Cancer Chemother Pharmacol (2011) 68:1009–1016
DOI 10.1007/s00280-011-1570-7

ORIGINAL ARTICLE

Bi-weekly docetaxel and gemcitabine regimen in her-2-negative and anthracycline-pretreated metastatic breast cancer patients: a multicenter phase II trial

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Received: 23 November 2010 / Accepted: 21 January 2011 / Published online: 16 February 2011

Abstract
Purpose Bi-weekly gemcitabine (G) in combination with docetaxel (D) is an effective treatment for metastatic breast cancer (MBC) previously treated with adjuvant/neoadjuvant anthracyclines containing regimens with a good toxicity profile. In the present phase II study, we investigated the activity of the same regimen as first-line treatment.
Methods Women with breast cancer pretreated in adjuvant/neoadjuvant setting with anthracyclines received bi-weekly G (1,250 mg/m^2 days 1, 15) and D (50 mg/m^2 days 1, 15) every 28 days with restaging after 3 and 6 cycles.
Results Overall 42 patients were enrolled. Median age is 48 years (range, 31–71 years). Eight patients (19%) achieved complete responses, 18 (43%) partial responses for an overall response rate (ORR) of 62%; five patients (12%) obtained stable disease (SD), and 8 (19%) patients had progressive disease (PD). After a median 17-month follow-up, the median time to disease progression was 12 months (95% CI, 3–26 months) and the median survival time was 27 months (95% CI, 4–57 months). No grade 4 toxicity was seen except in one patient who developed a grade 4 neutropenia. Grade 3 toxicities were leukopenia (2%), neutropenia (14%), anemia (2%), nausea and vomiting (2%), diarrhea (2%), asthenia (2%), and skin toxicity (12%).
Conclusion The GD bi-weekly regimen is well tolerated and active as first line in anthracyclines-pretreated women with MBC. It appears as an interesting alternative compared to a 3-week schedule whenever hematological toxicity is the main clinical concern.

Keywords Bi-weekly · Gemcitabine · Docetaxel · Metastatic breast cancer · Chemotherapy · Phase II

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Introduction

Breast cancer, the most frequent malignancy in women, is a leading cause of cancer mortality worldwide [1, 2]. The median survival after the diagnosis of metastatic disease is 2–3 years, with only a reported 5–10% survival beyond 5 years [3, 4]. New treatments are needed to prolong survival, control symptoms, and minimize toxicity. The Cochrane Collaboration showed that combination regimens significantly improve tumor response and time to disease progression compared with single-agent chemotherapy, with a modest improvement in overall survival [5].

Docetaxel is one of the most active drugs against metastatic breast cancer (MBC). When administered as a single agent in first-line therapy or following anthracycline treatment failure, docetaxel has been associated with response rates of 30–48% [6–11].

Gemcitabine has also shown promising activity in MBC [12, 13]. Various single-agent gemcitabine schedules have produced response rates as high as 42% with a remarkably low toxicity profile [14]. When administered in combination, gemcitabine and docetaxel demonstrated synergistic activity both in vitro and in vivo [15, 16]. This result has translated into good efficacy and acceptable toxicities in clinical trials, even in heavily pretreated patients [17–26].

Evidence suggests that a bi-weekly schedule could improve the activity of GD combination regimen compared with the more commonly used 3-week schedule by virtue of the longer drug exposure [27, 28]. Dose fractionation may allow dose intensification with reduced hematological and non-hematological toxicity [22, 27, 29–31]. In 2 previous phase I trials in which gemcitabine and docetaxel were administered once every 14 days, dose-limiting toxicities were neutropenia and asthenia, and maximum tolerated doses were 65 mg/mq for docetaxel and 2,500 mg/mq for gemcitabine [32, 33]. Two phase II studies demonstrated that lower doses of the two combined drugs maintained good efficacy, while reducing unwanted side effects [20, 22].

