Cancer Chemother Pharmacol (2006) 58: 742–748
DOI 10.1007/s00280-006-0236-3

ORIGINAL ARTICLE

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Pegylated liposomal doxorubicin in combination with vinorelbine as salvage treatment in pretreated patients with advanced breast cancer: a multicentre phase II study

Received: 21 October 2005 / Accepted: 8 March 2006 / Published online: 23 May 2006

Abstract *Purpose*: To investigate the activity and tolerance of pegylated liposomal doxorubicin in combination with vinorelbine in pretreated patients with metastatic breast cancer. *Patients and treatment*: Thirty-six women with metastatic breast cancer were enrolled. The median age was 64 years, 80% of the patients had a performance status of 0–1, 30 (83%) had visceral disease and 83% had received prior taxanes while 50% anthracyclines. Treatment consisted of pegylated liposomal doxorubicin (40 mg/m^2 on day 1) and vinorelbine (25 mg/m^2 on days 1 and 15) every 4 weeks. *Results*: In an intention-to-treat analysis 2 (6%) complete and 12 (33%) partial responses were observed (overall response rate 39%; 95% CI: 23–54.8%); 8 (22%) and 14 (39%) patients experienced stable and progressive disease, respectively. The median TTP was 6.5 months and the median survival time 14.2 months. The 1-year survival rate was 54.1%. Grade 3 and 4 neutropenia occurred in 21 (58%) patients, grade 3–4 anemia in four (11%) and grade 4 thrombocytopenia in one (3%). Two (6%) patients developed febrile neutropenia. Non-hematologic toxicity was mild and easily manageable. There was no clinically important cardiac toxicity or treatment-related deaths. *Conclusions*: The combination of pegylated liposomal doxorubicin and vinorelbine is an active and well tolerated salvage regimen in patients with metastatic breast cancer which merits further evaluation.

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Keywords Liposomal doxorubicin · Vinorelbine · Breast cancer · Salvage treatment

Introduction

Treatment of patients with metastatic breast cancer (MBC) is palliative. The main objective of palliative chemotherapy is the control of tumor-related symptoms and the prolongation of survival. Breast cancer is a relatively chemosensitive disease and patients with metastatic disease frequently receive several lines of chemotherapy; therefore, chemotherapy regimens used in the palliative setting in patients with MBC have to be well tolerated with no detrimental impact on the patients' quality of life.

Doxorubicin (Dox) is among the most active drugs in patients with untreated breast cancer [1]. However, doxorubicin is associated with severe myelosuppression, nausea/vomiting, alopecia and cardiotoxicity [2]. This dose-related cardiotoxicity of doxorubicin led to the development of less cardiotoxic anthracyclines (i.e., 4-epiadriamycin) [3] and cardioprotectors [4]. More recently, doxorubicin has been encapsulated into liposomes, the so-called Pegylated Liposomal Doxorubicin (PLD; Caelyx or Doxil) [5, 6]. This pharmacologic formula increases significantly the half-life of the drug and modifies its tissue distribution leading to relatively higher concentrations of the active drug into the tumor cells [5, 6]. Phase I studies demonstrated that PLD has a favorable toxicity profile, completely different from that of Dox; indeed, the dose-limiting adverse event of PLD was skin toxicity, while the incidence of myelosuppression, nausea/vomiting and alopecia was very low [7, 8]. Most importantly, PLD has significantly less cardiotoxicity when compared with Dox even in high cumulative doses [9]. PLD is active in both chemotherapy-naïve and

pre-treated patients with MBC with an objective response rate of 46 and 31%, respectively [10, 11]. The combination of PLD with either cyclophosphamide [12] or taxanes [13, 14], has shown promising efficacy as salvage treatment in pre-treated patients with MBC.

