients, 146 were assigned to the AC arm, 147 were assigned to the D arm, and 148 were assigned to the alternating AC–D arm. All major prognostic factors were well balanced among the treatment arms (Table 1).

**Table 1. Patient characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>AC ($n = 146$)</th>
<th>D ($n = 147$)</th>
<th>AC–D ($n = 148$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>54</td>
<td>54</td>
<td>56</td>
</tr>
<tr>
<td>Range</td>
<td>26–72</td>
<td>28–74</td>
<td>27–75</td>
</tr>
<tr>
<td>PS (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>71</td>
<td>70</td>
<td>68</td>
</tr>
<tr>
<td>1</td>
<td>25</td>
<td>25</td>
<td>26</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Disease status (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage IV</td>
<td>19</td>
<td>21</td>
<td>20</td>
</tr>
<tr>
<td>Recurrent</td>
<td>81</td>
<td>79</td>
<td>80</td>
</tr>
<tr>
<td>ER status (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>56</td>
<td>56</td>
<td>57</td>
</tr>
<tr>
<td>Positive</td>
<td>35</td>
<td>35</td>
<td>34</td>
</tr>
<tr>
<td>Unknown</td>
<td>8</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Adjuvant chemotherapy (%)</td>
<td>58</td>
<td>59</td>
<td>58</td>
</tr>
<tr>
<td>Adjuvant anthracyclines (%)</td>
<td>15</td>
<td>16</td>
<td>18</td>
</tr>
<tr>
<td>Adjuvant hormonal therapy (%)</td>
<td>50</td>
<td>54</td>
<td>50</td>
</tr>
<tr>
<td>Hormonal therapy for MBC (%)</td>
<td>43</td>
<td>42</td>
<td>45</td>
</tr>
<tr>
<td>Radiotherapy for MBC (%)</td>
<td>19</td>
<td>14</td>
<td>19</td>
</tr>
<tr>
<td>Metastatic sites (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>23</td>
<td>24</td>
<td>23</td>
</tr>
<tr>
<td>Lung</td>
<td>48</td>
<td>43</td>
<td>41</td>
</tr>
<tr>
<td>Bone</td>
<td>37</td>
<td>37</td>
<td>33</td>
</tr>
</tbody>
</table>

AC, doxorubicin and cyclophosphamide; D, docetaxel; AC–D, alternating AC and docetaxel; PS, performance status; ER, estrogen receptor; MBC, metastatic breast cancer.
More than half of all patients had received adjuvant chemotherapy, although the proportion of patients previously treated with adjuvant anthracyclines was relatively low.

treatment

Sixty-eight percent of the patients in the AC arm completed six cycles of treatment versus 76% in the D arm and 77% in the alternating AC–D arm (Table 2). The higher rate of discontinuing the protocol treatment in the AC arm than in the D arm and the alternating AC–D arm was mainly attributed to disease progression. The proportions of patients who discontinued due to toxicity or refused to continue treatment were low. Five patients assigned to alternating AC–D (3%) were mistakenly given the wrong sequence of chemotherapy by the physician in charge. Ten patients had protocol violations: six did not undergo adequate blood tests before chemotherapy; three received nonprotocol surgery after chemotherapy, but before disease progression; and one received nonprotocol concurrent irradiation with chemotherapy.

toxicity

Grade 3 or 4 leukopenia and neutropenia occurred frequently in the D arm and the alternating AC–D arm, and febrile neutropenia most frequently occurred in the alternating AC–D arm (Table 3). Non-hematologic toxic effects were mild in all three treatment arms. There was no treatment-related death. Grade 3 or 4 nausea and vomiting were more frequent in the AC arm and alternating AC–D arm than in the D arm. One patient had grade 4 diarrhea in the alternating AC–D arm, and acute myelogenous leukemia developed in one patient assigned to the D arm after 3 months of second-line AC.

response to treatment

Tumor response was assessed in all patients randomly assigned to treatment. The responses to first-line and the second-line chemotherapy are shown in Table 4. Objective responses to first-line chemotherapy were observed in 29% of patients with AC arm, 40% of patients with D arm, and 35% of patients with alternating AC–D arm (P = 0.05 for AC versus D and P = 0.32 for AC versus alternating AC–D). The duration of response did not differ among the three treatment arms. The numbers of patients who received second-line chemotherapy after treatment failure following first-line chemotherapy were similar in the AC arm (82%, 119 of 146 patients) and the D arm (80%, 117 of 147); only 57% of patients in the alternating AC–D arm (84 of 148) received second-line alternating AC–D regimens. The responses to second-line chemotherapy were observed in the 24% of patients receiving D, 20% of patients receiving AC, and 20% of patients receiving alternating AC–D (P = 0.53 for AC versus D and P = 0.61 for AC versus alternating AC–D). The proportion of patients with progressive disease was higher in the AC arm than in the other arms. The response rates were calculated on the basis of the results of central review.

