Treatment of Advanced Breast Cancer with Docetaxel and Gemcitabine with and without Human Granulocyte Colony-stimulating Factor

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ABSTRACT

Purpose: A multicenter Phase II trial was performed to investigate the efficacy and tolerance of combined docetaxel and gemcitabine ± recombinant human granulocyte colony-stimulating factor (G-CSF) in patients with metastatic breast cancer.

Patients and Methods: Fifty-two patients participated in this trial, 51 of whom are evaluable for response. Thirty-eight patients received this combination as first-line chemotherapy, and 14 patients received this combination as second-line chemotherapy, including 10 patients who had failed anthracyclines. Therapy consisted of 1500 mg/m² gemcitabine and 50 mg/m² docetaxel, both administered on days 1 and 15 every 4 weeks. Depending on the absolute neutrophil counts on the day of scheduled chemotherapeutic drug administration, a 5-day course of 5 µg/kg G-CSF was given.

Results: The overall response rate was 60.5% (95% confidence interval, 43.4–75.9%) in patients receiving docetaxel plus gemcitabine as first-line chemotherapy, including 4 complete responses (10.5%) and 19 partial remissions (50%); 9 patients (24%) had disease stabilization, and only 5 (13%) progressed. Second-line treatment with this regimen resulted in 6 of 14 (43%) objective responses, 5 had stable disease, and 3 progressive disease. The median time to progression was 8.5 months in the first-line setting and 6.6 months in the second-line setting, respectively. After a median follow-up time of 15 months, 36 patients (69%) are still alive with metastatic disease. Myelosuppression was commonly observed; WHO grade 3 or 4 neutropenia, however, occurred in only 15 (29%) patients and was complicated by septicemia in 2 cases; grade 3 anemia was seen in 1 patient (2%). Severe (grade 3) nonhematological toxicity except for alopecia was rarely observed and included nausea/vomiting in 3 (6%), stomatitis in 2 (4%), anaphylaxis in 2, and peripheral neuropathy, skin toxicity, and increase of liver enzymes each in one patient.

Conclusion: Our data suggest that docetaxel and gemcitabine with and without G-CSF is an effective and fairly well-tolerated regimen for the treatment of advanced breast cancer. It might be particularly useful in patients exposed previously to adjuvant or palliative anthracyclines and/or alkylating agents.

INTRODUCTION

Worldwide, breast cancer represents a major health problem, being responsible for 20% of cancer deaths in the Western world. Despite progress achieved in screening and management of early breast cancer including adjuvant treatment, 25–30% of patients with negative axillary lymph nodes and more than two-thirds of those with axillary node involvement at the time of diagnosis will have recurrent and/or metastatic disease within a decade after surgery and will subsequently die (1, 2).

Conventional combination chemotherapy has not been able to substantially change the natural history of advanced breast cancer, and current treatment approaches seem to have reached their maximum efficacy. The therapeutic value of available alternative treatment strategies, such as dose intensification or stem cell-supported, high-dose chemotherapy, remains uncertain (3, 4) or is spared for a selected group of patients (such as trastuzumab in those with primary tumors overexpressing HER2 receptors; Ref. 5). Therefore, the identification of new agents and/or drug combinations with a superior therapeutic index remains a principal goal of investigational efforts.

Among several different such promising new cytotoxic agents currently undergoing clinical evaluation in ABC is the novel nucleoside analogue of deoxyxycytidine gemcitabine, which possesses a broad range of activity against various solid tumors, and is characterized by a favorable toxicity profile (4–9). Used as single agent or in combination regimens, gemcitabine showed an objective response rate of 25–46% in ABC patients, depend-

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3 The abbreviations used are: ABC, advanced breast cancer; G-CSF, granulocyte-colony stimulating factor; ANC, absolute neutrophil count; CR, complete response; PR, partial response; PD, progressive disease.
ing on whether this drug was used as first- or second-line treatment (10–12).

Docetaxel is another novel anticancer agent of the taxane class that has also been demonstrated to be highly effective when given as a single agent or when combined with other drugs (13, 14). Docetaxel promotes tubulin assembly into microtubules, stabilizes microtubules, and inhibits depolymerization to free tubulin (14).

Favorable results have been reported recently when these two drugs were used in combination for the treatment of advanced non-small cell lung cancer (15, 16) and in two Phase II trials of chemorefractory ABC, yielding an objective response rate as high as 54% (17, 18).