Vinorelbine is also among the most active drugs against breast cancer; objective responses up to 35% and 16–32% have been achieved in chemotherapy-naïve and pretreated patients, respectively [15–19]. The combination of PLD and vinorelbine was studied in a phase I trial in previously untreated patients with MBC; vinorelbine was initially administered on day 1 and day 8 but the high incidence of dose omissions on day 8 because of neutropenia led to a modification of the schedule and, thus the drug was delivered on day 1 and day 15 every 4 weeks. The maximum tolerated doses were 40 mg/m^2 for PLD on day 1 and 30 mg/m^2 for vinorelbine on day 1 and day 15 [20]. In anthracycline-treated patients, an objective response rate of 36% was achieved with the combination of vinorelbine and PLD [21]. Based on these data the Breast Cancer Working Group of the Hellenic Oncology Research Group (HORG) conducted a multicenter phase II study of PLD in combination with vinorelbine in previously pre-treated patients with MBC.

Patients and methods

Patients

Women $\leq$75 years old with histologically confirmed and bidimensionally measurable metastatic adenocarcinoma of the breast, relapsing or not responding to prior taxane- or/and anthracycline-based chemotherapy were enrolled onto the study. Prior radiotherapy was allowed provided that the measurable lesions were outside the radiation fields. In addition, at least 4 weeks should have elapsed from the last chemotherapy, radiotherapy or hormonal treatment. Patients had to have a performance status (WHO) of 0–2 and adequate organ function, including an absolute neutrophil count $>$1,500/dl, platelet count $>$100,000/dl, total bilirubin level $<$1.5 mg/dl, AST $<$3 times the upper institutional normal limits, and serum creatinine concentration $<$1.5 mg/dl. Patients with brain metastases were allowed to participate providing that they had received brain irradiation with clinical and/or radiologic improvement. Other factors that rendered the patient ineligible included: radiotherapy to $>$25% of marrow-containing bones; a history of a second malignancy other than resected basal cell or squamous cell carcinoma of the skin; active and uncontrollable infection; severe cardiopulmonary insufficiency, a left ventricular ejection fraction (LVEF) $<$50%, unstable angina pectoris, myocardial infraction within the last 6 months, or severe malnutrition (loss of $>$20% of the body weight). All patients gave written informed consent to participate in the study. The protocol was approved by the Scientific and the Ethics Committees of the participating institutions.

Treatment

Pegylated Liposomal Doxorubicin (Caelyx; Schering Plough, Brussels, Belgium) was given at a dose of 40 mg/m^2 over a 1-hour intravenous (IV) infusion on day 1. Vinorelbine (Navelbine; Pierre Fabre, Castles, France) was given at the dose of 25 mg/m^2, diluted in 50 ml 0.9% saline solution, over a 10 min IV infusion on day 1 and day 15. The regimen was repeated every 28-days on an outpatient basis until maximum response, progressive disease or unacceptable toxicity was observed. No prophylactic administration of hematopoietic growth factors was allowed, except in patients experiencing grade 3 or 4 neutropenia or febrile neutropenia.

Dose adjustment criteria were mainly based on hematologic toxicity. Treatment was delayed if the absolute neutrophil count on the day of treatment was less than 1,500/dl and platelets less than 100,000/dl. In case of grade 3 or 4 neutropenia, the same doses of the drugs were given with prophylactic administration of recombinant human granulocyte-colony-stimulating factor (rhG-CSF; Granocyte, Aventis Pharma, Bridgewater, USA) at the dose of 150 μg/m^2 subcutaneously from day 2 to day 8 or/and from day 15 to day 21 according to the nadir of neutrophils. If grade 3 or 4 neutropenia reappeared, the doses of both drugs were reduced by 25%. In case of grade 3 thrombocytopenia or grade 2–4 hand-foot syndrome the dose of Caelyx was reduced by 25%. In case of decrease of the LVEF $>$15%, the Caelyx dose was reduced by 20%, whereas a decrease of LVEF below 40%, obliged the discontinuation of Caelyx, irrespectively of the presence or absence of clinical signs of heart failure.

Baseline and follow-up assessment

This included complete medical history and physical examination, complete blood cell count with differential and serum chemistry. Bidimensionally measurable disease was determined by standard imaging procedures at baseline [chest X-ray, ultrasound, computed tomography scans of the thorax, abdomen and brain, magnetic resonance imaging (MRI) if clinically was relevant and whole body bone scan]. Complete medical history and physical examinations, as well as complete blood cell count with differential and serum chemistry were performed every 4 weeks. Chest X-rays were performed every two chemotherapy cycles.

