Biweekly docetaxel and vinorelbine with granulocyte colony-stimulating factor support for patients with anthracycline-resistant metastatic breast cancer

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This phase II trial evaluated the efficacy and toxicity of vinorelbine 25 mg/m^2 plus docetaxel 60 mg/m^2 administered on day 1, every 2 weeks with granulocyte colony-stimulating factor support (G-CSF, 5 μg/kg/day, days 3–7) as primary prophylaxis in patients with histologically confirmed metastatic breast cancer (MBC) and previously treated with anthracyclines in the adjuvant or in the first-line setting. A total of 48 patients received 352 cycles (median 8, range 2–10). All patients were included in the efficacy and safety evaluation on an intent-to-treat analysis. Eight patients (17%) showed a complete response and 14 patients (29%) showed a partial response. Overall response rate was 46% [95% confidence interval (CI) 33–60]. The median duration of response was 10.0 months. With a median follow-up of 18.0 months, the median time to progression was 11.9 months and the median overall survival was 27.1 months. The most frequently reported grade 3/4 hematological toxicity was neutropenia (19% of patients, 4% of cycles). Febrile neutropenia was reported in six patients (13%) and 7 cycles (2%), but no toxic deaths were reported. The most common grade 3/4 non-hematological toxicity was asthenia (17% of patients, 6% of cycles) and nail toxicity (15% of patients, 3% of cycles). In conclusion, biweekly docetaxel plus vinorelbine with G-CSF support is active and well tolerated as chemotherapy for patients with MBC resistant to anthracyclines. G-CSF support is recommended for lowering the incidence and severity of neutropenia and febrile neutropenia. *Anti-Cancer Drugs* 16:77–82 © 2005 Lippincott Williams & Wilkins.

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Introduction

Cytotoxic chemotherapy is indicated for women with metastatic breast cancer (MBC) that is unresponsive to hormonal therapy or is rapidly progressing and, therefore, life threatening [1,2]. Anthracyclines such as doxorubicin or epirubicin are widely used as first-line chemotherapy for advanced MBC [3,4]. However, treatment options are limited for those patients in whom disease progresses during or following anthracycline therapy [2,5]. Second-line chemotherapy or salvage chemotherapy after adjuvant use of anthracyclines should consist of drugs lacking cross-resistance with anthracyclines. Docetaxel is one the most active cytotoxic agents in MBC [6–8]. Preclinical data have suggested synergistic antitumor activity when docetaxel and vinorelbine were combined [9], which may be due to a similar but different action on cell microtubules [10–12]. Clinical resistance to taxoids often results from decreased stability of tubulin complexes in tumor cells [13], but an advantage of combining docetaxel and vinorelbine may be that tumor cells become very sensitive to tubulin depolymerizing agents like vinorelbine.

Docetaxel has shown response rates (RRs) of up to 41% in patients with anthracycline-resistant breast cancer [14–16], thus confirming preclinical evidence of lack of cross-resistance between docetaxel and anthracyclines [17]. Single-agent vinorelbine as second-line chemotherapy for MBC achieved RRs of 20–30% [18]. A phase I trial recommended 3-weekly docetaxel 75–85 mg/m^2 and vinorelbine 20 mg/m^2 as doses for phase II trials [19]. However, few phase II studies have evaluated this combination in MBC patients previously exposed to anthracyclines [20–24]. Two studies administered docetaxel and vinorelbine every 4 weeks [25,26], but only one has evaluated an every-2-week schedule [27]. The biweekly combination of both agents was effective in anthracycline-resistant MBC with a RR of 50 and 33% in first and second line, respectively. However, treatment administration had to be delayed in 20% of cycles due to

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hematologic toxicity and grade 3/4 neutropenia was observed in 65% of patients when granulocyte colony-stimulating factor (G-CSF) was administered as secondary prophylaxis.

The primary objective of this phase II trial was to determine the incidence of grade 3/4 neutropenia of biweekly docetaxel plus vinorelbine when G-CSF was administered as primary prophylaxis to all patients and cycles. Secondary objectives included RR, time to disease progression (TTP), duration of response, overall survival (OS) and overall toxicity profile.

