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ORIGINAL ARTICLE

A phase I trial of gemcitabine, docetaxel and carboplatin administered every 2 weeks as first line treatment in patients with advanced breast cancer

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Abstract
Objective To determine the maximum tolerated doses (MTDs) and dose limiting toxicities (DLTs) of gemcitabine (GEM), docetaxel (DOC) and carboplatin (CARBO) combination.
Patients and methods A total of 33 previously untreated HER-2 negative patients with stage IIIB-IV breast cancer received escalated doses of GEM, DOC and CARBO all given sequentially on day 1 every 2 weeks. Twenty-three patients (70%) had previously received adjuvant or neoadjuvant chemotherapy.
Results The recommended MTDs are GEM 1,500 mg/m^2, DOC 50 mg/m^2 and CARBO 3AUC. Seven dose levels were evaluated and neutropenia was the primary dose-limiting event. Of 319 chemotherapy cycles delivered, grade 3–4 neutropenia occurred in 13.5% of them with two cases of febrile neutropenia. Diarrhea and asthenia were the most common non-hematological toxicities. Three (16%) complete and 6 (32%) partial responses were observed among 19 patients with measurable disease.
Conclusion The biweekly administration of GEM, DOC and CARBO is a well-tolerated regimen which merits further evaluation.

Keywords Gemcitabine · Docetaxel · Carboplatin · Chemotherapy · Breast cancer

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Introduction

Since metastatic breast cancer (MBC) remains an incurable disease that can only temporarily be controlled with endocrine therapy or chemotherapy, palliation of symptoms and prolongation of good quality life become the major therapeutic goals in the treatment of these patients [1]. Combination chemotherapy regimens for metastatic disease usually result in 35–75% objective responses as first line treatment with an average duration of response of about 8 months, depending on patient selection and type of regimen used [2].

Docetaxel has impressive single-agent activity in MBC producing an objective response rate of 59% as first line, 49% as second line treatment [3] and 41% in patients with anthracycline-resistant disease [4]. Its primary toxicity is dose-dependent and consists of short-duration myelosuppression (mainly neutropenia) [5]. Gemcitabine is also an active drug in MBC with response rates as single agent of 25–46%, depending on patient selection and dose administered, and has acceptable toxicity profile with mild myelosuppression and minimal nonhematological toxicity [6, 7]. In general, gemcitabine's favorable single-agent activity and novel mechanism of action, in addition to its largely mild to moderate toxicities, have facilitated its combination with a variety of chemotherapy agents, including taxanes [8, 9]. Carboplatin has a more favorable toxicity profile than cisplatin and has shown moderate activity in MBC with an overall response rate of 31% in chemotherapy-naïve and only 7% in pretreated patients [10]. Nevertheless, the combination of docetaxel with cisplatin produced high response rates (36–52%) including a number of complete responses in patients with anthracycline-resistant MBC [11].

Two phase II studies were conducted by the Hellenic Oncology Research Group using the docetaxel plus gemcitabine combination in pretreated and in chemotherapy-

naïve women with MBC, respectively [12, 13]. In both studies, the regimen was well tolerated and highly active. Following our initial report, the activity of the combination in pretreated patients with MBC has also been confirmed by other investigators [14–17]. Furthermore, in another study we found the docetaxel and carboplatin combination to be active in women with anthracycline-resistant MBC who received this regimen as salvage treatment [18].

The issue concerning combination versus single-agent sequential chemotherapy in MBC remains uncertain. Combination treatment is associated with an increased response rate, longer time to disease progression and symptom improvement, but improved survival was shown in some [19, 20] but not all trials [21]. Since there is no clear answer to the question of single-agent versus combination chemotherapy, at the present time there is no standard "optimal" chemotherapy for MBC. Treatment selection should be aimed at achieving the best balance between efficacy and toxicity. Therefore, in the light of better response, combination treatment could be an option especially for symptomatic patients [22]. Furthermore, based on recent data questioning the role of anthracyclines in HER2 non-overexpressing breast cancer [23], there is still a need to develop non-anthracycline combination regimens.

Based on the above rationale and the encouraging data from previous studies, we conducted a phase I trial to determine the maximum tolerated doses (MTDs) and dose limiting toxicities (DLTs) of gemcitabine (GEM), docetaxel (DOC) and carboplatin (CARBO) combination administered biweekly as first line treatment in patients with ABC.