Table 2. Reasons for off-treatment of first-line chemotherapy

<table>
<thead>
<tr>
<th>% Over total</th>
<th>AC (n = 146)</th>
<th>D (n = 147)</th>
<th>AC–D (n = 148)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completed</td>
<td>68</td>
<td>76</td>
<td>77</td>
</tr>
<tr>
<td>Progression</td>
<td>25</td>
<td>18</td>
<td>15</td>
</tr>
<tr>
<td>Toxicity</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Patient refusal</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Physician's decision</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Others</td>
<td>1</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

AC, doxorubicin and cyclophosphamide; D, docetaxel; AC–D, alternating AC and docetaxel.

Table 3. Grade3/4 toxic effects in first-line chemotherapy

<table>
<thead>
<tr>
<th>%</th>
<th>AC (n = 146)</th>
<th>D (n = 147)</th>
<th>AC–D (n = 148)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukopenia</td>
<td>21</td>
<td>34</td>
<td>34</td>
</tr>
<tr>
<td>Neutropenia*</td>
<td>26</td>
<td>45</td>
<td>46</td>
</tr>
<tr>
<td>Anemia</td>
<td>3</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>3</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>3</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

*Neutrophil counts were missed in three patients with both AC and D arm and in four patients with AC–D arm.

AC, doxorubicin and cyclophosphamide; D, docetaxel; AC–D, alternating AC and docetaxel.

Table 4. Responses

<table>
<thead>
<tr>
<th>First-line chemotherapy</th>
<th>AC (n = 146)</th>
<th>D (n = 147)</th>
<th>AC–D (n = 148)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response (%)</td>
<td>7</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Partial response (%)</td>
<td>22</td>
<td>35</td>
<td>31</td>
</tr>
<tr>
<td>Overall (%)</td>
<td>29</td>
<td>40</td>
<td>35</td>
</tr>
<tr>
<td>95% CI (%)</td>
<td>22–37</td>
<td>32–49</td>
<td>27–43</td>
</tr>
<tr>
<td>No change (%)</td>
<td>40</td>
<td>37</td>
<td>46</td>
</tr>
<tr>
<td>Progressive disease (%)</td>
<td>26</td>
<td>18</td>
<td>16</td>
</tr>
<tr>
<td>Not assessable (%)</td>
<td>5</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Response duration (months)</td>
<td>9</td>
<td>9.2</td>
<td>9.2</td>
</tr>
<tr>
<td>95% CI (%)</td>
<td>7.6–10.8</td>
<td>7.9–10.0</td>
<td>7.2–10.4</td>
</tr>
</tbody>
</table>

Second-line chemotherapy

<table>
<thead>
<tr>
<th>D (n = 119)</th>
<th>AC–D (n = 117)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response (%)</td>
<td>3</td>
</tr>
<tr>
<td>Partial response (%)</td>
<td>20</td>
</tr>
<tr>
<td>Overall (%)</td>
<td>24</td>
</tr>
<tr>
<td>95% CI (%)</td>
<td>16–32</td>
</tr>
<tr>
<td>No change (%)</td>
<td>39</td>
</tr>
<tr>
<td>Progressive disease (%)</td>
<td>35</td>
</tr>
<tr>
<td>Not assessable (%)</td>
<td>3</td>
</tr>
</tbody>
</table>

AC, doxorubicin and cyclophosphamide; D, docetaxel; AC–D, alternating AC and docetaxel; CI, confidence interval.
survival

Kaplan–Meier curves for TTF after the start of first-line chemotherapy were plotted on the basis of data available as of June 2004. TTF data were available for 437 of the 441 patients who were randomly assigned to treatment. Follow-up case report forms were not available for the other four patients (Figure 2). There was no significant difference among the arms: median TTF was 6.4 months in the AC arm and D arm and 6.7 months in the alternating AC–D arm. There was also no significant difference in TTF after multivariate adjustment for known prognostic factors, carried out with a Cox model. PFS also did not differ significantly: median PFS was 6.6 months [95% confidence interval (CI) 6.0–7.3] in the AC arm, 7.0 months (95% CI 6.2–7.9) in the D arm, and 7.1 months (95% CI 6.6–7.8) in alternating AC–D arm (one-sided log-rank test, \( P = 0.19 \) for arm AC versus D, \( P = 0.11 \) for arm AC versus AC–D). Primary OS was analyzed at the same time as TTF (June 2004). The median survival times were 22.4 months (95% CI 18.0–27.0) in the AC arm, 25.7 months (95% CI 20.9–31.7) in the D arm, and 25.0 months (95% CI 20.9–31.0) in the alternating AC–D arm (one-sided log-rank test, \( P = 0.09 \) for arm AC versus D, \( P = 0.08 \) for arm AC versus AC–D). An updated OS analysis carried out in June 2006 showed trends toward better median survival times in the D arm and alternating AC–D arm than in the AC arm (one-sided log-rank test, \( P = 0.09 \) for arm AC versus D, \( P = 0.13 \) for arm AC versus AC–D; Figure 3).

