

## Multicenter Phase II Trial of First-line Docetaxel/ Gemcitabine in Advanced Breast Cancer Pretreated with Adjuvant Anthracyclines

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**Abstract.** *The aim of this study was to evaluate activity and tolerability of docetaxel-gemcitabine combination as first-line treatment in patients with metastatic breast cancer previously treated with adjuvant anthracyclines. Patients and Methods: Sixty-eight women received gemcitabine 1,000 mg/m<sup>2</sup> as 30-minute infusion on days 1 and 8, and docetaxel 80 mg/m<sup>2</sup> as 1-hour infusion on day 8, with cycles repeated every 3 weeks. Results: Objective responses were observed in 32 out of 68 evaluable patients (45%; 95% confidence interval, 35.2-58.8%). Responses were 44%, 42%, 49% in soft tissue, bone and visceral lesions, respectively, 50%/52% in HER2-positive/-negative tumors, and 50% in both ER- positive/-negative tumors. Median time to progression and overall survival were 6 and 16 months, respectively. Treatment was usually well tolerated, with grade 3-4 neutropenia in 32%-7% of the patients, and neutropenic fever, grade 3 vomiting, mucositis and peripheral neurotoxicity in 3% of the patients. Conclusion: Gemcitabine-docetaxel combination is effective and well tolerated as first-line treatment in advanced breast cancer previously treated with adjuvant anthracyclines.*

Anthracyclines and taxanes are the cytotoxic drugs affording the best therapeutic results in women with breast cancer, and an increasing number of patients receive anthracyclines as adjuvant chemotherapy, becoming resistant to these agents at

the time of relapse. Thus, newer taxane-based combinations are needed (1). Initial trials have reported that docetaxel is one of the most active drugs in advanced breast cancer, and several subsequent studies have confirmed its activity, both as single agent and in combination regimens (2).

Over the past years, several new drugs have become available for the management of metastatic breast cancer, including the deoxycytidine analogue gemcitabine (3). Its unique mechanism of action and its favourable toxicity profile prompted many investigators to develop gemcitabine in combination with a number of other cytotoxic drugs. *In vitro* data in lung, breast and gastric cancer cell lines, indicate that gemcitabine and docetaxel interact synergistically (4-6), which could result in an additive clinical effect when used in combination. Different schedules of docetaxel-gemcitabine combination have been evaluated in phase I trials (7, 8), and very encouraging results were later observed in a number of phase II trials, mostly in anthracycline-pretreated patients (9, 10).

In a previous study, the combination of gemcitabine, 1000 mg/m<sup>2</sup> on days 1 and 8, with docetaxel, 80 mg/m<sup>2</sup> on day 8, with cycles repeated every 3 weeks, as second-line treatment for advanced breast cancer in anthracycline-pretreated patients was investigated. The choice of administering docetaxel on day 8 was aimed at avoiding frequent dose reduction or omission because of neutropenia. Preliminary results were very encouraging (11) and it was important to test the activity of this combination in previously untreated patients, and to evaluate the treatment schedule in a larger patient population. Thus, a multicenter phase II trial of gemcitabine/docetaxel combination was carried out in patients with metastatic breast cancer relapsing after an anthracycline-containing adjuvant regimen.

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*Key Words:* Docetaxel, gemcitabine, advanced breast cancer.

**Patients and Methods**

Eligibility criteria included histologically confirmed breast carcinoma, an ECOG performance status  $\leq 2$ , measurable or evaluable disease, an adequate bone marrow (absolute neutrophil count  $\geq 1,500/\text{mL}$ , platelet count  $\geq 100,000/\text{mL}$ , and hemoglobin  $\geq 11\text{ g/dL}$ ) renal and liver (total bilirubin and creatinine  $< 1.25$  times the upper normal limit) function, and a normal cardiac function. All of the patients had to have received an adjuvant regimen including an anthracycline. No previous chemotherapy for advanced disease was allowed. Exclusion criteria were pre-existent neuropathy, a history of other malignancies, symptomatic brain metastasis, and previous exposure to gemcitabine and/or docetaxel. Supportive treatment was at the discretion of the investigators.