Patients and methods

Patient selection

Patients with histologically or cytologically confirmed HER-2 negative advanced breast cancer, who had not received prior chemotherapy for metastatic disease, were enrolled onto the study. Prior adjuvant and/or neoadjuvant chemotherapy was allowed, if completed at least 1 year before entering the study. Hormone treatment or radiotherapy (to <25% of active bone marrow) was allowed with a treatment-free interval of at least 4 weeks.

Other inclusion criteria were as follows: age 18–75 years, a World Health Organization (WHO) performance status of 0–2, a life expectancy of at least 3 months, an adequate bone marrow (absolute neutrophil count > 1,500/dL, Hb > 10 g/dL, platelets > 100.000/dL), renal (serum creatinine < 1.5 mg/dL) and liver (total bilirubin < 1.5 mg/dL and SGOT/SGPT < 2 times the upper normal values) function. Absence of an active infection or severe malnutrition (loss > 20% of the body weight during the preceding 3 months) and absence of any psychiatric or social condition potentially hampering compliance with the study protocol. Patients with brain metastases were allowed to participate if they had been irradiated with clinical and/or radiographic improvement, while patients with prior history of congestive heart failure or active and uncontrolled coronary artery disease were not eligible. The presence of measurable disease by RECIST criteria was not required. All patients gave their written informed consent to participate in the study which has been approved by the Ethics and Scientific Committees of our Institution.

Treatment plan

Escalated doses of GEM (Gemzar; Eli Lilly, Indianapolis, Ind., USA) (starting dose: 1,000 mg/m^2 with increments of 500 mg/m^2) were administered as a 30-min intravenous (i.v.) infusion followed by DOC (Taxotere; Aventis Pharma, Bridgewater, NJ, USA) (starting dose 35 mg/m^2 with increments of 5 mg/m^2) as an 1-h i.v. infusion and followed by CARBO (Carboplatin; Bristol-Meyers Squibb, Co., Princeton, NJ, USA) (starting dose: 2AUC with increments of 1AUC) as 90-min i.v. infusion. All drugs were administered sequentially on day 1 and the regimen was repeated every 2 weeks without growth factor support. Premedication for DOC consisted of dexamethasone 6 mg orally 12 h and 1 h before treatment, ranitidine 300 mg i.v. and diphenhydramine 50 mg i.v. 30 min before treatment. Patients also received dexamethasone 3 mg orally every 12 h for the first 2 days post chemotherapy. The prophylactic anti-emetic regimen also included ondansetron 16 mg given i.v. 30 min before chemotherapy. The treatment was administered on scheduled days if the absolute neutrophil count was >1,500/dL, platelets > 100,000/dL, and all the other toxicities had resolved to ≤grade 1. Otherwise, treatment was postponed until the resolution of all toxicities and, then, was restarted with dose reduction at the previous dose level. Doses were also reduced at the previous dose level in case of grade 4 neutropenia or thrombocytopenia, febrile neutropenia or platelet transfusion. In case of repeated grade 4 hematological toxicity, an additional dose reduction by 20% for all drugs was implemented. Patients requiring more than 2 weeks treatment delay for any reason or experiencing grade 3–4 non-hematological toxicity (except for nausea, vomiting) were withdrawn from the study. Patients continued treatment until prohibitive toxicity, disease progression, completion of maximum 12 treatment cycles or withdrawal of consent.

Dose escalation

The following dose levels (mg/m^2) for the GEM/DOC/CARBO combination have been evaluated: 1000/35/2AUC, 1000/40/2AUC, 1000/45/2AUC, 1000/50/2AUC, 1500/50/

2AUC, 1500/50/3AUC and 1500/55/3AUC. The AUC for the carboplatin dose was calculated using the Calvert formula. No intrapatient dose escalation was allowed. At least three patients were enrolled at each dose level. If dose limiting toxicity (DLT) was observed in one of the three patients, three additional patients were treated with the same doses. Although toxicity was assessed during all cycles of treatment, the DLT which was used to decide when to proceed with further dose escalation at the next dose level was assessed during the first chemotherapy cycle (the first 14 days). The DLT was defined as the occurrence of any of the following: grade 4 neutropenia or thrombocytopenia, febrile neutropenia, any grade ≥ 3 non-hematological toxicity except for nausea/vomiting and any treatment delay on day 15 due to unresolved hematological or non-hematological toxicity. If 50% or more of the patients at a certain dose level experienced DLT, the study was completed and the MTD dose level, which is recommended for further phase II studies, was the previous level before the DLT dose level.

