Single-agent docetaxel (Taxotere) has been shown to be highly active in metastatic breast cancer, with an overall response rate of 47%, median time to progression of 4 months, and survival of 10 months when administered as a 1-hour intravenous infusion once every 3 weeks produced an overall response rate of 47% (range: 41% to 58%; 95% confidence interval), with a median time to progression of 4 months and survival of 10 months.[1-5]

These results are higher than those reported with doxorubicin (Adriamycin) monotherapy, which is considered to be the most active single agent in second-line therapy for patients with metastatic breast cancer. Response rates associated with doxorubicin in the second-line treatment of metastatic breast cancer have ranged from 25% to 33%, with a median time to progression of 3.6 months and a median survival of 8.9 months.[6-13]

Because docetaxel has shown significant second-line activity in phase II trials, a phase III study was performed to compare the effects of docetaxel and doxorubicin in patients with metastatic breast cancer in whom prior alkylating chemotherapy failed. This preliminary analysis presents comparative data on the median time to progression after treatment, response rates, and toxicity profiles following treatment with docetaxel and doxorubicin. Data are presented on 200 of the 326 recruited patients.

Methods

Patients
Women aged 18 to 75 years who had histologically or cytologically proven progressive metastatic adenocarcinoma of the breast and measurable and/or evaluable disease were considered for study participation, provided they met the following criteria: a performance status of at least 60% (Karnofsky index); no previous therapy with anthracyclines, anthracenediones, or taxanes; and failure after alkylating chemotherapy. Prior treatment with hormonal therapy for either advanced disease or in the adjuvant setting was permitted, as was radiation therapy. Response after alkylating chemotherapy was defined as:

- **Primary resistant**--patients who relapsed during adjuvant chemotherapy or disease progression as the best response to chemotherapy for metastatic breast cancer
- **Secondary resistant**--patients who relapsed within 12 months after adjuvant chemotherapy or disease progression on chemotherapy for metastatic breast cancer after an initial response
- **Not resistant**--patients who relapsed at least 12 months after receiving adjuvant (first-line) chemotherapy or had disease progression at least 30 days after chemotherapy for metastatic breast cancer.

Laboratory entry criteria included the following values: absolute neutrophil count ≥ 2.0 or greater × 10^9/L; a platelet count ≥ 100.0 × 10^9/L; total bilirubin ≤ 1.25 or less × upper normal limit (UNL); aspartate aminotransferase (ASAT) or alanine aminotransferase (ALAT) ≤ 3 × UNL; alkaline phosphatase ≤ 6 × UNL; ASAT or ALAT or both ≤ 1.5 × UNL associated with alkaline phosphatase ≤ 2.5 × UNL; serum creatinine ≤ 1.5 × UNL; and a resting left ventricular ejection fraction above the
lower normal limit of the institution, as measured by echocardiography or radionuclide angiography.

Specific criteria for exclusion were: local recurrence within partially resected breast or locally advanced inoperable breast cancer (stage IIIB) as the only manifestation of the disease; more than 1 line of chemotherapy for advanced or metastatic disease; history or presence of brain or leptomeningeal metastases; prior or concurrent malignancies, with the exception of adequately treated in situ carcinoma of the uterine cervix and cured nonmelanoma skin cancer, osteoblastic skeletal lesions, a single osteolytic lesion, lymphedema, pulmonary lymphangitic metastases, pleural effusion, or ascites as the only site of disease; and symptomatic peripheral neuropathy of at least grade 2 according to National Cancer Institute (NCI) Common Toxicity Criteria.

Patients were recruited from 42 centers worldwide. Ethics committee approval and informed patient consent were obtained before the start of the trial.

Study Design and Treatment Plan
This was a nonblinded, randomized, multicenter phase III study. The randomization was stratified by center, and patients were assigned randomly to receive an intravenous infusion of either docetaxel, 100 mg/m², for 1 hour once every 3 weeks, or doxorubicin, 75 mg/m², for 15 to 20 minutes once every 3 weeks. Premedication was specified for patients in the docetaxel group only, and was comprised of 8 mg of oral dexamethasone, given 13 hours, 7 hours, and 1 hour before docetaxel infusion, and for an additional 4 days at a dose of 8 mg twice daily, starting immediately after docetaxel infusion.

The maximum duration of treatment was 7 cycles for both groups, unless progression or unacceptable toxicity occurred. If a patient failed to respond to the assigned treatment, further treatment was at the discretion of the investigator. Patients withdrawn from the study before disease progression could not receive other antitumor therapy until progression was documented, unless deemed necessary by the investigator. Patients were observed for 1 month after their last study treatment infusion to document any late adverse events, with a follow-up every 3 months until death, to document time to progression and survival.