quality of life

QoL was assessed according to the FACT-B scale at baseline and 6 and 18 weeks after treatment had begun in the first 150 patients. Completed questionnaires were received from 99% of the patients (148 of 150) at baseline, 89% (134 of 150) at 6 weeks, and 87% (130 of 150) at 18 weeks. The maximum possible FACT-B score is 152 points; a higher score indicates a better QoL. The median scores at baseline were 93.1 (range 51.1–131.4), 105.9 (range 52.6–140.0), and 104.5 (range 38.6–141.0) in the AC arm, the D arm, and the AC–D arm, respectively. The median scores were 90.0 (range 44.0–127.0), 96.3 (range 45.0–133.0), and 96.3 (range 41.9–135.6) at 6 weeks, and 95.0 (range 56.4–139.0), 91.3 (range 34.8–144.0), and 94.1 (range 49.9–132.0) at 18 weeks, respectively. There was no statistically significant difference among the three treatment arms.

discussion

We compared AC, single-agent D, and alternating AC–D as first-line chemotherapy for MBC. Although the primary end point of TTF did not differ significantly between the D arm or the alternating AC–D arm and the AC arm, there was a trend toward a higher response rate and better OS in the D arm than in the AC arm. On treatment failure or disease progression during or after treatment, patients were crossed over from AC to D or from D to AC. In the AC–D arm, the same regimen was resumed. The rate of response to first-line chemotherapy as well second-line chemotherapy was higher in the D arm than in either the AC arm or alternating AC–D arm. Interestingly, patients continued to respond to second-line treatment with the same alternating AC–D regimen. Improved OS observed is usually associated with improved TTF and PFS. In this study, however, there was a trend toward better OS in the D arm, but no significant difference in TTF or PFS. There were also no differences in potential confounding factors, such as salvage therapy or non-cancer-related death. Our results are consistent with the findings of a meta-analysis of taxanes based on all relevant clinical trials of first-line treatment in MBC, which showed that single-agent taxanes were worse than single-agent anthracyclines in terms of TTP, but not in terms of response rates or survival [12]. A systematic review of the Cochrane Database showed that taxane-based regimens were significantly better than non-taxane-based regimens for MBC in terms of OS, TTP, and overall response [13]. On subgroup analysis, D was associated with significantly improved OS, TTP, and overall response, whereas paclitaxel was not. Our results agree with these findings.

When used as a single agent, docetaxel is generally used in a dose of 100 mg/m² in Western countries. We used a lower dosage of 60 mg/m² for single-agent docetaxel because this is
the approved dose for the treatment of MBC in Japan based on
the results of a phase II trial [10]. This low dose of docetaxel
might have led to the nonsignificant differences among the
treatment arms in our study. A recent randomized phase III
trial [14] comparing 60, 75, and 100 mg/m² of docetaxel in
women with MBC reported a significant relation between dose
and response rate, but no significant difference in TTP or OS;
moreover, the incidence and severity of adverse events were
higher in the high-dosage group. The optimal dosage of
docetaxel for MBC thus requires further study.

Alternating chemotherapy is one of the promising
approaches to improve the response to chemotherapy. In breast
cancer, Bonadonna et al. [9] reported that alternating
chemotherapy with doxorubicin and CMF was not superior to
sequential chemotherapy with doxorubicin followed by CMF.
Because docetaxel is a promising drug of non-cross resistance
to doxorubicin, we studied the response to different sequences
of AC and D. Our trial suggested that both single-agent D and
alternating AC–D were slightly superior to AC; however, the
effectiveness of AC–D did not warrant the complexity of this
regimen, and D might be a better regimen in terms of
simplicity. These results suggest that single-agent docetaxel is
the most promising candidate for first-line chemotherapy.

In conclusion, this phase III trial demonstrated that
docetaxel alone was associated with a trend toward better
response and OS than AC, with no significant difference in TTF
or PFS. The survival benefits of first-line treatment with single-
agent docetaxel should be reevaluated in further randomized
phase III trials with OS as the primary end point.

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