On these premises we designed the present study to assess antitumor activity and tolerance of a bi-weekly schedule of gemcitabine plus docetaxel in anthracycline-pretreated metastatic breast cancer (MBC) patients, using lower doses of the two drugs to improve toxicity profile.

Patients and methods

Patient selection

Patients 18 years of age and older with a histological or cytological diagnosis of locally advanced breast cancer or metastatic breast cancer (MBC) were eligible if they had measurable disease according to the WHO criteria, a Karnofsky performance status (KPS) > 70 and an estimated life expectancy >12 weeks. A prior treatment with an anthracycline regimen (neo/adjuvant setting) was required. Taxane pretreatment was permitted in the neo/adjuvant setting if completed 12 months or longer before enrollment. Patients under hormonal therapy could not be enrolled. Prior radiation therapy was permitted if less than 25% of the bone marrow was treated. Other eligibility criteria included adequate bone marrow reserve (leukocyte count > 3,500/uL, absolute neutrophil count [ANC] > 1,500/uL, platelet count > 100.000/uL, and hemoglobin level > 100 g/l).

Patients were excluded from the study for impaired renal function (creatinine level > 1.5 times above normal range) or inadequate hepatic function (abnormally high bilirubin level and/or aspartate aminotransferase [AST] and/or alanine aminotransferase [ALT] levels 2.5 times or higher than normal limits).

Patients were also excluded if they had serious concomitant disorders, active infection, central nervous system metastasis, or second primary tumor with the exception of skin cancer or melanoma. Written informed consent was obtained according to local institutional guidelines. The study protocol was approved by the institutional review board at each study center, and the study was conducted in accordance with the Declaration of Helsinki and the applicable guidelines on good clinical practice.

Treatment

In this multicenter, phase II trial, patients received gemcitabine (1,250 mg/m^2 30-minute intravenous [IV] infusion) on days 1 and 15 (GD arm) and docetaxel (75 mg/m^2 60-minute [IV] infusion) was given on days 1 and 15 before gemcitabine. Cycles were repeated every 14 days for 12 cycles. To avoid fluid retention and/or anaphylactic reactions, patients were premedicated with 8 mg of dexamethasone p.o. taken 12 h before and after the night before, morning of, and evening after treatment. Every patient received anti-emetic prophylaxis with a 5-HT3 inhibitor before cytotoxic drug administration.

Toxicity and dosage modification guidelines

Adverse reactions were evaluated according to National Cancer Institute Common Toxicity Criteria (NCI-CTC version 2.0). Before days 1 and 15 of each cycle, patients were required to have adequate absolute neutrophil and platelet counts.

Dose adjustments were based on hematological toxicities and the most severe non-hematological toxicities at any point during the cycle. For both docetaxel and gemcitabine, patients with grade 4 neutropenia (which lasted > 5 days) or with grade 4 thrombocytopenia received 75% of the dose. Patients who experienced thrombocytopenia with bleeding requiring transfusion received 50% of the dose. For most grade 3 or grade 4 non-hematological toxicities (except grade 3 nausea and vomiting), treatment was delayed until toxicity resolution to grade 1 and was then resumed at 75% of the initial dose. Patients whose therapy was delayed for more than 2 weeks were withdrawn from the study.

Doses of both the drugs were reduced by 20% if aminotransferase levels were 1.5–2.5 × upper limit of normality [ULN] and alkaline phosphatase level was 1.5–5 × ULN or

if aminotransferase levels were 2.5–5 × ULN and alkaline phosphatise level was 1.5–2.5 × ULN. Treatment was delayed if aminotransferase levels were 2.5–5 × ULN and alkaline phosphatise level was 2.5–5 × ULN or if either was >5 × ULN. The docetaxel dose was reduced by 25% if patients experienced grade 2 myalgia or grade 2 peripheral neuropathy. For grade 3 myalgia docetaxel dose was reduced by 50% and was temporarily suspended if grade 3 peripheral neuropathy occurred. The dose of gemcitabine was reduced by 25% in the event of grade 3 myalgia or grade 3 peripheral neuropathy. Dose reescalation was not allowed. Patients were dropped off the study after 3 dose reductions, a 4-week cycle delay or for any grade 4 non-hematological toxicities.