The protocol was approved by the Ethics Committees of the participant institutions, was carried out according to the Declaration of Helsinki, and all patients gave their written informed consent to participate in the trial.

Treatment consisted of gemcitabine of  $1,000\text{ mg/m}^2$  as a 30-minute infusion on days 1 and 8, and docetaxel  $80\text{ mg/m}^2$  as a 1-h infusion on day 8, with cycles repeated every 3 weeks, without prophylactic granulocyte-colony stimulating factor (G-CSF) support. Antiemetic treatment consisted of an antiserotonin agent plus dexamethasone in a 15-min infusion before starting chemotherapy. Standard premedication for docetaxel was delivered.

Treatment was postponed by a maximum of two weeks if the absolute neutrophil count was  $< 1,500/\mu\text{L}$ , or the platelet count was  $\leq 100,000$  on day 21; a 25% drug dose reduction and the use of G-CSF were planned in cases of grade 4 neutropenic fever (absolute granulocyte count  $< 500/\mu\text{L}$  at the time of a documented temperature of  $38^\circ\text{C}$  (or higher)). A 25% dose reduction was also planned in cases of grade 3 mucositis or grade 3 neurotoxicity. In cases of grade 4 mucositis or neurotoxicity, treatment was discontinued.

Treatment was administered for a maximum of twelve cycles and was discontinued in cases of unacceptable toxicity, treatment delay longer than 2 weeks, disease progression, or patient refusal.

Pretreatment evaluation included clinical history and physical examination, automated blood cell count, biochemical profile, chest x-ray, liver ultrasound or computed tomography (CT) scan, bone scan and electrocardiogram (ECG). Blood counts were obtained weekly; the biochemical profile was repeated every 3 weeks. All measurable or evaluable disease parameters were re-evaluated every 3 cycles, and every 3 months during the follow-up period.

Responses were evaluated every 3 cycles of treatment by at least two observers. The RECIST criteria were used to evaluate clinical response (12), and all objective responses were confirmed at least 4 weeks after the initial documentation of response. Responses were evaluated according to hormonal receptor status and HER2 status, measured on primary tumors. Time to progression and overall survival were calculated starting from the beginning of treatment to the date of disease progression and death or last follow-up evaluation, respectively. Toxicity was assessed in each treatment cycle by the National Cancer Institute Common Toxicity Criteria, version 3.0 (13).

The primary end-point of this study was to estimate the overall response rate of the regimen. The optimal Simon's two-stage phase II design was used to determine the sample size. An interim analysis was carried out when the first 27 assessable patients had been recruited. If more than 17 responses were

Table I. Patient characteristics.

Characteristic	No. of patients
Entered/evaluable	68/64
Median age, years (range)	59 (30-71)
Median ECOG PS (range)	1 (0-2)
Pre/postmenopausal	18/50
ER status: positive/negative/unknown	40/24/4
HER2 status: positive/negative/unknown	15/45/8
Disease free-interval (years)	
<1	10
1-5	41
>5	17
Prior adjuvant anthracyclines	68
Prior hormonal treatment (adjuvant/advanced)	31/15
Dominant disease site	
Viscera	47
Bone	12
Soft tissue	9
No. of metastatic sites	
1	25
2	35
3	8

observed, 40 additional patients were to be recruited; otherwise, the study was to be terminated. If more than 46 responses were observed in the 67 patients, the regimen was considered sufficiently active with a significance level of 5% and power of 80% to be submitted for further evaluation. Secondary end-points, time to progression and overall survival, were assessed using the Kaplan-Meier method.

**Results**

From July 2002 to February 2004, 68 patients with advanced breast cancer were enrolled by 4 Italian oncology centers of the Gruppo Oncologico Italia Meridionale (GOIM). Four patients were not assessable for response, 2 of them because of severe anaphylactic reaction to the first docetaxel infusion, one patient refused further treatment after the first cycle, and another one was lost to follow-up after the second cycle. All patients were evaluable for toxicity.