Patients' evaluation

Baseline evaluation included patient history, physical examination, complete blood count with differential and platelet count, serum chemistry, measurement of tumor markers CEA and Ca 15–3, chest X-rays, electrocardiogram (ECG), thoracic and abdominal computed tomography (CT) scans and whole body bone scintigraphy. Complete blood counts were performed weekly for all patients or in case of grade 3–4 hematological toxicity daily until recovery. Serum chemistry as well as a detailed toxicity questionnaire and a physical examination were performed before each treatment administration. Disease status was assessed every four cycles or earlier in case of clinical evidence of disease progression. Toxicities were graded according to the National Cancer Institute (NCI) Common Toxicity Criteria version 3.0 and evaluation of response was performed according to RECIST criteria [24]. All patients receiving at least one cycle of treatment were evaluable for toxicity and patients receiving at least four chemotherapy cycles were evaluable for response. After treatment, patients were followed monthly until disease progression by physical examination, blood tests, serum tumor markers, and any other test that the responsible physician considered appropriate for disease evaluation.

Results

Patients' demographics

From January 2004 to March 2007, 33 patients with ABC were enrolled in the study. All patients were evaluable for toxicity. Median age was 62 years, the performance status (WHO) was 0–1 in 94% of patients, and 23 (70%) of them had previously received adjuvant or neoadjuvant chemotherapy which included docetaxel in eight of them. Patients' characteristics are shown in Table 1.

Table 1 Patients' characteristics

	No. of patients	(%)
Patients enrolled	33	
Evaluable for toxicity	33	
Evaluable for response	19	
Age		
Median (range)	62 (34–75)	
Menopausal status		
Premenopausal	5	15
Postmenopausal	28	85
Stage		
IIIB	4	12
IV	29	88
Performance status (WHO)		
0	15	45.5
1	16	48.5
2	2	6
Hormone receptors		
ER+/PR+	13	39.5
ER+/PR−	5	15
ER−/PR−	13	39.5
Unknown	2	6
Previous treatment		
Surgery	30	91
Adjuvant/neoadjuvant CT	23	70
Anthracycline-based	8	
Taxane-based	1	
Anthracycline/taxane based	7	
Other	7	
RT	17	51.5
None	3	9

Dose-limiting toxicities

The administration of the three drugs every 14 days was considered as one cycle of treatment. Table 2 shows the dose escalation levels, the number of patients enrolled at each dose level and the observed DLTs during the first cycle of treatment. The main toxicity observed during the first chemotherapy cycle was neutropenia; indeed, four patients developed grade 4 and three patients grade 2 ($n = 2$ patients) and grade 3 ($n = 1$ patient) neutropenia leading to treatment delay on day 15. An additional patient at dose level V developed grade 4 anemia which was considered as

Table 2 Dose escalation levels, number of patients enrolled at each level and DLTs observed during the first cycle of treatment

Dose level	GEM (mg/m^2)	DOC (mg/m^2)	CARBO (AUC)	Patients enrolled	DLT (number of patients)
1	1,000	35	2	3	–
2	1,000	40	2	6	Grade II neutropenia (1)[a]
3	1,000	45	2	3	–
4	1,000	50	2	3	–
5	1,500	50	2	6	Grade IV neutropenia (1) Grade IV anemia (1)[a]
6	1,500	50	3	6	Grade IV neutropenia (1) Grade III neutropenia (1)[a]
7	1,500	55	3	6	Grade IV neutropenia (2) Grade II neutropenia (1)[a]

[a] Was considered DLT because it resulted in treatment delay

Table 3 Cycles of chemotherapy complicated by grade 2–4 hematological and non-hematological toxicities

Dose level	Cycles	Neutropenia grade 2/3/4	Anemia grade 2/3/4	Trombocytopenia grade 2/3/4	Nausea/vomiting grade 2/3/4	Diarrhea grade 2/3/4	Mucositis grade 2/3/4	Neurotoxicity grade 2/3/4	Asthenia grade 2/3/4
1			4/–/–	1/–/1	2/–/–	2/–/–	–/–/–	–/–/–	3/–/–
2	56	3/1/–	1/–/–	1/–/–	9/–/–	–/–/–	–/–/–	7/–/–	7/–/–
3	14	1/2/2	1/–/–	4/–/1	2/–/–	1/–/–	–/–/–	–/–/–	1/–/–
4	31	5/5/–	–/–/–	–/–/–	–/–/–	–/3/–	–/–/–	–/–/–	8/–/–
5	56	2/2/1	6/–/1	–/–/–	–/–/–	–/–/–	–/–/–	–/–/–	8/1/–
6	67	7/9/4	10/–/–	1/–/–	–/–/–	1/–/1	2/–/–	–/–/–	13/–/–
7	67	6/6/7	3/–/–	2/–/1	1/–/–	–/–/–	–/–/–	2/–/–	6/–/–