Methods

Selection of patients

Patients included showed histologically confirmed MBC with at least one measurable or evaluable lesion, previous treatment with anthracyclines (either in the adjuvant setting or as first-line treatment for advanced disease), prior taxanes were allowed, age 18–75 years, and ECOG performance status < 2. Adequate bone marrow (leukocytes $\geq 3 \times 10^9$/l, neutrophils $\geq 1.5 \times 10^9$/l, platelets $> 100 \times 10^9$/l and hemoglobin ≥ 10 g/dl), renal (creatinine ≤ 1.6 mg/dl) and hepatic functions [total bilirubin < 1.25 mg/dl $\times$ upper limit of normal (ULN), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $\leq 2.5 \times$ ULN, and alkaline phosphatase $< 5 \times$ ULN were also required. Patients who had received prior radiotherapy were only eligible if measurable lesions were located outside the radiation field. Previous hormonal therapy was allowed in both the adjuvant and the metastatic setting.

Exclusion criteria included more than one chemotherapy regimen for metastatic disease, peripheral neuropathy grade $\geq$ II, pulmonary lymphangitis pleural effusion, ascites or bone metastases as only sites of metastasis, previous malignancies other than non-melanoma skin cancer or cervical carcinoma *in situ*, brain metastasis, severe concomitant disease, contraindication for the use of corticosteroids, or were pregnant or lactating.

This study was conducted in compliance with the standards of the Responsible Institutional Committees on Human Experimentation and the Helsinki Declaration of the World Medical Association amended in 1975 and following revisions. All patients provided their written inform consent.

Chemotherapy regimen and other treatments

Patients received vinorelbine 25 mg/m^2 administered as an i.v. 15-min infusion followed by docetaxel 60 mg/m^2 as an i.v. 60-min infusion. The treatment cycles were repeated every 14 days for a total of 8 cycles. Premedication included dexamethasone 8 mg administered orally every 12 h on days –1, 0 and 1 of each cycle. Equivalent doses of other corticosteroids (prednisone or methylprednisone) were allowed. Serotonin antagonists were used as antiemetics. Prophylactic granulocyte colony-stimulating factor (G-CSF) was administered to all patients from day 3 to 7 at a dose of 5 μg/kg/day.

Blood counts and serum biochemistry tests were conducted before each cycle. Chemotherapy was delayed for 1 week if the neutrophil count was $< 1.5 \times 10^9$/l and/or the platelet count was $< 100 \times 10^9$/l.

Evaluation of safety and response

Pre-study evaluations included a medical history and physical examination, tumor measurements, hematology and biochemistry tests, and other examinations as clinically indicated. All patients were evaluated before each cycle of treatment (including hematology and biochemistry tests) and upon completion of the treatment schedule.

All patients were included in the efficacy analysis. Tumor measurements were repeated every 4 cycles according to ECOG criteria [28]. Complete response (CR) was defined as the complete disappearance of clinically detectable malignant disease. Partial response (PR) required a $\geq 50\%$ decrease in tumor area without a $> 25\%$ increase in size of any area of known malignant disease or appearance of new areas of malignant disease. Both CR and PR had to be maintained for more than 4 weeks. Stable disease (SD) was defined as no significant changes in measurable or evaluable disease, including a $< 50\%$ decrease in malignant disease without any increases in the size of known malignant disease or new lesions. Progressive disease (PD) was defined as a significant increase in size of lesions present at the start of therapy or after a response, or as the appearance of new metastatic lesions.

Safety analysis was performed in all patients and was based on WHO guidelines [29].

Data analysis

According to Fleming's single-stage procedure for phase II trials [30], a sample size of 47 patients to be enrolled was determined assuming a minimal objective response rate of 38% with a power of 80%, an α value of 0.05 and a withdrawal rate of 10%.

Toxicity and efficacy analyses were performed on patients who received at least 1 cycle (safety and efficacy population). Primary objective of the study was the incidence of grade 3/4 neutropenia. Secondary objectives included RR, TTP, duration of response, OS and overall toxicity profile.

Statistical analyses were performed using the SPSS 10.0 program. Descriptive methods were used to analyze all

the study variables. Continuous variables were described with mean, SD, median and range. Qualitative data were described with relative and absolute frequency distributions. Objective response rates were calculated with 95% confidence intervals (CI). TTP was defined as the period of time from the start of the treatment to first evidence of progression or death. Survival was calculated from the date of first administration of treatment to the date of death by any cause. Actuarial survival curves were constructed using the method of Kaplan and Meier [31].