The aim of the present study was to evaluate the antitumor activity and tolerance of gemcitabine plus docetaxel in previously untreated patients with ABC as well as in those who had failed one prior palliative chemotherapy regimen. To minimize acute toxicities and counteract myelosuppression that was likely to constitute the dose-limiting toxicity of this combination, we have decided to use a biweekly administration schedule (19–21); in addition, the hematopoietic growth factor G-CSF was given depending on absolute neutrophil counts on the day of treatment courses were repeated every 4 weeks and were to be continued in patients achieving CR, PR, or stabilization of disease for a total of six courses. To avoid fluid retention and/or anaphylactic reactions, patients were premedicated with 8 mg of dexamethasone p.o. taken the night before, morning of, and evening after treatment (total dose, 24 mg/week). In addition, 3 mg of granisetron was routinely administered before cytotoxic drug administration.

**Toxicity and Dosage Modification Guidelines.** Adverse reactions were evaluated according to WHO standard criteria (22). Treatment could be delayed for up to 2 weeks if the ANC was <1,000/µl and/or the platelet count was <75,000/µl. Prolonged administration of G-CSF was recommended in the former group of patients. Drug doses of both chemotherapeutic agents were reduced by 25% in case of febrile neutropenia grade 4, if the lowest platelet count was <25,000/µl, or any severe (≥WHO grade 3) nonhematological toxicity was observed in the previous cycle. A 25% dose reduction of docetaxel was effected in patients with grade 2 peripheral neuropathy. Patients experiencing ≥ grade 3 neurotoxicity were taken off the study, as were those who required >2 weeks for recovery of adverse reactions.

**Pretreatment and Follow-Up Evaluation.** Pretreatment evaluation included a complete medical history and physical examination with measurement of all tumor-associated lesions. Laboratory evaluation consisted of a complete blood count with platelet count and leukocyte differential count and an 18-function biochemical profile. Imaging procedures included chest X-ray, bone scan, skeleton bone survey, and computed tomographic scan of the abdomen. Complete blood cell counts and differential counts were performed weekly, and biochemical profiles were assessed before each treatment cycle. Tumor size was measured every 8 weeks by computed tomographic scan, X-ray, or any other technique that allows retrospective and independent reassessment.

**Assessment of Response.** The primary efficacy end point was response rate. A CR required the complete disappearance of all objective evidence of disease on two separate measurements at least 4 weeks apart. A PR was defined as a >50% reduction in the sum of the products of the perpendicular diameters of measurable bidimensional lesions without CR, no progression of any lesion by >25% or the appearance of any new lesion, confirmed on two separate measurements that were 4 weeks apart. In case of bone metastases, CR was attributed only when there was complete disappearance of all lesions on X-ray, and PR was attributed when decrease in size and/or calcification of lytic lesions occurred. Decreased density of blastic lesions or improvement in bone scan positive, X-ray negative disease were not taken into account. PD was defined as the enlargement of any existing measurable lesion by >25% or the development of new metastatic lesions. Stable disease was any measurement that did not fulfill the criteria for PR or PD. All tumor measurements in patients who responded were reviewed and confirmed by an independent panel of radiologists and oncologists. Secondary efficacy end points included the duration of response (measured from the onset of the best response to the date of disease progression), time to treatment failure (calculated from the start of treatment to the time of progression or relapse), and overall survival.

**PATIENTS AND METHODS**

**Patients Selection.** Patients eligible for this study had histologically confirmed metastatic breast cancer with documented progressive, bidimensionally measurable disease. All patients were required to be 75 years of age or younger, to have a WHO performance status of <3, an expected survival time of >12 weeks, and to have adequate bone marrow (ANC ≥2,000/µl and platelet count ≥100,000/µl), adequate renal (serum creatinine concentration <132 μmol), and adequate hepatic function (serum bilirubin level and serum transaminase level less than two times the upper limit of normal). Prior radiation therapy (with at least one target lesion outside the radiation port), prior hormonal therapy for advanced disease, and a maximum of one prior regimen of palliative chemotherapy were allowed. Prior therapy must have been completed at least 4 weeks before study entry with full resolution of toxicities. Adjuvant treatment was acceptable if the time interval between adjuvant therapy and the chemotherapy for metastatic disease was >1 year. All patients gave informed consent according to institutional regulations. Patients with osteoblastic bone lesions as the only site of disease, patients with central nervous system metastases, and those with a prior or second coexisting invasive malignancy were excluded.