Dose reductions were permitted for severe hematologic and nonhematologic toxicities other than alopecia and anemia, graded according to NCI Common Toxicity Criteria. A maximum of 2 dose reductions were allowed per patient--ie, from 100 to 75 mg/m² and from 75 to 55 mg/m² for docetaxel, and from 75 to 60 mg/m² and from 60 to 45 mg/m² for doxorubicin.

Concomitant bisphosphonate treatment was not allowed unless initiated more than 3 months before the start of the study.

Study Assessments
A complete tumor assessment was performed during the 3 weeks before the first infusion of study medication, and included chest x-ray, bone scintigraphy and bone radiological examination, abdominal computed tomography scan, or ultrasound and physical examination. Bone scintigraphy could be performed 4 weeks before the first infusion of study medication. All evaluable and nonevaluable lesions were to be assessed at least every 2 treatment cycles.

The primary efficacy variable was time to progression, calculated from the date of randomization to the first progression. Response rate, defined as the percentage of patients in the group who achieved a complete or partial response, was a secondary efficacy variable. Patients with disease progression before the end of the second treatment cycle were considered to have early progression, whereas patients who received at least 2 cycles of therapy had their response to treatment classified as follows: complete response, partial response, stable disease, or progressive disease, according to the World Health Organization response criteria.

Weekly blood counts were performed. An initial assessment of left ventricular ejection fraction was made during the 2 weeks before study entry, using a multiple-gated acquisition scan or echocardiography; left ventricular ejection fraction was reassessed after a 400 mg/m² cumulative dose in the doxorubicin group, and at the end of the study in both treatment groups. Two types of analysis were performed on left ventricular ejection fraction: relative decrease in left ventricular ejection fraction from baseline according to NCI Common Toxicity Criteria, and absolute decrease in left ventricular ejection fraction from baseline according to the Schwartz criteria--ie, a decrease in left ventricular ejection fraction of at least 10 absolute percentage points and below the lower normal limit.[14]

Statistical Analyses
A two-tailed log-rank test was used to compare differences in the median time to progression between treatment groups. A significance level of 0.001, according to Peto sequential procedure,[15] was used for this preliminary evaluation, which was performed after patient accrual was completed.
Patients were required to have received at least 2 cycles of treatment and to have had at least 1 follow-up tumor assessment to be evaluable for efficacy, unless disease progression occurred. Two subpopulations were analyzed for efficacy: a second-line population comprised of patients who relapsed during treatment or within 12 months of the end of adjuvant chemotherapy containing an alkylating agent, or patients who had received 1 previous alkylating chemotherapy regimen for advanced or metastatic disease; and a first-line population, comprised of patients who relapsed more than 12 months after the end of adjuvant chemotherapy containing an alkylating agent and who had not received chemotherapy for advanced disease. All patients who received at least 1 infusion of study medication were evaluable for safety. Times-to-event variables were analyzed by the Kaplan-Meier method. All analyses were performed at least on the randomized (intent- to-treat) population.

**Preliminary Results**

**Patient Demographics**

This preliminary analysis reports on data from 200 patients randomized to receive either docetaxel (N = 102) or doxorubicin (N = 98). No difference in patient and tumor characteristics was found in the treatment groups (Table 1). With regard to metastatic sites, patients in this study had large tumor burdens, as indicated by liver involvement in approximately 39% of patients and by the 39% of patients with 3 or more involved sites. In addition, measurable disease was noted in approximately 83% of patients.

**Treatment Administration**

A median of 7 cycles (range: 1 to 10) of docetaxel was administered to 101 patients with a median cumulative dose of 620 mg/m² (range: 5 to 992 mg/m²). For doxorubicin, a median of 5 cycles (range: 1 to 7) was administered with a median cumulative dose of 353 mg/m² (range: 73 to 540 mg/m²). The median relative dose intensity was 0.98 (range: 0.5 to 1.07) for docetaxel and 0.95 (range: 0.49 to 1.05) for doxorubicin, with almost all patients in both treatment groups receiving a relative dose intensity of more than 70% of the planned dose.