Results

Characteristics of patients

Between March 1999 and September 2001, a total of 48 patients were enrolled in two Spanish hospitals. The characteristics of these patients are shown in Table 1. Median age was 57 years (range 33–75). The median time since first diagnosis was 39 months. All the patients had received previous anthracycline-containing chemotherapy. Previous chemotherapy was administered in the adjuvant setting (79%), as neoadjuvant treatment (21%) and/or as first-line treatment for advanced disease (46%). Previous treatment for the disease also included surgery (92%), radiotherapy (50%) and hormonal therapy (58%). Most patients (84%) showed a disease-free interval longer than 12 months. The median number of metastatic lesions was 1, located in bone (52%), lung (31%), lymph nodes (29%) and liver (27%).

Table 1 Patient and disease characteristics at baseline ($n=48$)

Characteristics	*N*	%
Age (years)		
Median	57	
Range	33–75	
Histology		
infiltrating ductal carcinoma	43	90
infiltrating lobular carcinoma	3	6
both infiltrating ductal and lobular	1	2
inflammatory carcinoma	1	2
Hormonal status		
premenopausal	20	42
perimenopausal	2	4
postmenopausal	26	54
Estrogen receptor status		
positive	22	46
negative	17	35
unknown	9	19
Median time since first diagnosis (months)	38.7	
Disease-free interval (months)[a]		
0–12	7	16
>12	37	84
Previous chemotherapy		
advanced disease	22	46
neoadjuvant	10	21
adjuvant	38	79
No. locations		
1	29	60
2	11	23
>2	8	17
Metastatic sites		
bone	25	52
lung	15	31
lymph nodes	14	29
liver	13	27
other	9	19

[a]Four patients were not previously subjected to surgery.

Treatment

A total of 352 cycles were administered, with a median number of 8 cycles per patient (range 2–10). Fourteen cycles were delayed due to hematologic toxicity (52%), non-hematologic toxicity (24%) and non-drug-related causes (24%). Dose was reduced in 3 cycles due to hematologic toxicity (febrile neutropenia, $n=2$; grade 4 neutropenia plus grade 3 thrombocytopenia, $n=1$). The median RDI was 100% for both drugs.

Thirty patients (63%) completed treatment according to protocol and 18 patients discontinued due to progression of their disease ($n=12$) or toxicity ($n=6$). Toxicity-related withdrawals were due to grade 4 nail toxicity ($n=2$), febrile neutropenia ($n=2$), grade 3 neutropenia ($n=1$) and asymptomatic cardiac toxicity ($n=1$).

Response

Table 2 shows the overall objective RR. Eight patients (17%) showed a CR and 14 patients (29%) showed a PR for an overall RR (ORR) of 46% (95% CI 32–60). The median duration of response was 10.0 months (95% CI 5.6–14.4). Moreover, 13 patients (27%) showed SD and 12 patients (25%) had PD. One patient was considered not evaluable (2%) due to early withdrawal caused by severe toxicity (febrile neutropenia).

With a median follow-up of 18.0 months, the median TTP was 11.9 months (95% CI 8.9–14.9) (Fig. 1) and the median OS was 27.1 months (95% CI 17.3–36.9) (Fig. 2). The median disease-free survival for those patients who showed a CR was 28.0 months (95% CI 2.4–53.6).

