Docetaxel vs Mitomycin Plus Vinblastine in Anthracycline-Resistant Metastatic Breast Cancer

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This nonblinded, multicenter, randomized phase III study compares the median time to progression (primary endpoint), response rate, and quality of life, safety, and survival of

Introduction

Metastatic breast cancer is an incurable disease, and, to date, there is no standard chemotherapy for patients with metastatic breast cancer in whom anthracycline-containing chemotherapy has failed. Tubulin-binding agents, such as vinblastine (Velban), vindesine (Eldisine), vinorelbine (Navelbine), or paclitaxel (Taxol) have yielded response rates of 15% to 35%[1-6] and mitomycin (Mutamycin), another commonly used agent in second-line regimens, has achieved objective response rates ranging from 15% to 25% at doses of 10 to 20 mg/m² administered every 4 to 8 weeks.[7,8]

Before the approval of paclitaxel and docetaxel (Taxotere), mitomycin and vinblastine (bolus or continuous infusion), either alone or in combination, were the backbone of most combinations used in patients in whom a prior anthracycline-containing regimen had failed.[1] Several authors regard the combination of mitomycin and vinblastine as producing the highest antitumor activity compared with each drug used as a single agent[7,9-16], even though no advantage in survival was observed.[1] So far, no large phase III study comparing paclitaxel to another chemotherapy regimen in patients with anthracycline-resistant advanced breast cancer has been reported.

Phase II Studies

Data from numerous phase II studies indicate that 100 mg/m² of docetaxel administered as a 1-hour infusion once every 3 weeks produces response rates of up to 58% in this group of patients.[17-21] These results appear significantly superior to other single agents and at least equivalent to the various combination therapy regimens. This present trial represents the first phase III randomized study comparing a taxane (docetaxel) to an accepted salvage regimen (mitomycin/vinblastine) in patients in whom an anthracycline-containing regimen has failed. This preliminary analysis performed on 200 patients among the 392 recruited presents comparative data on the median time to progression, response rates, and toxicity profiles following treatment with docetaxel or the mitomycin/vinblastine combination regimen.

Patients and 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: Karnofsky performance status of at least 60% and failure of previous therapy with an anthracycline-containing regimen defined as:

- **Primary resistant**—patients who relapse on adjuvant chemotherapy or whose disease progresses
- **Secondary resistant**—patients who relapse within 12 months after adjuvant chemotherapy or disease progression on chemotherapy for metastatic breast cancer after an initial response
- **Not resistant**—patients with progression of metastatic disease at least 30 days after
chemotherapy for metastatic breast cancer or exposure to previous anthracycline in an adjuvant and/or neoadjuvant setting, provided that further chemotherapy was given for advanced disease.

Laboratory entry criteria included the following values: absolute neutrophil count $\geq 2.0 \times 10^9$/L; a platelet count $\geq 100.0 \times 10^9$/L; total bilirubin $\leq 27.5$ µM/L (1.5 g/dL); aspartate aminotransferase (ASAT) or alanine aminotransferase (ALAT) $\leq 3 \times$ upper normal limit (UNL); alkaline phosphatase $\leq 6 \times$ UNL; ASAT or ALAT or both $1.5$ or less $\times$ UNL associated with alkaline phosphatase $\leq 2.5 \times$ UNL; serum creatinine $\leq 175$ µM/L (2 mg/dL); normal cardiac function using multiple-gated acquisition scan or echocardiography in patients who have received cumulative doses of doxorubicin exceeding 550 mg/m² or 900 mg/m² of epirubicin.

Specific criteria for exclusion were: more than one line of chemotherapy for advanced or metastatic disease; 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, and/or an osteoblastic skeletal lesion, and/or a single osteolytic lesion, and/or lymphedema, and/or pulmonary lymphangitic metastases and skin lymphangitis, and/or ascites, as the only site of disease; symptomatic peripheral neuropathy of at least grade 2 according to National Cancer Institute (NCI) Common Toxicity Criteria; unstable heart disease requiring treatment; congestive heart failure; angina pectoris or significant arrhythmias; and history of myocardial infarction within 6 months of study entry.