DLT because it resulted in treatment delay. There was no case of febrile neutropenia during the first cycle. At the dose level VII, three out of six patients developed DLTs (two patients grade 4 neutropenia and one patient treatment delay because of grade 2 neutropenia), and therefore, this was considered as the DLT level. The MTDs which are the doses recommended for future phase II studies were GEM 1,500 mg/m^2 followed by DOC 50 mg/m^2 and CARBO 3AUC administered sequentially on the same day every 2 weeks, without growth factor support (Table 2).

Hematological and non-hematological toxicities

A total of 319 chemotherapy cycles were administered with a median of 11 cycles/patient (range, 2–12). The median duration of cycle per patient was 16 days (range, 14–20). Forty-eight (15%) cycles were delayed, because of hematological toxicity ($n = 17$ cycles; 5.3%) and late admission for reasons unrelated to the disease or treatment ($n = 31$; 9.7%). Table 3 shows the number of chemotherapy cycles complicated with grade 2–4 toxicities and Table 4 shows the worst grade 2–4 hematological and non-hematological toxicities per patient by dose-level, during all cycles. No treatment-related deaths were observed. Overall, the hematological toxicity of the regimen was acceptable since 28 (9%) and 15 (5%) cycles out of the 319 administered were complicated with grade 3 and 4 neutropenia, respectively. This corresponds to 12 (36%) and 11 (33%) patients, respectively. There were two cases of febrile neutropenia at the dose levels IV and V. One patient, at the dose level V, developed grade 4 anemia and another three, at the dose levels I, III and VII, respectively, developed grade 4 thrombocytopenia. No grade 3 anemia or thrombocytopenia was observed (Table 4). The most severe non-hematological toxicities were grade 2–3 asthenia complicating 14.7% of the cycles and grade 2–4 diarrhea complicating 2.5% of the cycles; other non-hematological toxicities were rare (<5% of cycles) and mild (≤grade 2; Table 3). Due to the toxicities observed, 48 (15%) of the treatment cycles were delayed and 18 (5.7%) were administered with a dose reduction. All patients have discontinued treatment for the following reasons: progressive disease ($n = 9$ patients), completion of treatment ($n = 17$ patients), consent withdrawn ($n = 1$ patient), neutropenia ($n = 2$ patients) and other reasons unrelated to treatment ($n = 4$ patients).

Response to treatment

Of the 33 patients enrolled in this study, only 19 patients had measurable disease and were evaluable for response.

Table 4 Worst (grade 2–4) hematological and non-hematological toxicities per patient during all cycles

Dose level	Patients	Neutropenia grade 2/3/4	Anemia grade 2/3/4	Trombocytopenia grade 2/3/4	Nausea/vomiting grade 2/3/4	Diarrhea grade 2/3/4	Mucositis grade 2/3/4	Neurotoxicity grade 2/3/4	Asthenia grade 2/3/4
1	3	1/–/1	1/–/–	–/–/1	1/–/–	1/–/–	–/–/–	–/–/–	–/–/–
2	6	1/2/–	2/–/–	1/–/–	4/–/–	–/–/–	–/–/–	1/–/–	3/–/–
3	3	–/1/2	1/–/–	1/–/1	2/–/–	1/–/–	–/–/–	–/–/–	1/–/–
4	3	–/3/–	–/–/–	–/–/–	–/–/–	–/1/–	–/–/–	–/–/–	1/–/–
5	6	–/2/1	1/–/1	–/–/–	–/–/–	–/–/–	–/–/–	–/–/–	2/1/–
6	6	–/2/4	4/–/–	1/–/–	–/–/–	–/–/1	1/–/–	–/–/–	4/–/–
7	6	–/2/3	2/–/–	–/–/1	1/–/–	–/–/–	–/–/–	1/–/–	2/–/–

Three patients achieved a complete and six patients a partial response (overall response rate 47.4%). Seven patients (36.8%) had stable disease. The median duration of response was 3.5 months (range 2.5–13.8) and the median time to tumor progression for the whole group of patients ($n = 33$) was 14.9 months (range 1.0–50.6).