Baseline and treatment assessments

Medical history and physical examinations, KPS evaluations, and complete serum biochemistry evaluation were performed at baseline. Radiological assessments were performed at baseline and were repeated after every third cycle. The same method used at baseline was used consistently for tumor assessment. Long-term follow-up included radiological assessments for every 4 months until progressive disease (PD) occurred and every 6 months thereafter until death.

Patients were evaluable for efficacy if they had bi-dimensionally measurable MBC and had received at least one cycle.

Patient examination included tumor measurement by radiological imaging tests according to the standard WHO criteria. A complete response (CR) was defined as the complete disappearance of all known disease. A partial response (PR) was defined as a reduction of more than 50% in the sum of the products of the perpendicular diameters of all measurable lesions; both CR and PR were required to persist for at least 4 weeks. Stable disease was defined as a less than 50% reduction or a less than 25% increase in the sum of the products of two perpendicular diameters of all measured lesions. Progressive disease was defined as an increase in the product of two perpendicular diameters of any measured lesion by more than 25% or the appearance of new lesions.

Progression-free survival (PFS) was measured since the first treatment day to the date of disease progression; if disease progression had not occurred by the time of this analysis, progression-free survival was considered to have been censored at the time of the last follow-up visit. Overall survival (OS) was measured from the date of diagnosis to the date of death or last follow-up. If death had not occurred, survival time was considered to have been censored at the last follow-up time.

During therapy, bi-weekly blood count and biochemistry evaluation, physical examination, and toxicity assessments were performed. All patients who received at least one cycle of therapy were evaluated for toxicity. All toxicities were graded according to NCI-CTC version 2.0.

Statistical analysis

The primary endpoints of this phase II were the activity and the toxicity of the bi-weekly two-drug chemotherapy regimen. Drug activity was evaluated in terms of overall response rate (complete + partial response). All patients were considered for response rate according to intention-to-treat analysis.

Secondary endpoints were progression-free survival (PFS) and overall survival (OS). PFS and OS curves were obtained with the Kaplan–Meier method. Statistical analyses were performed with Graphpad Prism 5.0 (Graphpad Software, San Diego, CA).

Results

Patient characteristics

From April 2005 to November 2009, 42 patients with MBC treated at 7 institutions were enrolled into the study. Their baseline characteristics are summarized in Table 1. Median age was 48 years (range; 31–71 years). Fifty-seven percent of the patients had only one disease site while 80% had concomitant visceral disease. All the patients had their primary tumors resected, and 36% of them received radiation therapy for early-stage breast cancer. Seventy-nine percent of the patients had been administered to hormonal therapy in adjuvant/neoadjuvant setting. All the patients had received chemotherapy in the adjuvant/neoadjuvant setting with an anthracycline-based regimen. In particular 29% of them had been treated with an anthracycline-taxane regimen.

Dose administration

A total of 223 cycles were administered. Six percent of the cycles were delayed or required dose reductions, mainly due to neutropenia, asthenia, or skin toxicity. No doses were omitted.

Median dose intensities were 555 mg/mq/week for gemcitabine and 22 mg/mq/week for docetaxel. The relative dose intensities (delivered dose divided by planned dose × 100) were 88.0% for gemcitabine and 88.8% for docetaxel.