**Response Rate and Median Time to Progression**

Using an intent-to-treat analysis, the overall response rate for patients receiving docetaxel was 47% (37% to 57%; 95% confidence interval) compared with 27% (18% to 36%; 95% confidence interval) for the doxorubicin-treated patients (Table 2). In the docetaxel group, 10% of patients achieved a complete response compared with 3% of patients in the doxorubicin group. More patients in the doxorubicin group (22%) experienced disease progression compared with docetaxel-treated patients (10%).

Preliminary analysis indicated that patients who received docetaxel had a median time to progression of 29 weeks compared with 21 weeks for the doxorubicin-treated patients. The response rates reported here are preliminary and need to be confirmed based on data derived from the entire patient population.

In the subpopulation analysis, overall response rates favored docetaxel both as first- and second-line subgroups (Table 3). As first-line therapy, the response rate was 56% in the docetaxel group and 46% in the doxorubicin group. In addition, more patients achieved a complete response (15% vs 4%) and fewer patients had progression as the best response (5% vs 13%) in the docetaxel group compared with the doxorubicin group.

As second-line therapy, a response rate of 41% (range: 29% to 54%; 95% confidence interval) was noted in patients receiving docetaxel compared with 20% (range: 12% to 31%; 95% confidence interval) in doxorubicin-treated patients. As in the first-line subanalysis, fewer patients had progression as best response on docetaxel therapy (13%) as compared with doxorubicin therapy (26%).

**Safety**

The most common reason for treatment discontinuation among the 200 patients was disease progression (docetaxel: N = 30; doxorubicin: N = 39). The two groups differed with regard to the adverse events that led to discontinuation of treatment. For example, cardiotoxicity was exclusively found in the doxorubicin arm (N = 7) and was responsible for 2 deaths. The cumulative dose of doxorubicin for those 2 patients was 350 and 450 mg/m². One patient was a 44-year-old woman with a history of diabetes mellitus and the second, a 73-year-old women, who had a history of arterial hypertension. Neither patient had received prior chest-wall radiotherapy. In contrast, neuropathy (3 patients) and fluid retention (1 patient) accounted for discontinuation in 4 patients who were receiving docetaxel.
The primary hematologic toxicity noted during the study was neutropenia, which was comparable between the 2 groups (Table 4). However, febrile neutropenia was more prevalent in the doxorubicin-treated patients (11.3%) compared with the docetaxel group (5.9%). Grade 3 to 4 infections due to neutropenia were also more common in the doxorubicin group (6.2%) compared with the docetaxel group (3.0%). The largest difference was seen with the incidence of grade 3 to 4 thrombocytopenia, with incidences of 1.0% in the docetaxel group vs 16.9% in the doxorubicin group.

With regard to acute nonhematologic toxicities, patients receiving doxorubicin tended to experience more severe nausea (17.5% vs 4%), vomiting (14.4% vs 3%), and stomatitis (14.4% vs 5%) compared with docetaxel-treated patients (Table 5). On the other hand, diarrhea was more common in the docetaxel group (9.9%) compared with the doxorubicin group (1.0%). The chronic nonhematologic toxicities for both treatment groups have been noted in previous trials (Table 5).

Discussion

The preliminary analysis of this large, multicenter phase III trial suggests that 100 mg/m² of docetaxel administered as a 1-hour infusion once every 3 weeks is more active than 75 mg/m² of doxorubicin administered once every 3 weeks in patients with metastatic breast cancer in whom previous alkylation chemotherapy failed. The complete response (10% vs 3%) and overall response (47% vs 27%) rates achieved with docetaxel were greater than those achieved by doxorubicin. The response rates reported in this preliminary analysis are consistent with those from phase II trials.[7,16,17] In addition, there were fewer patients in the doxorubicin group who had progressive disease as the best response (10% vs 22%), and there was a trend for longer median time to progression (29 vs 21 weeks) compared with the doxorubicin group.

Although both regimens caused the same incidence and severity of neutropenia, patients treated with doxorubicin had a higher incidence of infection and febrile neutropenia. In addition, doxorubicin produced a higher incidence of grade 3 to 4 thrombocytopenia. Cardiotoxicity associated with doxorubicin at doses of 450 mg/m² or less led to the death of 2 patients. By contrast, the fluid retention associated with docetaxel is reversible, manageable, and not life-threatening, as evidenced by the fact that it was responsible for the discontinuation of treatment in only 1 patient and no fatalities.

In conclusion, the preliminary results of this multicenter, randomized phase III study indicate that docetaxel is more active and appears to be safer than doxorubicin in patients with metastatic breast cancer in whom previous alkylation chemotherapy failed. Final analysis is awaited to confirm these preliminary results.

References:


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