Response and toxicity evaluation

All patients had tumor measurements (by physical examination, ultrasound, CT scans or MRI) every three chemotherapy cycles. Hematologic toxicity was monitored with weekly blood cell counts with differential, except in cases of grade 4 neutropenia or febrile neutropenia where daily monitoring was performed. Cardiotoxicity was monitored by measuring the LVEF by ultrasound every three chemotherapy cycles. Toxicity was graded

according to the National Cancer Institute (NCI) Common Toxicity Criteria [22].

Moreover, the standard response criteria were used [23]. All complete and partial responses were confirmed radiologically after four or more weeks. All responses were evaluated by an independent panel of radiologists. The duration of response was measured from the first documentation of response to disease progression. Time to tumor progression (TTP) was determined by the interval between the initiations of therapy to the first date that disease progression was objectively documented. The follow-up time was measured from the day of first treatment administration to last contact or death.

Statistical analysis

This was a two-step phase II study with an initial enrollment target of 15 evaluable patients. If 5 or more objective responses were observed, 20 additional patients had to be enrolled. The primary endpoint of the study was the objective tumor response rate. Fleming's method was used to calculate the number of patients required [24]. A sample of 35 patients would be sufficient to give an 80% probability of rejecting a baseline response rate of 20% with an exact 5% one-sided significance test when the true response is at the clinically relevant rate of 40%. A minimum of 12 objective responses among 35 enrolled patients were required to consider the regimen active. The probability of survival was estimated by the method of Kaplan and Meier [25], and confidence intervals for response rates were calculated using methods for exact binomial confidence intervals [26].

Results

Patients' characteristics

Between April 2001 and September 2002, 36 women with measurable metastatic breast cancer were enrolled in this multicenter phase II study. All patients were evaluable for response and toxicity. Patients' characteristics are shown in Table 1. Twenty-nine (80%) patients had PS of 0–1 and 30 (83%) had visceral disease. The study treatment was a 3rd-line regimen in 22 (61%) patients. The median interval between the end of the prior chemotherapy regimen and the enrollment to the study protocol was 5.5 months (range, 1.0–45.3). Thirty (83%) patients had already received a taxane-based regimen, 18 (50%) an anthracycline-based combination while 25 (69%) patients had received endocrine treatment for the metastatic disease. Twenty (56%) patients had disease refractory to 1st- and/or 2nd -line chemotherapy while 15 (42%) patients had disease relapsing after an initial response (the median duration of response to prior treatment was 2.8 months; range, 1.0–18.6); for one (2%) patient there was no information concerning the response to prior treatment.

Table 1 Patients' characteristics

	n	%
Patients enrolled	36	
Age (median, range)	64 (31–75)	
Menopausal status		
Premenopausal	7	19.0
Postmenopausal	29	81.0
Performance status (WHO)		
0	17	47.0
1	12	33.0
2	7	19.0
Histology		
Ductal	26	72.0
Lobular	3	8.0
Mixed	2	6.0
Unknown	5	14.0
Estrogen receptor status		
ER-positive	19	53.0
ER-negative	12	33.0
Unknown	5	14.0
Prior treatment		
Surgery	30	83.0
Adjuvant chemotherapy	35	100.0
Taxane-based regimen (metastatic disease)	30	83.0
Hormone treatment (metastatic disease)	25	69.0
Prior lines of treatment		
1	36	100.0
2	22	61.0
3	14	39.0
Disease localization		
Lung	14	39.0
Liver	23	64.0
Locoregional	8	22.0
Lymph nodes	8	22.0
Bones	13	36.0

Response and survival

A total of 152 chemotherapy cycles were administered with a median of 4 courses/patient (range, 1–8). In an intention-to-treat analysis, there were two (6%) complete (CRs) and 12 (33%) partial (PRs) responses for an overall response rate (ORR) of 39% (95% CI: 23–54.8%). In addition, eight (22%) and 14 (39%) patients experienced stable (SD) and progressive (PD) disease, respectively. Response rates were 41% for liver, 20% for lung, 22% for lymph nodes and 22% for local disease. The objective response rate was 25% among the 20 patients who experienced progression or stable disease as best response to prior chemotherapy while it was 60% among the 15 patients who had an initial response to prior chemotherapy ($P=0.036$) (Table 2). Moreover, the ORR was 62% in patients who received the study regimen more than 6 months after the completion of the prior chemotherapy and 20% in patients treated in less than 6 months ($P=0.025$). Finally, the ORR was 71% in patients who had not received prior taxanes and 31% in those pretreated with taxane-based regimens ($P=0.049$; Table 2).

