Optimal management of locally advanced breast cancer (stage III) generally includes a combination of primary chemotherapy followed by surgery (if feasible), and local radiotherapy and adjuvant chemotherapy with or without endocrine therapy. The substantial antitumor activity of docetaxel (Taxotere) in first- and second-line chemotherapy for patients with metastatic breast cancer provides the rationale for further investigation of this agent in other breast cancer treatment settings.[1-11] One area is the incorporation of docetaxel into multimodality regimens in which chemotherapy and/or endocrine therapy is combined with surgery and radiation.

Earlier studies have shown that induction chemotherapy may result in significant reductions in the size of the primary tumor, thereby increasing the number of candidates for breast conservation by a combination of surgery and radiation.[12-16] One benefit of using neoadjuvant therapy in this setting is that it allows clinical and pathological assessment of tumor response to the chemotherapy regimen.[17,18]

In a randomized study by Powles and colleagues,[17] use of neoadjuvant chemoendocrine therapy and postsurgery chemotherapy in 212 women with primary operable breast cancer was evaluated. Of these 212 patients, 105 were randomized to receive neoadjuvant treatment and received 4 cycles of chemotherapy for 3 months before surgery, followed by another 4 cycles after surgery. For comparison, 107 patients were randomized to adjuvant therapy and received 8 cycles of chemotherapy over 6 months after surgery. The findings from this trial showed that neoadjuvant therapy results in an overall response rate of 85% and a complete response in 10% of patients. In addition, there was a significant reduction in the requirement for mastectomy in patients who received neoadjuvant treatment (13%) compared with those who received adjuvant therapy (28%) (P < .005).

We conducted a phase II study to determine the clinical response rate to primary therapy with docetaxel followed by surgery, cyclophosphamide (Cytoxan, Neosar), and doxorubicin, and radiation with or without adjuvant tamoxifen (Nolvadex) in patients with stage III breast cancer. This preliminary analysis addresses the response rate, side effects, and toxicity profile of this therapeutic approach.

**Methods**

**Patients**
Women aged 18 to 75 years with stage III breast cancer were accrued into this open-label, phase II multicenter study. Patients with locally advanced adenocarcinoma of the breast and measurable or evaluable disease were eligible for entry into the study provided they had a performance status of at least 60% (Karnofsky index) and had not received previous chemotherapy. Laboratory entry criteria included the following values: absolute neutrophil count ≥ 2.0 × 10⁹/L; a platelet count ≥ 100.0 × 10⁹/L; total bilirubin ≤ 1.25 × 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; a resting left ventricular ejection fraction above the lower normal limit of the institution, as measured by echocardiography or radionuclide angiography.

**Treatment Plan**
Patients with locally advanced stage III breast cancer were initially treated with 4 cycles of 100
mg/m² of docetaxel administered as a 1-hour intravenous infusion once every 3 weeks. Following the 4 cycles of docetaxel, patients underwent either breast-conserving surgery or mastectomy. Standard-dose doxorubicin/cyclophosphamide chemotherapy—4 cycles of 60 mg/m² of Adriamycin and 600 mg/m² of cyclophosphamide—was initiated following surgery. Radiation therapy was then delivered, which varied according to the type of surgery performed. For patients who had undergone breast-conserving surgery, radiation consisted of conventional fractionation at a dose of 5,000 or greater cGy (180 to 200 cGy/day) and a boost to a total tumor dose of 6,040 cGy. For patients who had undergone modified radical mastectomy, radiation therapy to the chest wall and supraclavicular region was employed to a total dose of 5,000 or greater cGy. Tamoxifen therapy (20 mg/day for 5 years) was provided to all patients who were hormone-receptor positive or who were over the age of 50 years. All patients received premedication with 8 mg of oral dexamethasone twice daily for 5 days, starting 1 day prior to docetaxel administration. Growth factor support with granulocyte colony-stimulating factor (G-CSF) (filgrastim [Neupogen]) was provided to patients who developed febrile neutropenia (and was initiated prophylactically to these patients on subsequent cycles).

**Study Assessment**

Tumor measurements were performed before initiation of therapy and every two cycles thereafter, according to the World Health Organization criteria. The primary efficacy variable was clinical response rate, defined as the percentage of patients who achieved a complete or partial response. In patients who received at least 2 cycles of therapy, response to treatment was classified as follows: complete response, partial response, stable disease, or progressive disease. A complete response was defined as the complete resolution of all known lesions on 2 separate measurements at least 4 weeks apart. A partial response was defined as a reduction of tumor volume by at least 50%. Stable disease was defined as a decrease of < 50% or an increase of < 25%. Progressive disease was defined as a > 25% increase in an existing tumor or the appearance of new lesions.

The secondary efficacy variable was time to progression, calculated from the date of the administration of the first cycle of chemotherapy to the first sign of disease progression.

**Results**

**Patient Demographics**

This preliminary analysis is based on data from 33 patients. The demographics are listed in Table 1. The mean age of patients was 50 years (range, 27 to 68 years). Thirty-two of the 33 patients had a Karnofsky performance status of 90%. A total of 12 patients (36%) had stage IIIA disease and 16 (49%) had stage IIIB disease. The remaining 5 patients (15%) were unspecified stage III, but appeared to have large primary tumors > 5 cm, with no clear indication of the nodal status on clinical examination. A total of 120 cycles were administered during the study.

**Response Rate**

Partial and complete responses were achieved in 22 (67%) and 6 (18%) patients, respectively, for an overall response rate of 85% (Table 2). Disease was stable in 4 patients (12%) and progressed in 1 (3%). Of the 6 patients with complete clinical responses, 1 patient was actually confirmed to have achieved a complete pathologic response at the time of surgery.

Data on the time-to-progression and disease-free survival after 1 and 2 years of treatment are not yet available.

**Toxicity**

The primary toxicity observed during the docetaxel administration portion of this trial was myelosuppression (Table 3). Febrile neutropenia was noted in 8 patients (24%) and in 8 of the 120 treatment cycles (7%) administered. Grade 4 neutropenia was experienced by 31 patients (94%) during at least 1 cycle. The majority of patients (88%) experienced grade 4 neutropenia during the first cycle, with a median duration of 7 days or less. Thrombocytopenia did not occur. Although anemia did occur, no patient required a blood transfusion. Nonhematologic toxicities are shown in Table 4. The most common National Cancer Institute (NCI) gradeable toxicities included alopecia (97%), nausea (51%), diarrhea (46%), and stomatitis (35%). Grade 3 nonhematologic toxicities were uncommon and included diarrhea (6%), stomatitis (6%), allergy (3%), and nausea (3%). Grade 3 to 4 or severe neurotoxicity was not observed in any patient. Other toxicities not graded using the NCI criteria included asthenia, which was noted in 70% of patients, but was severe in only 9%. Peripheral edema and nail disorders were mild to moderate in severity, with no reports of severe cases.
Conclusion

The preliminary results from this phase II study suggest that single-agent docetaxel has significant antitumor activity as neoadjuvant therapy in patients with stage III breast cancer. The overall response rate was 85%, with 18% complete responses. The most common toxicity was neutropenia; however, only a small fraction of cases were associated with febrile neutropenia. Future trials aimed at increasing the number of pathologic complete responses in patients with stage III breast cancer may require the use of docetaxel in combination with other active agents or the use of dose-dense scheduling schemes.

References:


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