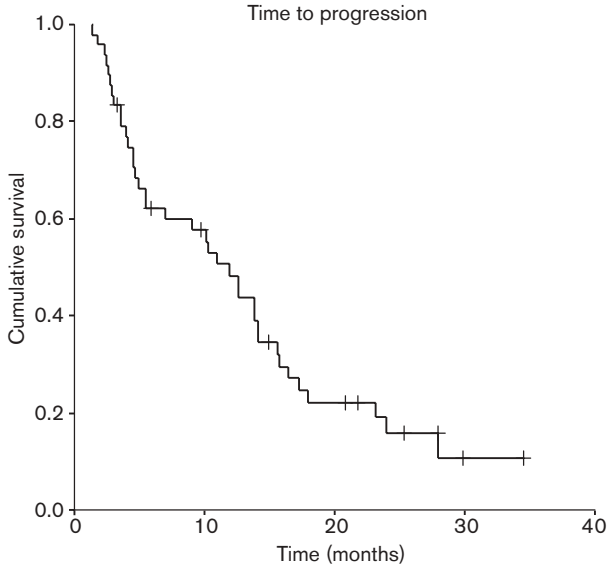
Toxicity

All patients were evaluable for toxicity (Table 3). The most common grade 3/4 hematological toxicity was neutropenia (19% of patients, 4% of cycles). Febrile neutropenia was reported in six patients (12%) and 7 cycles (2%), but no toxic deaths were found. Grade 3/4 non-hematological toxicities included asthenia (17% of patients, 6% of cycles), nail toxicity (15% of patients, 3% of cycles) and mucositis (2% of patients, 0.6% of cycles).

Table 2 ORR on intention to treat basis ($n=48$)

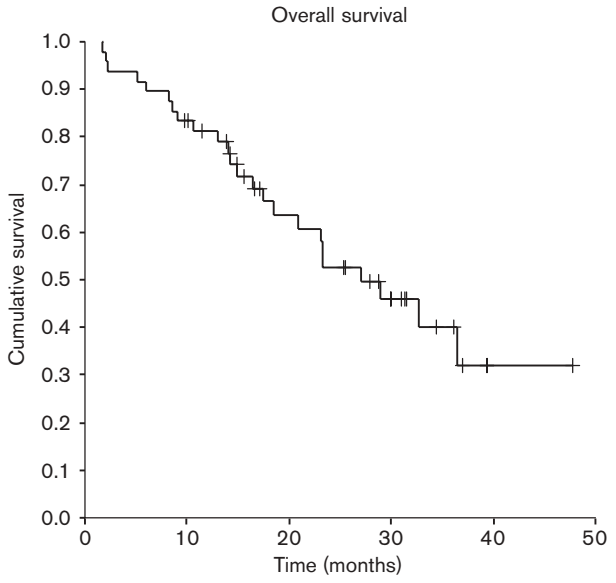
	N	%
CR	8	17
PR	14	29
SD	13	27
PD	12	25
Non-evaluable	1	2
ORR (95% CI)	22	46 (32–60)

Fig. 1



TTP ($n=48$; median follow-up=18.0 months). Median TTP=11.9 months (95% CI 8.9–14.9).

Fig. 2



OS ($n=48$; median follow-up=18.0 months). Median OS=27.1 months (95% CI 17.3–36.9).

Discussion

Results of this study show that the administration of biweekly docetaxel plus vinorelbine with G-CSF as primary prophylaxis is a feasible, active and well-tolerated treatment for patients with anthracycline-resistant MBC. Our findings are consistent with those of previously reported in phase II studies of anthracycline-resistant MBC (Table 4). The RR found here (46%) was similar to the 45% (41% on intention to treat analysis) previously reported for the same regimen [27] and was within the range of RRs (44–61%) found with 3-weekly schedules of docetaxel (60–80 mg/m^2) plus vinorelbine (24–30 mg/m^2) [20–24]. Although slightly higher RRs of 51 and 53% [25,26] have been reported for the every-4-week schedule, these studies included 6 and 37% [25,26] patients not previously treated with anthracyclines, which may account for the higher antitumor response.

Table 3 **Grade 3/4 treatment-related toxicity [*n* (%)]**

Toxicity	Patient ($n=48$)	Cycle ($n=352$)
Hematological		
Anemia	3 (6)	3 (1)
Neutropenia	9 (19)	13 (4)
Febrile neutropenia	6 (12)	7 (2)
Thrombocytopenia	1 (2)	1 (0.3)
Non-hematological		
Asthenia	8 (17)	21 (6)
Mucositis	1 (2)	2 (1)
Nail toxicity	7 (15)	11 (3)

The median TTP found here (11.9 months) was within the range previously reported for the various docetaxel plus vinorelbine regimens (4.8–13.0 months), but the median OS of 27.1 months compares favorably with the range of 10.8–20.0 months previously found [20–27]. Different baseline characteristics of patients may account for these differences in survival outcome, especially regarding to the presence of visceral metastasis.

