Docetaxel/Doxorubicin/Cyclophosphamide in the Treatment of Metastatic Breast Cancer

Introduction

The integration of the taxanes in combination chemotherapy regimens for a variety of cancers, including metastatic breast cancer, is becoming a fundamental therapeutic approach in oncology. In patients with anthracycline-resistant metastatic breast cancer, 100 mg/m² of Taxotere (docetaxel) administered as a 1-hour intravenous infusion once every 3 weeks produced overall response rates of up to 57%.[1,2] This lack of cross-resistance, in addition to the substantial antitumor activity of both docetaxel and doxorubicin (Adriamycin) provides the rationale for investigating this combination in patients with metastatic breast cancer.

Kalla and colleagues[3] recently reported that an intravenous bolus dose of 50 mg/m² of doxorubicin followed by 75 mg/m² of docetaxel administered as a 1-hour infusion once every 3 weeks, without granulocyte colony-stimulating factor support (G-CSF) (filgrastim [Neupogen]), produced a response rate of 90% in patients with metastatic breast cancer. The most encouraging finding from this trial, as well as from a trial by Itoh and colleagues,[4] was the lack of clinically significant cardiac toxicity. Kalla et al[3] found that none of the 42 patients treated with this combination developed congestive heart failure, which typically occurs at a rate of 3% to 4% in patients who receive a cumulative dose of 450 mg/m² of doxorubicin single-agent therapy.[5-7] This is in contrast to the findings observed with the combination of doxorubicin and paclitaxel (Taxol), as reported by Gianni et al[8] and Gehl et al,[9] who noted, respectively, that 18% and 20% of patients with metastatic breast cancer developed reversible congestive heart failure.

TAC for First-Line Therapy

Based on these preliminary data, our group performed a phase II trial to determine the antitumor activity and tolerability of Taxotere and Adriamycin with cyclophosphamide (TAC) as first-line therapy without prophylactic G-CSF support, in patients with metastatic breast cancer.[10] In addition to measuring response rate, duration of response, and time to progression, we were interested in confirming the favorable toxicity profile—in particular, the lack of cardiac side effects as reported previously[3,4] with the combination of docetaxel and doxorubicin.

The inclusion criteria for this study consisted of patients with bidimensionally measurable (80% of cases) or evaluable (20%) metastatic breast cancer who had received no prior chemotherapy for metastatic disease and were anthracycline naive. In addition, study participation was open to patients with a Karnofsky performance status of at least 60% and who had normal left ventricular ejection fractions on a multiple-gated acquisition scan at baseline.

The schema of treatment was doxorubicin, given at a dose of 50 mg/m² as an intravenous bolus over 3 to 5 minutes, followed by 500 mg/m² of cyclophosphamide, also as an intravenous bolus, and then 1-hour later, 75 mg/m² of docetaxel, administered as a 1-hour intravenous infusion. This cycle was repeated once every 3 weeks. Patients also received 500 mg of oral ciprofloxacin (Cipro) twice daily on days 5 through 15 of each cycle for prophylaxis against infection and 8 mg of dexamethasone twice daily for 3 days, beginning the day prior to chemotherapy. As mentioned previously, no prophylactic G-CSF was given in this trial.

Demographics and Treatment Discourse

Of 55 patients accrued in this trial, preliminary results are available for 52 patients. Median patient
age was 52 years (range: 33 to 70 years), with a good median Karnofsky performance status of 90% (range: 60% to 100%). A total of 31% of patients had received prior adjuvant chemotherapy, which consisted exclusively of cyclophosphamide, methotrexate, and fluorouracil (5-FU). The median number of organs involved by the disease was 3 (range: 1 to 6), with 3 or more organs involved in 52% of patients. Visceral disease was seen in 60% of cases (liver involvement: 32% of patients). Bone metastases were seen in 48% of patients.

To date, a total of 251 cycles are evaluable, with a median of 5 cycles per patient (range: 1 to 8). The median cumulative doses were 254 mg/m² (range: 49 to 419 mg/m²) for doxorubicin and 379 mg/m² (range: 75 to 617 mg/m²) for docetaxel. The relative dose intensity was .99 for doxorubicin and .98 for docetaxel.

**Antitumor Activity**

To date, 38 patients are evaluable for response. In 31 patients with measurable disease, the preliminary response rate is 80%, consisting of 2 complete responses and 23 partial responses (Table 1). The overall response rate, which included 7 patients with evaluable disease, was 74%. Overall, there were 3 cases of complete response and 25 cases of partial response. In addition, the objective response rate of this combination was consistent across sites of involvement: liver (83%), lung (76%), visceral disease (76%), and soft tissue (75%). The preliminary activity of this combination is similar to that seen with other docetaxel/doxorubicin combinations.[3]

**Tolerability**

A total of 49 patients were included in the preliminary safety evaluation. As expected with a combination regimen consisting of 3 myelosuppressive agents, grade 4 neutropenia was common, occurring in approximately 68% of the cycles and 96% of patients (Table 2). Febrile neutropenia, with or without sepsis, which appears to be a more clinically relevant indicator of toxicity, occurred in 24.5% of patients, but in only 5.5% of administered cycles. Similarly, grade 3 to 4 infections were noted in 4% of patients and .8% of cycles. Despite the high incidence of grade 4 neutropenia, the median absolute neutrophil count on day 21 of each cycle was greater than 2,000/mm³, which allowed for the continuation of treatment without delay and with high dose intensity. Interestingly, no grade 4 acute nonhematologic toxicities were noted. Grade 3 nonhematologic toxicities were infrequent and consisted primarily of nausea (8%), stomatitis (6%), and diarrhea (4%). Of the chronic nonhematologic toxicities, severe asthenia was noted in 10% of patients and severe fluid retention in 1%. The classical toxicities, such as fluid retention, hypersensitivity reactions, skin toxicity, and nail changes, seen with Taxotere alone were rarely seen with the TAC combination. This contrasts with the toxicity profile seen with 100 mg/m² of docetaxel in single-agent chemotherapy. One could hypothesize the existence of a partial threshold of toxicity between 75 and 100 mg/m² of docetaxel, which could favor the use of TAC.