**Treatment Protocol.** Chemotherapy consisted of 1500 mg/m² gemcitabine on days 1 + 15, followed by 50 mg/m² docetaxel on days 1 and 15, both diluted in 250 ml of saline and infused over 30 min (gemcitabine) or 1 h (docetaxel). When the ANC was 1,000 to 2,000 on the day of planned chemotherapeutic drug administration, to maintain dose intensity, a 5-day course of the hematopoietic growth factor G-CSF (5 μg/kg/day given s.c.) was to be started on the subsequent day. In patients experiencing neutropenia, G-CSF support was not continued routinely during subsequent courses; the decision was always dependent on actual ANC's. Treatment courses were repeated...
RESULTS

Statistical Methods. A response rate of 50% was believed to be of clinical interest, and patients were accrued in a two-stage design (23). If fewer than four responses were noted in the first 17 eligible patients, accrual would be halted. Because responses were observed, additional patients were enrolled to a final accrual of 52 women to better estimate efficacy and characterize the toxicity profile. This sample size was considered sufficient to estimate 95% confidence intervals for the true response rate with a maximum width of ~30%. For the response rates, 95% confidence intervals were calculated as described previously (24). The distribution of time to death from the date of study entry was estimated using the Kaplan-Meier product-limit method (25). All patients who were enrolled onto the study were included in the intent-to-treat analysis.

RESULTS

Patient Characteristics. Between July 1999 and November 2000, a total of 52 patients took part in this trial, all of whom were evaluable for toxicity assessment and 51 patients for response evaluation; 1 patient discontinued therapy early because of a severe anaphylactic reaction during the first treatment course. The demographic data, sites of metastatic tumor, and prior therapies are listed in Table 1. The median age was 60 years (range, 29–75 years), and the median WHO performance status was 1 (range, 0–2). Except for 21 patients, all had multiple metastases involving two or more organ systems with predominant visceral, bone, and soft tissue sites in 36, 9, and 7 patients, respectively. Adjuvant systemic treatment consisted of endocrine therapy in 11 patients and/or cytotoxic chemotherapy in 13 and 8 patients, respectively. The median time interval from initial diagnosis to relapse was 20 months (range, 0–276 months) for the entire study population. Fourteen patients had prior cytotoxic chemotherapy for metastatic disease, and 18 patients had palliative hormonal therapy. Fifteen patients underwent palliative radiation therapy for skeletal manifestations or soft-tissue lesions. Previous palliative chemotherapy consisted of cyclophosphamide/methotrexate/5-fluorouracil in 4 patients and anthracycline-containing regimens in 10 patients.

A total of 252 courses of study treatment were administered to the 52 patients. The median number of treatment cycle was 6 (range, 1–6), and the median duration of follow-up at the time of this analysis was 15 months (range, 7–24 months).

Response to Treatment. The overall response rate was 60.5% for patients who had not received prior chemotherapy for metastatic disease (95% confidence interval, 43.4–75.9%), including 4 complete (10.5%) and 19 partial remissions (50%); 9 patients (24%) had disease stabilization, and 5 (13%) progressed. Second-line treatment with this regimen resulted in 6 of 14 (43%) objective responses (1 CR and 5 PRs), 5 had stable disease, and 3 had tumor progression. The median time to progression was 8.5 months (range, 2.0–19+ months) in the first-line setting and 6.6 months (range, 2.0–19+ months) in the second-line setting (Table 2). After a median follow-up time of 15 months (range, 7–24 months), 36 patients (69%) are still alive with metastatic disease.

The predominant sites of tumor involvement in patients who experienced CR were visceral in 3 patients and soft-tissue and bone in 1 patient. Thirteen of 24 patients (54%) who achieved PR had multiple metastases with predominant visceral (58%), bone (17%), and soft tissue (25%) involvement. The previous palliative chemotherapy in those patients who experienced CR or PR included anthracyclines in 5 patients and cyclophosphamide/methotrexate/5-fluorouracil in 1 patient.

