Docetaxel (Taxotere) and doxorubicin (Adriamycin) have each demonstrated significant activity in metastatic breast cancer. Thus, the combination of docetaxel and doxorubicin has been evaluated in phase I trials to

**Introduction**

Docetaxel (Taxotere) and doxorubicin (Adriamycin) are considered 2 of the most active chemotherapeutic agents for patients with metastatic breast cancer. When used as first-line therapy, single-agent docetaxel, administered at a dose of 100 mg/m² as an intravenous infusion over 1-hour once every 3 weeks, has produced response rates ranging from 57% to 69%. At the same dose, docetaxel also has a high level of activity in second- and third-line regimens, as well as in anthracycline-resistant or -refractory patients with metastatic breast cancer. Doxorubicin is widely considered the agent of choice for metastatic breast cancer in first-line therapy. Response rates with doxorubicin in first-line regimens range from 29% to 43%, and the median survival time is approximately 2 years. The rationale for using docetaxel and doxorubicin in combination for patients with metastatic breast cancer includes the facts that doxorubicin-containing regimens are among the most active and that there is at least a partial clinical cross-resistance between the two agents.

**Docetaxel/Doxorubicin Combination Trials**

Two phase I trials, one being performed in France and the other in Japan, characterize the ongoing efforts to investigate the potential benefit of docetaxel/doxorubicin combination regimens in patients with metastatic breast cancer. Both trials are designed to determine the dose-limiting toxicity, the maximum tolerated dose, the recommended dose for phase II and III trials, and the safety profile of the combination. The study by Itoh and colleagues also examined the clinical and pharmacokinetic impact of the sequence of administration of docetaxel and doxorubicin. Inclusion criteria for study participation in both trials included patients with measurable and/or evaluable disease who had not received prior chemotherapy for metastatic disease and no prior adjuvant chemotherapy for at least 1 year. In the French study, prior adjuvant anthracycline therapy was allowed, provided patients had received a cumulative dose that was less than or equal to the following: 300 mg/m² of doxorubicin, 500 mg/m² of epirubicin, or 500 mg/m² of tetrahydropyranyl (THP) doxorubicin. In the Japanese study, no anthracycline-based chemotherapy was allowed, and Eastern Cooperative Oncology Group (ECOG) performance status had to be less than 3. Patients were also required to have normal baseline left ventricular ejection fraction levels by multiple-gated acquisition scan.

**Dose-Escalation Study**

**Treatment Plan**

In the French study, the treatment plan included doxorubicin administered intravenously as a bolus over 15 minutes, followed 1 hour later by docetaxel, which was given by intravenous infusion over 1 hour. This schedule was later repeated every 3 weeks on an outpatient basis. A total of 6 dose levels of doxorubicin/docetaxel were studied: 40 mg/m² of doxorubicin/50 mg/m² of docetaxel (level 1); 40 mg/m² of doxorubicin/60 mg/m² of docetaxel (level 2); 50 mg/m² of doxorubicin/60 mg/m² of docetaxel (level 3); 50 mg/m² of doxorubicin/75 mg/m² of docetaxel (level 4); 50 mg/m² of doxorubicin/85 mg/m² of docetaxel (level 5); 60 mg/m² of doxorubicin/60 mg/m² of docetaxel (level 6) (Table 1).
Patients did not receive prophylactic granulocyte colony-stimulating factor (G-CSF) (Granocyte). Premedication for the prevention of hypersensitivity reactions and fluid retention included 8 mg of dexamethasone administered every 6 hours for 3 days, beginning the day prior to chemotherapy; 10 mg of cetirizine (Zyrtec) administered 7 hours and 1 hour before the infusion with docetaxel; and 300 mg of ranitidine (Zantac) administered once daily for 3 days, starting 1 day prior to chemotherapy.

**Preliminary Results**

Currently, there are 42 patients entered in this trial. Median age is 48 years (range: 30 to 69 years). A total of 24 of 42 patients (57%) had received prior adjuvant chemotherapy, of whom 22 of 24 (92%) received anthracycline-based adjuvant chemotherapy. Of these 42 patients, 79%, had visceral involvement, 36% with 2 or more metastatic sites, 43% with liver involvement, and 41% with bone lesions.

Overall, the median number of cycles of the combination administered was 7 (range: 2 to 10). The overall median cumulative dose of doxorubicin was 310 mg/m² (range: 99 to 534 mg/m²) and of docetaxel 423 mg/m² (range: 149 to 707 mg/m²). At all dose levels, the most frequent toxicity was neutropenia ([Table 1](#)). Although grade 4 neutropenia occurred in more than 73% of the cycles for dose levels 2 through 6, febrile neutropenia occurred in less than 14% of the cycles. Febrile neutropenia was complicated by infection in 2 patients at dose level 5, thus defining the maximum tolerated dose as 50 mg/m² of doxorubicin combined with 85 mg/m² of docetaxel without prophylactic G-CSF support.