The main patient characteristics are outlined in Table I. All of the patients had been previously treated with anthracyclines as adjuvant treatment, none of them had previously received any chemotherapy for advanced disease, and none had previously received docetaxel or gemcitabine. Thirty-one patients had had adjuvant hormonal treatment and 15 patients had been treated with endocrine treatment for metastatic disease. Sixty-nine percent of the enrolled patients had visceral disease. Some biological characteristics of the primary tumors are also reported in Table I.

As an intent-to-treat analysis on all 68 enrolled patients, the response rate was 47% (95% confidence interval (CI), 35.2-58.8%). Among 64 evaluable patients, 5 complete

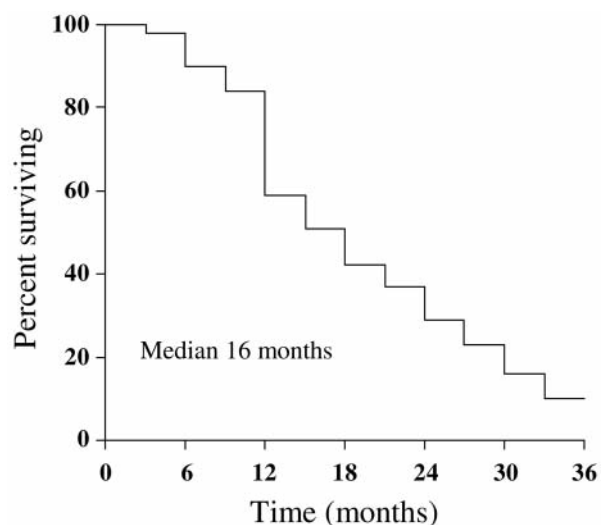


Figure 1. Overall survival for all patients.

responses (8%) and 27 partial responses (42%) were observed, for an overall response rate of 50% (95% CI, 37.75-62.25%). Disease remained stable in 12 patients (19%). Responses by site were 44% in soft tissue, 42% in bone and 49% in visceral lesions; and 54% in one, 48.5% in two, 43% in three disease sites. The activity of the regimen was similar in HER2-positive and -negative tumors, with response rates of 50% and 52%, respectively. The response rate was 50% both in ER-positive and ER-negative tumors.

The median number of cycles administered was 7 (range, 1 to 12 cycles). The median time to progression was 6 months (95% CI, 4-7 months) and median overall survival was 16 months (95% CI, 12-19.8 months) (Figure 1).

The main toxicities are reported in Table II. Among 68 evaluable patients, hematological toxicity was usually manageable, with G4 neutropenia occurring only in 7% of the patients; G3 neutropenia was encountered in 32% of the patients, whereas neutropenic fever occurred only in 3% of the cases. Grade 3 thrombocytopenia and anemia were reported in 3% of the patients. Extrahematological toxicity was usually mild, including nausea/vomiting and mucositis in 18% of the patients. Grade 3 peripheral neurotoxicity was observed in only 3% of the patients. Five patients (7%) experienced G3 asthenia. Transient hypertransaminitis was encountered in 6% of the cases, and mild and transient fluid retention in 3% of the patients. Five patients (7%) experienced hypersensitivity reactions, and in two of them treatment was discontinued. A 25% dose-reduction was required in 6 (9%) patients, whereas treatment was postponed for a maximum of two weeks in 4 (6%) patients. No clinical cardiac toxicity nor toxic deaths were observed.

Table II. Main toxicities in 68 patients (%).

Toxicity	NCI-CTC grade		
	1/2	3	4
Neutropenia*	61	32	7
Anemia	56	3	-
Thrombocytopenia	10	3	-
Nausea/vomiting	18	3	-
Mucositis	18	3	-
Diarrhea	3	-	-
Neurotoxicity	6	3	-
Fluid retention	3	-	-
Asthenia	44	7	-

\*Neutropenic fever: 2 patients (3%).