Toxicity. All 52 patients, who received a total of 252 courses, were assessable for toxicity. Side effects associated with treatment are listed in Tables 3 and 4. Myelosuppression was the most common adverse reaction, although according to
the ANC-adapted use of a hematopoietic growth factor, the time to WBC/ANC recovery was generally short; in 96%, episodes of leucopenia/neutropenia were resolved within 7 days. Administration of G-CSF because of ANCs of 1,000–2,000/µl on the day of scheduled chemotherapeutic drug administration, as indicated in the protocol, was effective in 44 patients (85%), most commonly on day 15 of the cycle. A total of 102 5-day courses of G-CSF were delivered, with most of the patients (93%) receiving fewer than 4 courses. Leukopenia occurred in 42 patients (81%) and was grade 3 or 4 in 8 cases (15%). Thrombocytopenia was rather uncommon (12%) and was only grade 1 or 2. Similarly, only 1 patient developed severe anemia requiring packed RBC transfusion, and 5 additional patients received recombinant human erythropoietin at a dose of 10,000 IU s.c. × 3/week; mild, asymptomatic anemia was recorded in 32 patients (61%). Six patients (12%) developed documented infection, and 2 of them required hospitalization for i.v. antibiotics.

Nonhematological side effects are listed in Table 4. Gastrointestinal symptoms were the most frequently encountered toxicities. Except for 3 patients (6%), nausea and vomiting was in general mild or moderate, however, confined to the day of drug administration, and responsive to standard antiemetic therapy. Stomatitis was noted in 16 patients (31%) including only 2 cases (4%) with WHO grade 3 symptoms. Mild to moderate diarrhea was seen in 10 patients (20%). Twenty patients (38%) developed peripheral neurotoxicity including 1 patient who experienced severe symptoms. Skin toxicities, including 1 severe reaction, were noted in 22 patients (42%), and a total of 17 patients (27%) experienced mild tearing. Alopecia occurred in 37 patients with complete hair loss in 18 (35%). Gemcitabine-associated increases of liver enzymes were noted in 16 patients (31%) including one severe reaction, and drug-related fever was observed in 10 patients (19%).

Treatment was discontinued prematurely in 7 cases because of anaphylactic reactions (n = 2), grade 3 peripheral neurotoxicity (n = 1), and 4 patients wanted early discontinuation for personal reasons after 4 or 5 courses, respectively. Ten patients (19%) had at least one treatment delay of 1 week at some time during therapy, and the total number of delayed courses was 18 (7%). The reasons for delayed courses were neutropenia in 6, nonhematological side effects in 2, both in 1 case, and personal reasons in 1. Nine patients had a 25% dose reduction of cytotoxic drugs during treatment according to the study protocol, because of febrile neutropenia (n = 3), WHO grade 3 stomatitis (n = 2), vomiting (n = 2), or grade 2 peripheral neurotoxicity (n = 2).

Dose intensity was calculated for each patient and for each drug. The mean given dose intensity of the combination was 95% of the projected dose with no difference between first-line (95%) and second-line (95%) patients. The mean dose of gemcitabine was 710 mg/m²/week (range, 510–750 mg/m²/week), and the mean dose of docetaxel was 23.6 mg/m²/week (range, 17–25 mg/m²/week).

**DISCUSSION**

Despite high response rates achieved with some anticancer drug combinations in the treatment of advanced breast cancer, overall survival is only marginally prolonged (3, 26–28). The role of chemotherapy in patients with disseminated disease thus remains palliation of symptoms and maintenance of quality of life. In view of a significant association between symptom improvement and objective tumor regression (29), ideally, high response rates should be achieved, but not at the expense of substantial adverse effects.

According to the continuing need for the development of active combinations with a favorable toxicity profile, particularly in patients with prior adjuvant or palliative anthracycline exposure, the present study was undertaken. The rationale for combining gemcitabine and docetaxel included: (a) their distinct mechanism of action with different intracellular targets; (b) high