Table 1 Patients' characteristics ($N = 42$)

Median age	48 (31–71)
N° metastasis sites	
1	22 (57)
>1	20 (48)
Metastasis sites	
Lymph node	19 (45)
Liver	15 (36)
Lung	13 (31)
Bone	7 (16)
Skin	5 (12)
Histology	
Ductal	36 (86)
Lobular	3 (7)
Mixed or other	3 (7)
Hormonal receptors	
Positive	37 (88)
Negative	5 (12)
Previous therapy	
Surgery	42 (100)
Radiation therapy	15 (36)
Systemic endocrine therapy	33 (79)
Prior taxane	
Yes	12 (29)
No	32 (71)

Table 2 WHO clinical response criteria on intent-to-treat population

Type of response	Number of patients $n = 42$ (%)
Complete response	8 (19)
Partial response	18 (43)
Stable disease	5 (12)
Progression disease	8 (19)
Not assessable for response	3 (7)

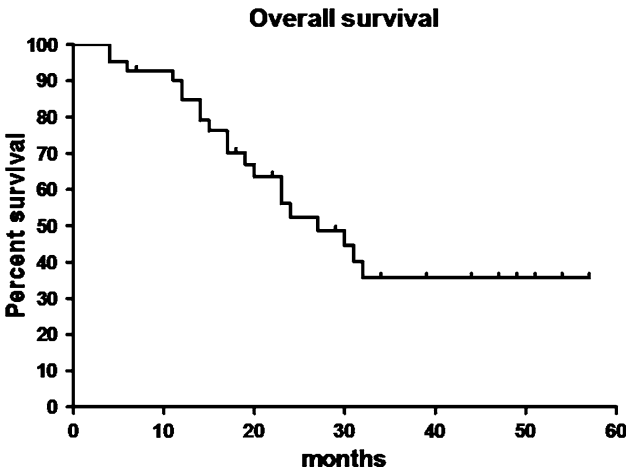

Fig. 1 Progression-free survival (PFS) of 42 patients [12 months (95% CI, 3–26 months)]

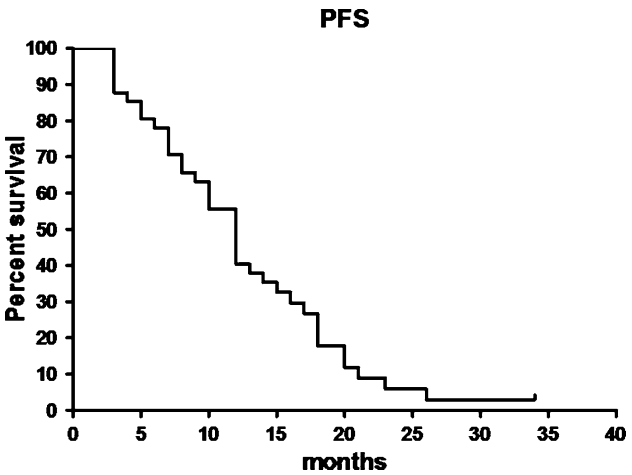

Fig. 2 Overall survival (OS) of 42 patients [27 months (95% CI, 4–57 months)]

Treatment efficacy

All patients were analyzed for the response according to the intention-to-treat principle with the following results: we observed 8 complete responses (CR) (19%) and 18 partial responses (PR) (43%) for an overall response rate (ORR) of 62%. Five patients achieved stable disease (SD) (12%) and 8 patients had progressive disease (PD) (19%). The predominant sites of tumor involvement in patients who underwent CR were lymph nodes (6 patients) and liver (2 patients). Response assessments were not performed in 3 patients (7%) who discontinued treatment after the first cycle: one patient for grade 3 hand–foot syndrome (HFS), one for an exfoliative cutaneous rash, and the third for grade 3 diarrhea. These findings are summarized in Table 2. After a median follow-up of 15 months the median time to disease progression was 12 months (95% CI, 3–26 months; Fig. 1), and the median survival time was 27 months (95% CI, 4–57; Fig. 2).

Treatment toxicity

All 42 patients were assessable for toxicity. Side effects associated with treatment are listed in Table 3. No grade 4 toxicity was seen except in one patient who developed a grade 4 neutropenia.