The three complete responses were observed at dose levels 5 ($n = 1$) and 6 ($n = 2$), while the six partial responses were observed at dose levels 1 ($n = 1$), 2 ($n = 1$), 4 ($n = 1$), 6 ($n = 2$) and 7 ($n = 1$), respectively.

Discussion

Despite the recent progress in the adjuvant treatment, about one-third of patients with early breast cancer and no axillary lymph node involvement and two-thirds of those with positive lymph nodes will relapse within 10 years from surgery and eventually die of metastatic disease [25]. The taxanes, and especially docetaxel, have been shown to be non-crossresistant with anthracyclines, and therefore, effective in the treatment of these patients [26, 27]. However, the increasing use of anthracyclines in the adjuvant setting mandates the development of non-anthracycline-containing, taxane-based regimens for treating patients when metastatic relapse occurs.

The combination of docetaxel with gemcitabine represents an attractive regimen for clinical use due to the predictable and favorable toxicity profile that lacks cardiotoxicity and avoids severe myelosuppression [12]. Moreover, the sequence of administration with gemcitabine preceding docetaxel was shown to result in superior synergy and less toxicity [28]. Clinical experience with the combination from several studies showed high activity in patients with ABC, even among the heavily pretreated ones [12–17]. Moreover, the biweekly administration schedule which has been proved to be feasible and less toxic, allows significant dose escalation for both agents [29]. We have already demonstrated that the biweekly docetaxel-gemcitabine combination regimen is active and well-tolerated as first-line treatment for patients with ABC [13]. Additionally, the combination of docetaxel with carboplatin is an active salvage regimen for the treatment of women with ABC relapsing or not responding to anthracycline-based front-line therapy [18].

In response to the need of developing effective and safe taxane-based combination regimens that can be easily administered in an out-patient setting, we conducted this phase I trial to evaluate the gemcitabine, docetaxel, and carboplatin combination as first-line treatment in patients with ABC. Due to its high activity in MBC, emphasis was given primarily to the dose escalation of the docetaxel dose. Overall, the toxicity of the regimen was manageable. Indeed, grade 3–4 neutropenia and febrile neutropenia were the main hematological toxicities occurring in 70 and 6% of the patients, respectively. However, there were no toxic deaths due to myelosuppression or sepsis. It is noteworthy that severe thrombocytopenia was uncommon with the gemcitabine/docetaxel/carboplatin combination, since grade 3–4 occurred in three (9%) patients. Non-hematological toxicities were mild with the most common ones being diarrhea and asthenia. Accordingly, the recommended doses for future phase II studies were GEM 1,500 mg/m^2 followed by DOC 50 mg/m^2 and CARBO 3AUC administered sequentially on the same day every 2 weeks, without growth factor support. Concerning efficacy, this non-anthracycline combination regimen was active as first-line treatment in patients with ABC (ORR 47.4%).

Triplet combination regimens containing gemcitabine, anthracycline and paclitaxel (PCX) have been tested in phase II studies and have produced impressive response rates of 82.9% with GEM, doxorubicin and PCX [23] and 92% with GEM, epirubicin and PCX (GET) regimen [24]. However, the addition of GEM to the PCX/anthracycline combination was associated with an increased incidence of severe neutropenia ranging from 62 to 72% of patients [30–32]. The Central European Cooperative Oncology Group has evaluated the GET regimen versus a

regimen containing 5-FU, epirubicin and cyclophosphamide (FEC) in a randomized phase III study [33]. The GET regimen was well-tolerated but produced more grade 4 neutropenia (72 vs. 53%) and significantly more grade 4 thrombocytopenia (10 vs. 1%) than FEC. Febrile neutropenia occurred in 12.3% of the GET patients.

Recently, the benefit of anthracyclines in HER2-negative breast cancer has been increasingly questioned [23]. Moreover, preclinical and early retrospective clinical data suggest that platinum agents may be promising for the treatment of women with triple negative breast cancer [34]. In this context, the evaluation and development of the gemcitabine–docetaxel–carboplatin combination may prove to be useful for the treatment of selected subgroups of patients with increased sensitivity to these drugs.

In conclusion, the current phase I study demonstrated that the triplet combination of gemcitabine plus docetaxel and carboplatin given every 2 weeks is a well-tolerated regimen which merits further phase II evaluation, as first-line treatment, in patients with ABC.

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