The median duration of response was 9.9 months (range, 1.0–15.6) and the median time to tumor progres-

Table 2 Efficacy of PLD and vinorelbine regimen in subgroups of patients

Subgroup	No of patients	ORR (%)	*P*-value
Response to 1st line chemotherapy			
Responders (CR+PR)	16	60	0.036
Non-responders (SD+PD)	20	25	
Response to 2nd line chemotherapy			
Responders (CR+PR)	3	33.3	0.631
Non-responders (SD+PD)	10	20.0	
Interval from last chemotherapy			
<6 months	19	21.0	0.025
>6 months	17	59.0	
Prior taxanes-based -chemotherapy			
Yes	29	31	0.049
No	7	71	

sion 6.5 months (range, 1.0–18.7). After a median follow-up time of 7.3 months (range, 1.6–21.7), 10 (28%) patients have died because of disease progression. The median overall survival time was 14.5 months (range, 1.5–21.5) and the Kaplan-Meier estimated probability of 1-year survival for the entire group was 54.2% (Fig. 1).

Toxicity

The treatment had to be delayed in 37 (24%) of 152 administered cycles due to hematologic ($n=21$ cycles), non-hematologic ($n=3$ cycles) toxicity or other reasons, (i.e., pending imaging studies for response evaluation or for patients' personal reasons; $n=13$ cycles). The median duration of treatment delay was 8 days (range, 5–33) and the median time interval between chemotherapy courses was 30 days (range, 22–35). There was no treatment discontinuation or death due to toxicity. Grade 3 and 4 neutropenia occurred in 21 (58%) patients or 28 (18%) cycles (Table 3). Grade 4 thrombocytopenia was observed in one (3%) patient and in 1 (1%) cycle. Four (11%) patients developed grade 3 or 4 anemia. Febrile neutropenia occurred in two (6%) patients; both patients were hospitalized and were successfully treated with antibiotics and granulocyte-colony stimulating factor (G-CSF) support. Prophylactic administration of G-CSF was administered in 15 (10%) cycles. Three patients required red blood cell transfusions and 14 (39%) patients with ≥ grade 2 anemia were treated with recombinant erythropoetin. No patient required platelet transfusions. Non-hematologic toxicity was generally mild to moderate and transient (Table 2). Cardiac toxicity (a decrease of the LVEF≥15%) was observed in four (11%) patients; all these patients had already received epirubicin (median cumulative dose 475 mg/m^2; range, 420–750 mg/m^2). There was no patient complaining of symptoms suggesting cardiac failure. Dose reductions were required in 18 (12%) cycles either for hematologic or non-hematologic toxicity. The median administered dose intensity was 8.9 mg/m^2/week

Table 3 Hematologic and non-hematologic toxicity (WHO)

	Number of patients			
Grade	1	2	3	4
Neutropenia	4 (11.1%)	4 (11%)	17 (47.2%)	4 (11%)
Anaemia	16 (44.4%)	10 (27.8%)	3 (8.3%)	1 (2.8%)
Thrombocytopenia	7 (2.8%)	4 (11%)	–	1 (2.8%)
Febrile neutropenia	1 (2.8%)	–	–	1 (2.8%)
Alopecia	4 (11%)	5 (13.9%)	–	–
Nausea/vomiting	1 (2.8%)	7 (19.4%)	–	–
Diarrhea	1 (2.8%)	1 (2.8%)	1 (2.8%)	–
Mucositis	2 (5.6%)	–	2 (5.6%)	–
Constipation	4 (11%)	–	–	–
Hand–foot syndrome	1 (2.8%)	–	–	–
Fever	2 (5.6%)	1 (2.8%)	–	–
Neurotoxicity	2 (5.6%)	2 (5.6%)	–	–