Patients were recruited from 49 centers worldwide. Ethics committee approval and patient written informed 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 list was stratified by center, and patients were assigned randomly to receive an intravenous infusion of either 100 mg/m² of docetaxel for 1 hour every 3 weeks, or 12 mg/m² of mitomycin every 6 weeks plus 6 mg/m² of vinblastine every 3 weeks (1 cycle is defined on the basis of vinblastine administration; ie, every 3 weeks).

Premedication was specified for patients in the docetaxel group only, comprising 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 after the docetaxel infusion.

The maximum duration of treatment was 10 cycles, 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 progression could not receive other antitumor therapy until progression was documented, unless deemed necessary by the investigator. Patients were assessed every 3 months during follow-up 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, from 12 to 8 mg/m² and from 8 to 5 mg/m² for mitomycin, and from 6 to 4 mg/m² for vinblastine.

**Tumor Assessments and Outcome Analysis**

A complete tumor assessment was performed during the 3 weeks before the first infusion of study medication, comprising physical examination, chest x-ray, bone scintigraphy and bone radiological examination, abdominal computed tomography scan or ultrasound, and physical examination. All evaluable and nonevaluable lesions were to be assessed at cycles 3, 6, 8, and 10. Weekly blood counts were performed.

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. All patients who received at least one infusion of study medication were evaluable for safety.

A two-tailed log-rank test was used to compare median time to progression between treatment groups. A significance level of 0.001, according to Peto sequential procedure,[22] was used for this interim evaluation, which was performed after patient accrual was completed. 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 (105 patients) or mitomycin plus vinblastine (95 patients). 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 the incidence of visceral involvement (74% in the docetaxel group and 73% in the mitomycin/vinblastine group), liver metastases (43% and 48%), and by 46% of patients having 3 or more metastatic sites involved. Measurable disease (as opposed to evaluable disease) was noted in a high percentage of cases (80% for the docetaxel group and 76% for mitomycin/vinblastine).

Treatment Administration
A median of 6 cycles (range: 1 to 12) of docetaxel was administered to 104 patients and a median of 3 cycles (range: 1 to 10) of mitomycin/vinblastine was administered to 94 patients. The median relative dose intensity was 0.96 (range: 0.62 to 1.04) for docetaxel and 0.99 (range: 0.67 to 1.43) for mitomycin and 0.98 (range: 0.66 to 1.24) for vinblastine. A high percentage of patients in both treatment groups received a relative dose intensity of more than 70% of the planned dose (94% for the docetaxel group and 98% for the mitomycin/vinblastine group).

Response Rate and Median Time to Progression
The overall response rate for patients (intent-to-treat analysis) receiving docetaxel was 28% (range: 20% to 36%; 95% confidence interval) compared with 13% (range: 7% to 21%; 95% confidence interval) for the mitomycin/vinblastine group (Table 2). This trend in response rates was also seen in patients with bidimensionally measurable lesions, with 32% (range: 21% to 44%; 95% confidence interval) of docetaxel patients responding compared with 12% (range: 5% to 23%; 95% confidence interval) of patients receiving mitomycin/vinblastine. Of the docetaxel-treated patients, 5% achieved a complete response compared with 2% of the mitomycin/vinblastine group. More patients in the mitomycin/vinblastine group (48%) experienced disease progression as their best response to treatment compared with docetaxel-treated patients (29%). Preliminary analysis indicates that patients who received docetaxel had a longer median time to progression (17 weeks) compared with patients treated with mitomycin/vinblastine (9 weeks) (P = .015) (Figure 1).