A commonly observed side effect was hematological toxicity: leukopenia occurred in 5 patients (12%),

Table 3 Toxicity profile (NCI-CTC version 2.0)

Toxicity	Grade 1 Number of patients (%)	Grade 2 Number of patients (%)	Grade 3 Number of patients (%)	Grade 4 Number of patients (%)
Leukopenia	3 (7)	1 (2)	1 (2)	0
Neutropenia	2 (5)	3 (7)	6 (14)	1 (2)
Febrile neutropenia	–	–	1 (2)	0
Anemia	6 (14)	3 (7)	1 (2)	0
Thrombocytopenia	1 (2)	1 (2)	0	0
Asthenia	4 (9)	4 (9)	1 (2)	0
Nausea	5 (12)	4 (9)	0	0
Vomiting	4 (9)	4 (9)	1 (2)	0
Mucositis	6 (14)	5 (12)	0	0
Cutaneous rash	1 (2)	3 (7)	2 (5)	0
Ungual	2 (5)	1 (2)	2 (5)	0
Hyperpigmentation	0	0	1 (2)	0
HFS	1 (2)	1 (2)	0	0
Neuropathy	5 (12)	0	1 (2)	0
Diarrhea				

classified as grade 3 in one case (2%). Neutropenia occurred in 12 patients (29%) and reaching grade 3 in 6 patients (14%).

One patient had febrile neutropenia and was treated with G-CSF and iv. antibiotics without hospitalization. Seven patients (17%) required granulocyte colony-stimulating factor (G-CSF) support. Thrombocytopenia was rather uncommon (5%) and was only grade 1 or grade 2. Similarly, only 1 patient developed grade 3 anemia requiring packed RBC transfusions, and 3 more patients received recombinant human erythropoietin; 9 patients (21%) developed grade 1 or grade 2 anemia.

Gastrointestinal symptoms and asthenia were the most frequently encountered toxicities.

Non-hematological toxicities were nausea and vomiting of grade 1 or grade 2 in 17 patients (40%) and grade 3 vomiting in only 1 patient; grade 1 or grade 2 stomatitis in 11 patients (26%); grade 1 or grade 2 diarrhea in 5 patients (20%) and grade 3 in only 1 patient; grade 1 or grade 2 asthenia in 8 patients (19%) and grade 3 in only one patient; grade 3 skin toxicities including cutaneous rash, ungual hyperpigmentation, and hand–foot syndrome, were detected in 5 patients (12%). Three patients (7%) discontinued the treatment because of drug-related toxicity: 1 patient was withdrawn from the study because of grade 3 HFS, 1 for an exfoliative cutaneous rash, and the other 1 for grade 3 diarrhea. There were no toxicity-related deaths.

Only 2 patients developed grade 1 or grade 2 peripheral neurotoxicity.

The reasons for chemotherapy administration delays were neutropenia, asthenia, and skin toxicity.

Discussion

The goals of systemic therapy, including chemotherapy, in the advanced and metastatic settings were to maximize control of symptoms, to prevent serious complications, and to prolong survival while maintaining an acceptable quality of life [34]. To achieve these goals, the adverse effects of palliative chemotherapy should be predictable, reversible, and manageable. Anthracyclines (e.g., doxorubicin, epirubicin) and taxanes (e.g., paclitaxel, docetaxel) are commonly used chemotherapies for treating breast cancer, especially in the adjuvant setting. However, as a result of previous exposure to anthracyclines and taxanes, the proportion of patients with MBC whose disease is resistant to these agents is likely to increase.

FDA approved the results of a Phase III trial performed among 529 patients who had relapsed after adjuvant treatment with anthracyclines. In this study, patients were treated in the first-line MBC setting with gemcitabine (1,250 mg/m^2 IV on days 1 and 8 every 3 weeks) plus paclitaxel (175 mg/m^2 IV on day 1 every 3 weeks) or paclitaxel alone. Gemcitabine plus paclitaxel combination regimen achieved higher ORR (41.4% vs. 26.2%; $P < 0.001$), a longer median TTP (6.1 vs. 4.0 months; $P < 0.001$), and longer OS (18.6 vs. 15.8 months; $P < 0.049$) than did those treated with paclitaxel alone [35]. However, gemcitabine used every 3 weeks is myelosuppressive, so that the occurrence of neutropenia and thrombocytopenia observed with this agent is a concerning limiting factor in its suitability as treatment for relapsed MBC. Docetaxel is the only single agent, which has shown a survival advantage, that has been demonstrated