The nonhematologic toxicities associated with the combination of doxorubicin and docetaxel were minor, with maximum severity being a grade 2 or less. The most common nonhematologic toxicities were those typically seen with most chemotherapeutic regimens, namely, nausea, vomiting, diarrhea, and stomatitis. Of particular note was the lack of severe fluid retention in this study, with a mean cumulative dose of docetaxel of 460 mg/m² and the lack of grade 3 mucositis. Moderate fluid retention was noted in 19% of the patients.

Decreased left ventricular ejection fraction was noted in 4 patients, and no patient presented with congestive heart failure after a median follow-up of 18 months and a median cumulative dose of doxorubicin of 392 mg/m² (range: 240 to 559 mg/m²). No patients were discontinued from the study, even though most of the patients (55%) had received doxorubicin at cumulative doses greater than 360 mg/m².

The overall response rate across all dose levels was 72%. However, at the dose level of 50 mg/m² of doxorubicin combined with 75 mg/m² of docetaxel, the response rate was 90%. In addition, patients with metastasis to the liver achieved a response rate of 83% at all dose levels.

**Dose-Sequence Study**

Itoh and colleagues[7] recently reported the preliminary results of an ongoing trial that assessed the impact of alternating the sequence of administration of doxorubicin and docetaxel when used in combination for patients with advanced breast cancer. The treatment plan includes 4 dose levels. For dose level 1, patients receive 50 mg/m² of docetaxel followed by 40 mg/m² of doxorubicin for 1 cycle. In the second cycle, 40 mg/m² of doxorubicin was administered first followed by 50 mg/m² of docetaxel.

Similarly, patients in dose level 2 receive 60 mg/m² of docetaxel followed by 40 mg/m² of doxorubicin for 1 cycle. In the second cycle of dose level 2, 40 mg/m² of doxorubicin is administered first, followed by 60 mg/m² of docetaxel. In dose level 3, patients receive 50 mg/m² of doxorubicin followed by 60 mg/m² of docetaxel. Patients in dose level 4 receive 50 mg/m² of doxorubicin followed by 70 mg/m² of docetaxel. The sequences in dose levels 3 and 4 are not switched.

Dose-limiting toxicity was defined as: grade 4 neutropenia for 7 days or longer, grade 4 neutropenia for more than 3 days, accompanied by fever associated with an infection, grade 4 thrombocytopenia; or any grade 3 or 4 nonhematologic toxicity, except alopecia, vomiting, and general malaise. The maximum tolerated dose has not been reached for the sequence of doxorubicin followed by docetaxel. Profound grade 4 neutropenia was noted in 3 patients with the sequence of 60 mg/m² of docetaxel, followed by 40 mg/m² of doxorubicin. Although the sequence of administration did not affect the pharmacokinetic parameters of either drug, these preliminary results suggest that drug sequence may play a role in the duration of neutropenia. The authors noted that patient accrual is ongoing at dose level 2, with the sequence of 50 mg/m² of doxorubicin followed by 60 mg/m² of docetaxel.
Discussion

Based on the results from the phase I trial by Dieras and colleagues,[6] the regimen of doxorubicin followed by docetaxel appears to be a very active combination, with an overall response rate of 90% at the highest feasible dose without G-CSF support. The recommended dose and sequences for future phase II and III trials is 50 mg/m² of doxorubicin followed by 75 mg/m² of docetaxel, or 60 mg/m² of both drugs, once every 3 weeks without prophylactic G-CSF support. In 10 patients at the former dose level, the response rate was 90%. Although asymptomatic abnormal left ventricular function was noted in 4 patients (and reversible in 3 patients), there were no cases of doxorubicin-related congestive heart failure. This is of particular importance because retrospective studies have estimated that the incidence of doxorubicin-related congestive heart failure is 3% to 4% in patients who receive a cumulative dose of 450 mg/m² of doxorubicin as single-agent therapy.[8-10]

The incidence of congestive heart failure following the combined use of doxorubicin and paclitaxel (Taxol) was reported by Gianni and colleagues.[11] These authors noted that reversible congestive heart failure occurred in 21% (range: 7% to 35%; 95% confidence interval) of patients who had received a 3-hour infusion of paclitaxel combined with a bolus dose of doxorubicin. Of the 6 affected patients 5 had received a total dose of 480 mg/m² of doxorubicin, with the remaining 1 patient experiencing congestive heart failure only after receiving a total dose of 120 mg/m².[11] The same cardiotoxicity profile was observed in another study of the combination of paclitaxel and doxorubicin. Gehl et al[12] reported that 50% of the patients developed an abnormal left ventricular ejection fraction, resulting in congestive heart failure in 20% of the patients.

In summary, doxorubicin followed by docetaxel appears to be a promising combination regimen for patients with untreated metastatic breast cancer. Except for grade 4 neutropenia and/or its complications, no severe nonhematologic toxicities were observed with this combination. Based on the high level of activity noted, additional studies are warranted to determine the optimal integration of docetaxel in combination with anthracyclines in the adjuvant setting.

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