Evaluation of cardiotoxicity was a primary endpoint in this study. There were no cases of congestive heart failure in the 35 patients who received doxorubicin as a median cumulative dose of less than 360 mg/m². Of the 14 patients who received a cumulative dose of more than 360 mg/m², 1 patient (2%) developed congestive heart failure, which occurred 60 days after completing the combination regimen. Overall, only 1 patient had an asymptomatic reduction of left ventricular ejection fraction on multiple-gated acquisition scan (Table 3).

The low incidence of clinical cardiotoxicity observed with the docetaxel/doxorubicin combination in this trial is consistent with the results from earlier phase I trials (Table 4).[3,11] These results suggest that the addition of docetaxel to doxorubicin does not appear to increase the incidence and severity of cardiotoxicity typically seen with doxorubicin used as a single-agent[12] or with the 5-FU/doxorubicin/cyclophosphamide regimen.[13] This contrasts with the apparent increase in congestive heart failure reported with the addition of paclitaxel to doxorubicin in patients with metastatic breast cancer.[8,9] Until further trials are performed, one can only speculate as to why there appears to be a difference between these two taxanes with respect to cardiotoxicity when combined with doxorubicin.

**Discussion**

The preliminary results from this trial demonstrate that the combination of 75 mg/m² of docetaxel, 50 mg/m² of doxorubicin, and 500 mg/m² cyclophosphamide as first-line chemotherapy is an active combination, with a response rate of 80% among patients with measurable metastatic breast cancer. Overall, the hematologic toxicity associated with this combination is acceptable, not dose-limiting, and easily manageable. The low incidence of febrile neutropenia by cycle (5.5%) observed with TAC is in contrast with the incidence observed by Kalla et al[3] (11.8%) and raises the issue related to the
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Potential role of prophylactic antibiotherapy in the context of this type of chemotherapy combination. No cytokines were used in this trial. The nonhematologic toxicities noted in this trial were usually mild, with only 8% of patients experiencing grade 3 nausea (no grade 3 vomiting), 6% grade 3 stomatitis, and 4% diarrhea. Severe asthenia was seen in 10% of patients. Docetaxel-specific toxicities (fluid retention, allergic reactions, and skin and nail changes) were not a clinical issue, with no reports of treatment discontinuation related to these effects.

The favorable extrahematologic toxicity profile of TAC chemotherapy leads to the hypothesis of a potential partial threshold of docetaxel-specific toxicities between doses of 75 mg/m², as in TAC, and the 100 mg/m² dose used in single-agent chemotherapy. This series also confirms the lack of added cardiac toxicity for the docetaxel/doxorubicin combination and is in sharp contrast with the data available with short-infusion paclitaxel plus doxorubicin (Table 4).[8,9] In these conditions, phase III trials are warranted to define further the potential role of TAC as first-line therapy as well as its use in the adjuvant setting in patients with metastatic breast cancer.

Future Directions

The promising results from the use of TAC as first-line treatment for metastatic breast cancer have led to the development of two phase III trials looking at this combination Taxotere/Adriamycin/Cyclophosphamide in the adjuvant setting. These trials are being conducted by the Breast Cancer International Research Group.

The first trial is a multicenter, randomized phase III study comparing 75 mg/m² of docetaxel in combination with 50 mg/m² of doxorubicin and 500 mg/m² of cyclophosphamide with 500 mg/m² of 5-FU, 50 mg/m² of doxorubicin, and 500 mg/m² of cyclophosphamide. Patients with operable breast cancer who have positive axillary nodes will be randomized to receive 1 of the 2 combinations for 6 cycles.

A second trial is addressing the role of high-dose chemotherapy following induction chemotherapy with TAC. This prospective, randomized phase III trial, which is being conducted in tandem with the previous trial, is designed to compare 6 cycles of TAC to 4 cycles of TAC followed by 1 cycle of high-dose chemotherapy. The patient population consists of operable breast cancer patients with 4 or more positive axillary nodes.

Finally, a separate group, known as the Breast European Adjuvant Studies Team, is conducting a randomized study based on the concept of sequential chemotherapy. Patients in this study will be randomized to receive doxorubicin followed by cyclophosphamide/methotrexate/5-FU, docetaxel plus doxorubicin followed by cyclophosphamide/methotrexate/5-FU, or doxorubicin followed by docetaxel followed by cyclophosphamide/methotrexate/5-FU.

The taxanes are a major entry in the armamentarium of medical therapy for breast cancer and will be recalled in the future as the new breast cancer drugs of the 1990s. Docetaxel appears to be the most promising of these agents. Further, docetaxel/doxorubicin-based combinations, such as the TAC regimen, are currently being compared in a randomized fashion with standard therapy in the first-line treatment setting of patients with metastatic breast cancer, and in the near future, the adjuvant setting. These studies will assess the real role of the taxanes in breast cancer and help define their potential for improving treatment.

References:


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