in anthracycline-pretreated MBC [9]. No large, well-controlled studies have thus far been conducted, to the best of our knowledge, to support sequential taxane therapy in MBC. Two retrospective studies suggested that cross resistance between docetaxel and paclitaxel may be incomplete, as demonstrated by the significant efficacy advantage (ORR, 20–25%) achieved when one taxane was administered to MBC patients previously treated with the other compound of the same category, even in those patients whose disease was resistant to the first used taxane [36, 37]. This is the rationale for the use of docetaxel in our study where 29% patients had received paclitaxel in the neo/adjuvant setting.

The most frequently used drug combination is a 3-week schedule of docetaxel (D) 75 mg/m^2 on day 1 and gemcitabine (G) 1,000 mg/m^2 on days 1 and 8. This regimen has been proved to be active and safe [18]. GD combination therapy was compared with docetaxel plus capecitabine combination in anthracycline-pretreated breast cancer in a European study [23] had already been treated for metastatic disease, therefore becoming less responsive to chemotherapy. In that study, neutropenia was the most frequently observed toxicity (84% of patients, with 9% developing febrile neutropenia -FN). Such values are higher than in our study (17% of neutropenia and 2% of FN) and are also higher than in all studies using bi-weekly DG regimens.

We have chosen a bi-weekly administration schedule, because for both drugs there is evidence that dose fractionation may allow dose intensification along with reduced hematological and non-hematological toxicity [8, 19–21].

Our efficacy results compare favorably with those of other non-anthracycline-based, docetaxel-containing regimens [11, 25, 26, 29, 30, 32, 33]. Grade 3 or grade 4 hematological and non-hematological toxicities were extremely low in our experience, when compared with those observed after different DG combinations [11, 13, 15–17, 19]. We detected only unexpected higher skin toxicity (12%) compared to 3-week schedules [23].

With an overall response rate of 62%, including 19% complete responses and a median progression-free survival of 12 months, our data suggest a significant antitumor activity of this drug regimen in the subgroup of patients with metastatic breast cancer.

The tolerability of this regimen is highlighted by the low incidences of dose reduction (only 6% of cycles). Treatment discontinuation related to toxicity was needed in only 3 patients.

Our results were obtained in a cohort of unselected patients who had been previously treated with anthracyclines (plus taxanes in 29% patients) in the adjuvant/neoadjuvant setting.

Three similar studies have explored bi-weekly regimens of DG in MBC. Pelegri et al., administered gemcitabine 2,500 mg/mq and docetaxel 65 mg/mq bi-weekly as first therapy [11]. ORR was 75% and median PFS was 10.7 months. Neutropenia was the most frequent toxicity, seen at grade 3 or grade 4 in 44% of patients, a higher percentage than in our study (17%). Kornek et al., and Mavroudis et al., administered gemcitabine 1,500 mg/mq and docetaxel 50 mg/mq every 2 weeks (with prophylactic G-CSF support in Kornek's study), a similar dosage to our experimental schedule. ORR was, respectively, 57 and 76%, and PFS was 8.5 and 8 months. Neutropenia was the most frequent toxicity, seen at grade 3 or grade 4 in 29% of patients [21, 22]. The efficacy and the safety profile were very similar to those found in the present study.

Results from this trial suggest that bi-weekly administration schedule of gemcitabine and docetaxel produces good response rates and has a favorable tolerability profile. This schedule could be considered as an interesting option in patients who have previously failed treated with anthracycline and in some cases also taxanes. In particular, it appears to be an appealing alternative when compared to a 3-week schedule if the hematological toxicity is the main concern.

Conflict of interest The Authors indicated no potential conflicts of interest.

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