## Discussion

Over the past several years, anthracyclines and taxanes have been used earlier in the course of treatment for advanced breast cancer and, increasingly, as a part of adjuvant treatment. Accordingly, novel and more effective therapies are required to treat patients with prior exposure to anthracyclines.

In a previous study with the same dosages and schedule of the present study, a relatively high response rate was shown with the combination of docetaxel and gemcitabine as salvage treatment in anthracycline-pretreated patients (11, 14). In the present study, when this combination was used as first-line treatment, the response rate was 50%. This is noteworthy, since about 70% of patients had visceral disease, mostly located in the liver. All disease sites responded to treatment, even if the small sample size precludes any firm conclusion about the relative occurrence of responses according to sites of disease. In this study, no differences in response rates between HER2-positive or -negative, and ER-positive or -negative tumors were observed, perhaps due to the small sample size. However, this is not in contrast with other reports, indicating conflicting results about the predictive value of these markers (15).

As expected, the main toxicity was myelosuppression, with neutropenia occurring in most patients. Nevertheless, neutropenic fever was observed only in two patients. Among non-hematological toxic effects, nausea/vomiting and mucositis were more frequently encountered. Overall, toxicity was manageable and compared favourably with that of other taxane-based regimens not including an anthracycline (16, 17).

In addition to standard three-weekly regimens, recent phase II trials have focused on optimizing doses and schedules using a biweekly or weekly administration. The biweekly schedule has been tested in three phase II trials, showing objective responses in 60.5%, 59% and 75% of previously untreated

patients, with a slightly higher hematological toxicity in comparison to the present schedule (16-18). The weekly schedule was evaluated in two studies, with an overall response rate of 64% and 33% , and manageable toxicity (19). However, in all the above studies, only a portion of the patients had been previously treated with adjuvant anthracyclines. Recently, a European randomized phase III trial in anthracycline pretreated patients evaluating a gemcitabine-docetaxel *versus* capecitabine-docetaxel regimen, showed comparable efficacy (27% *vs.* 31%), but lower toxicity in the gemcitabine-docetaxel arm (20).

Taxane-based combinations not including anthracyclines have been extensively evaluated in several other studies. A phase III randomized trial of docetaxel-capecitabine compared with single agent docetaxel showed a more favourable response rate, time to progression and overall survival in the combination arm (21); recently, a large phase III trial of 3-weekly paclitaxel *versus* gemcitabine plus paclitaxel yielded superior results in the combination arm (22), confirming the activity of taxane-based combinations *versus* single agent regimens.

A recent report from the Hellenic Cooperative Oncology Group showed a similar response rate but a shorter survival for the gemcitabine/docetaxel arm in comparison to weekly paclitaxel, but about half of the patients had never received adjuvant chemotherapy, and anthracycline-containing adjuvant regimens had been employed in about one third of the entire population (23)

At present, doubts still exist on which taxane should be preferred in combination with gemcitabine, since no head-to-head comparison between docetaxel-gemcitabine and paclitaxel-gemcitabine has been performed. Preliminary results of a phase II randomized trial showed similar response rates and toxicity profiles (24).

With the exception of hormonal receptor and HER2 status, up to now clinical decision-making has been driven by established clinical and pathological criteria, chemotherapy generally being chosen on an empirical basis. In the last few years, several efforts have been made in an attempt to identify molecular predictors of response to anticancer drugs. In the adjuvant setting, gene expression profile was related to a highly accurate prediction of pCR to a combination therapy containing gemcitabine, epirubicin and docetaxel (25). In other studies, it has been used to predict responses to single agent docetaxel (26, 27). Although the results obtained are quite promising, only limited experience is available as a guide for selecting treatment in advanced disease.

Until the advent of more "tailored" treatments in advanced breast cancer, the choice of chemotherapy remains substantially empirical, and effective and well-tolerated regimens, such as the combination of docetaxel and gemcitabine, may be of value in relieving symptoms and

prolonging time to progression. Moreover, the efficacy of this combination may hopefully be further increased by adding molecularly targeted agents.

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Received September 18, 2008

Revised December 2, 2008

Accepted February 25, 2009