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<th>Table 3</th>
<th>Highest grade of hematological toxicity experienced (n = 52)</th>
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<td>No. of patients (%) with toxic effects of WHO</td>
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<td></td>
<td>Grade 1</td>
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<tr>
<td>Leukocytopenia</td>
<td>16 (31%)</td>
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<tr>
<td>Neutropenia</td>
<td>6 (12%)</td>
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<td>Thrombocytopenia</td>
<td>4 (8%)</td>
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<td>Anemia</td>
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<th>Table 4</th>
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<td>No. of patients (%) with toxic effects of WHO</td>
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<td></td>
<td>Grade 1</td>
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<tr>
<td>Nausea/vomiting</td>
<td>16 (31%)</td>
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<td>Stomatitis</td>
<td>7 (13%)</td>
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<td>Diarrhea</td>
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<td>Alopecia</td>
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<td>Infection</td>
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<td>Phlebitis</td>
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<td>Neurotoxicity</td>
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<tr>
<td>Peripheral</td>
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<td>Central nervous system</td>
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<tr>
<td>Constipation</td>
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<td>Fatigue</td>
<td>22 (42%)</td>
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<td>Skin/nail alterations</td>
<td>17 (27%)</td>
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<td>Tearing</td>
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<td>Anorexia</td>
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<td>Peripheral edema</td>
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<td>Liver enzymes</td>
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<td>Fever (drug related)</td>
<td>2 (4%)</td>
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<tr>
<td>G-CSF-related fever/myalgias</td>
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levels of single activity of both drugs in ABC (8–14, 19–22); and (c) encouraging results of recently conducted Phase III trials evaluating this combination as second-line therapy in ABC (17, 18). A Greek trial investigated the combination of gemcitabine (800 mg/m² on days 1 and 8) and docetaxel (100 mg/m² on day 1 every 3 weeks) plus prophylactic G-CSF in anthracycline-pretreated patients and reported an overall response rate of 54% with a 1-year survival of 55% (17). The second trial examining this combination as second-line therapy in heavily pretreated patients was a small Phase II study with an overall response rate of 3 of 19 (16%), and 11 additional patients experienced stabilization of disease (18). Both authors reported an acceptable to favorable tolerance of treatment.

The present study is the first to report mature results on the efficacy of front-line chemotherapy in ABC with a combination of gemcitabine plus docetaxel. We have chosen a biweekly administration schedule, because for both drugs there is evidence that dose fractionation may allow dose intensification along with reduced hematological and nonhematological toxicity (8, 19–21). With an overall response rate of 60.5%, including 10.5% complete responses, and a median performance status of 8.5 months, our data suggest a significant antitumor activity of this drug regimen in chemotherapy-naïve patients with metastatic breast cancer. It seems noteworthy that the therapeutic effectiveness was not influenced by adverse prognostic factors such as visceral disease and multiple metastatic sites, both of which were present in about two-thirds of our patients. Clinical responses achieved were durable, and after a median follow-up duration of 15 months, more than two-thirds of the study population are still alive. A somewhat lower, although still notable, response activity of 43% was noted in our 14 patients failing previous palliative chemotherapy.

As it concerns the tolerance of treatment, neutropenia was the most frequent and dose-limiting side effect associated with this regimen. Despite realization of a higher dose intensity of gemcitabine (138%) and use of an almost equivalent dose intensity of docetaxel (89%) when compared with the above-mentioned Greek trial, WHO grade 4 or 5 neutropenia occurred in less than one-third (29%) of our patients. According to the ANC-adapted use of G-CSF, treatment delays for hematological reasons were required in only 6 patients, and there was also a particularly low incidence of febrile neutropenic episodes. Similarly, the rate of thrombocytopenia was very low (12%) with no grade 3 or 4 toxicity. The latter observation might be explained by: (a) the biweekly administration schedule of gemcitabine, which is known to be associated with a low incidence of hematological toxicities (8, 15, 30); and/or (b) the bone marrow-sparing effect of taxane-based combination regimens, such as described for docetaxel-gemcitabine (31) and paclitaxel-carboplatin (32) in patients with non-small cell lung cancer. Nonhematological toxicity, which usually interferes with quality of life, was generally mild and fully reversible in all patients. The most common adverse reactions included nausea/vomiting and stomatitis, although grade 3 symptoms occurred only in 3 and 2 patients, respectively. Significant hair loss, which is an important factor in female patients, was observed in only one-third of the study population, a finding which is likely to be related to the fractionated administration schedule of docetaxel.

In conclusion, the results of this trial indicate that biweekly gemcitabine and docetaxel and without G-CSF is an effective, safe, and well-tolerated first-line therapy for ABC. Its advantage over other commonly used and more intensive, equally effective regimens such as anthracyclines and taxanes or platinum-containing combinations seems to be its superior tolerance, particularly as it concerns the incidence of nausea and vomiting, complete alopecia, and/or hematological complications. These side effects of therapy are of significant subjective burden and represent important issues when discussing treatment options with patients. Results from this study suggest that the combination of gemcitabine plus docetaxel warrants further investigation in larger, randomized trials, including formal measurements of quality of life. In agreement with a previous Phase II investigation (17), this combination also seems to be of considerable interest in patients exposed previously to anthracyclines and/or alkylating agents.

REFERENCES


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