Grade 3/4 neutropenia was the dose-limiting toxicity in a phase I trial of docetaxel plus vinorelbine administered every-3-weeks [19] and neutropenia was reported as a prominent toxicity in all the docetaxel plus vinorelbine schedules evaluated (Table 4). For instance, in a study of 3-weekly docetaxel 75 mg/m^2 plus vinorelbine 30 mg/m^2, hematological dose-limiting toxicities prompted a 20% dose reduction for both drugs (to 60 plus 24 mg/m^2) after the first group of patients had been treated [20]. However, despite this frequent hematological toxicity, few studies have used G-CSF support [23,26]. Comparing the results in each schedule, the incidence of neutropenia and febrile neutropenia was lower in those trials which used prophylactic G-CSF [23,26] (see Table 4). These findings prompted us to administer G-CSF as primary prophylaxis to all patients and cycles.

As a consequence, although neutropenia was still the main grade 3/4 toxicity observed during the study (19% of patients, 4% of cycles), the incidence was much lower than with G-CSF as secondary prophylaxis [27] (65% of patients, 17% of cycles), and similar to grade 3/4 neutropenia (18% of patients) and febrile neutropenia

Table 4 Phase II studies with docetaxel plus vinorelbine in anthracycline-resistant MBC

Reference	*n*	Docetaxel (mg/m^2)	Vinorelbine (mg/m^2)	G-CSF	CT (%)	A (%)	ORR (%)	Grade 3/4 neutropenia (%)	Febrile neutropenia (%)
Every-4-week									
[25]	35	80 (d1)	30 (d1, d14)	no	80	94	51	37 (pts)	–
[26][a]	57	30 (d1, d8, d15)	30 (d1, d15)	no	26	67	53	32 (pts)	NS
Every-3-week									
[20]	50	60 (d1)	24 (d1)	no	48	100	46	34 (pts)	7 (cy)
[21]	40	80 (d1)	20 (d1)	no	63	100	61	78 (cy)	9 (cy)
[22]	34	70 (d1)	30 (d1)	no	27	94	56	16 (cy)	12 (cy)
[24]	27	75 (d1)	25 (d1)	no	NS	100	44	59 (pts)	41 (pts)
[23]	36	60 (d1)	27.5 (d8, d15)	yes	NS	100	59	18 (pts)	9 (pts)
Every-2-week									
[27]	49	60 (d1)	25 (d1)	no	27	100	45	65 (pts); 17 (cy)	14 (pts); 3 (cy)
Present study	48	60 (d1)	25 (d1)	yes	46	100	46	19 (pts); 4 (cy)	12 (pts); 2 (cy)

G-CSF, prophylactic granulocyte colony-stimulating factor used as primary prophylaxis in all patients; CT, patients with prior chemotherapy for advanced disease; A, patients with previous anthracycline therapy; d, day; w, weeks; pts, patients; cy, cycles.
[a]Only data on second-line setting are shown. NS, not specified.

(9% of patients) observed with docetaxel plus vinorelbine every-3-week with concurrent G-CSG support [23].

Apart from the reduction of severe neutropenia, another relevant finding of the present study was that patients were able to receive the entire scheduled doses. The median RDI for both drugs was 100%. This compares favorably with the median RDI of 91% previously reported with the same schedule with G-CSF as secondary prophylaxis [27]. The excellent tolerability allowed the administration of 8 cycles in most patients and resulted in 7 out of 352 (2%) cycles delayed due to hematological toxicity compared with 64 out of 323 (20%) reported in a previous study for this combination [27]. In agreement with previous findings, severe non-hematological toxicity was not troublesome in most patients, and they were mainly 3/4 asthenia (17% of patients, 6% of cycles) and nail toxicity (15% of patients, 3% of cycles). Peripheral neuropathy and diarrhea did not reach grade 3 in any patients.

In conclusion, the present study shows that biweekly docetaxel plus vinorelbine with G-CSF support as primary prophylaxis is an active, feasible and well-tolerated chemotherapy regimen for the treatment of patients with MBC resistant to anthracyclines. Although a randomized trial will be necessary to draw final conclusions, it seems that the administration of G-CSF support as primary prophylaxis with a dose-dense chemotherapy regimen reduces the incidence of severe neutropenia and allows the administration of the full-dose with minimal modifications.

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