Safety
The primary hematologic toxicity noted during the study was grade 3 to 4 neutropenia, which was seen in 89% of patients treated with docetaxel and 67% of patients receiving mitomycin/vinblastine (Table 3). Febrile neutropenia was more prevalent in the docetaxel-treated patients (11%) compared with patients in the mitomycin/vinblastine group (1%). Grade 3 to 4 infections due to neutropenia were also more common in the docetaxel group (12%) compared with the mitomycin/vinblastine group (1%). In contrast, more patients in the mitomycin/vinblastine group (12%) experienced grade 3 to 4 thrombocytopenia than docetaxel-treated patients (6%). With regard to acute nonhematologic toxicities, patients receiving docetaxel experienced more severe stomatitis (12% vs 1%) and diarrhea (9% vs 0%) compared with mitomycin/vinblastine-treated patients (Table 4). Grade 3 to 4 vomiting and nausea were uncommon in both treatment groups. The grade 3 to 4 or severe chronic nonhematologic toxicities noted in the docetaxel and mitomycin/vinblastine treatment groups included asthenia (16% vs 9%), constipation (1% vs 6%), and pulmonary disorder (3% vs 6%). Reports of grade 3 to 4 docetaxel-specific side effects were infrequent in this treatment group: fluid retention (10%), nail disorders (4%), and neurosensory toxicity (2%). Alopecia was more frequent with docetaxel (64% vs 17%). The most common reason for treatment discontinuation among the 200 patients was disease progression: docetaxel (54% of cases; 57 of 105 patients) and mitomycin/vinblastine group (61%; 58 of 95 patients). Disease progression led to the deaths of 4 patients in each treatment group. The 2 groups differed with regard to the adverse events that led to discontinuing treatment. Thrombocytopenia in the mitomycin/vinblastine arm (7% of patients) and fluid retention (6% of patients) in the docetaxel arm were the main treatment-ending adverse events.

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 12 mg/m² of mitomycin every 6 weeks plus 6 mg/m² vinblastine every 3 weeks in patients with metastatic breast cancer in whom previous anthracycline-containing chemotherapy has failed. The overall response rate achieved with docetaxel (28%) was greater than that achieved by the combination regimen (13%) in a population of patients with a high proportion of true resistance (primary and secondary) to anthracyclines. An advantage in response rate was also seen in patients with bidimensionally measurable disease (32% vs 12%). In addition, there were fewer patients in the docetaxel group who had progressive disease as a best response (29% vs 48%), and in this preliminary analysis, there was already a difference in terms of median time to progression (17 vs 9 weeks) in favor of docetaxel compared with mitomycin/vinblastine. The present trial represents the first large phase III trial comparing a taxane (docetaxel) to mitomycin plus vinblastine in patients with metastatic breast cancer in whom previous anthracycline-containing chemotherapy had failed. The response rates and median times to progression reported in this preliminary analysis were consistent with those from earlier phase II trials.\[22\]

Diéras and colleagues[22] reported a median response rate of 15% and time to progression of 15 weeks in 36 patients receiving 175 mg/m² of paclitaxel administered as a 3-hour intravenous infusion once every 3 weeks. In contrast, 36 patients receiving 12 mg/m² of mitomycin once every 6 weeks achieved a response rate of 5% and a median time to progression of 7 weeks. However, the results from this study are limited due to the small sample size (72 patients) and the dose of mitomycin (12 mg/m²), which was lower than what is typically used for monotherapy with this agent. Survival data were not yet available at the time of this preliminary analysis. Both agents were myelosuppressive; neutropenia and its clinical consequences (febrile neutropenia and grade 3 to 4 infection) were more common in the docetaxel arm. However, the incidence of febrile neutropenia was in keeping with the data known from phase I and II trials using the same dose of docetaxel.[17] Patients treated with mitomycin/vinblastine experienced more thrombocytopenia than patients in the docetaxel arm. In terms of gastrointestinal toxicity, diarrhea and stomatitis were more frequent in the docetaxel arm, whereas nausea and vomiting were seldom seen in both arms. Alternatively, constipation was more common in the group treated with mitomycin/vinblastine. Severe docetaxel-specific toxicities, such as (fluid retention, skin toxicity, nail disorders, and neurosensory toxicity) were infrequent, in keeping with the observations from phase II trials using the same corticosteroid premedication given over 5 days.[17]

**Conclusions**

The preliminary results of this multicenter, randomized phase III study in patients with metastatic breast cancer in whom previous anthracycline-containing chemotherapy has failed, indicate that docetaxel is more active than the mitomycin/vinblastine combination, with higher response rates and a difference in terms of time to progression. Toxicity profiles were acceptable in both arms, in keeping with previous reports. These results should be interpreted with caution because this analysis was conducted on the first 200 patients who finished the study treatments, and these preliminary results may underestimate response and overstate treatment discontinuation rates. Thus, the final analysis on the entire patient population is necessary to confirm these findings.

**References:**