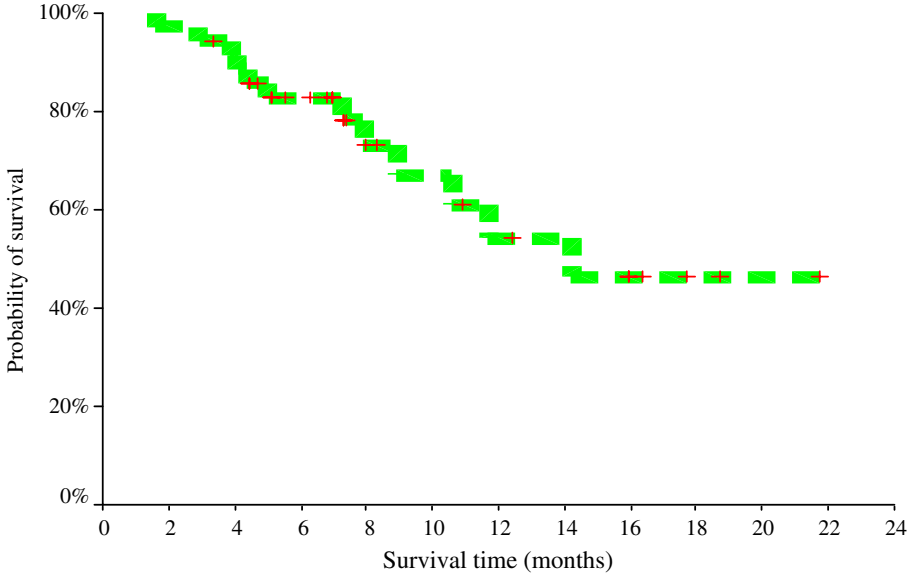

Fig. 1 Kaplan-Meier estimates of overall survival curve of breast cancer patients treated with PLD and vinorelbine

(range, 6.9–12.3) for PLD and 10.8 mg/m^2/week (range, 6.3–15.2) for vinorelbine corresponding to the 89% and 86% of the protocol planned dose.

Discussion

Metastatic breast cancer is an incurable disease and the goals of treatment are palliation from disease-related symptoms and prolongation of survival; therefore, there is an unmet need to develop chemotherapy regimens which are active against breast cancer while preserving the patients' quality of life. In this context, the results of the present multicenter phase II study showed that the combination of pegylated liposomal doxorubicin and vinorelbine resulted in an overall objective response rate of 39% with a median survival time of 14.5 months. The vinorelbine-PLD combination had a favorable toxicity profile since there were only two episodes of febrile neutropenia while grade 4 neutropenia occurred in only 11% of the patients. These results are encouraging since enrolled patients had poor characteristics: indeed, 83% of them presented visceral disease, 61% had already received two prior chemotherapy regimens for the treatment of metastatic disease whereas 83% of them were already pre-treated with a taxane-based regimen. These results compare favorably with those of other studies which evaluated second-line chemotherapy in breast cancer patients. In a recent study PLD was combined with vinorelbine in anthracycline pre-treated patients with advanced breast cancer [21]; an objective response rate of 35% was observed. However, in this trial the PLD/vinorelbine regimen was given in both the first-and second-line setting with practically a similar efficacy (response rate: 31 and 38%, respectively). In addition, the comparison of doxorubicin and epirubicin as second-line chemotherapy demonstrated that there was no significant differences between the two antitumor agents in terms of response rate, median time to tumor progression and median overall survival (overall response rates ranging from 28 to 36%; median overall survival time ranging from 44 to 47 weeks) [27]. However, in a recent study second-line pegylated liposomal doxorubicin failed to demonstrate any antitumor activity in 11 patients with anthracycline-resistant metastatic breast cancer [28] whereas another study evaluating the combination of pegylated liposomal doxorubicin with vinorelbine was prematurely closed due to lack of activity [29]. These discrepancies could be attributed to differences concerning both patients' characteristics, as well as dosages and schedules of the administered drugs. This hypothesis is strongly supported by our findings of the subgroup analysis; indeed, the PLD/vinorelbine regimen showed an encouraging activity in terms of response rate in patients responding to front-line chemotherapy as well as in patients who experienced a clinical relapse more than 6 months after the completion of first-line treatment, which suggests that these patients probably had no chemo-resistant disease.

The observed promising median survival with the PLD/vinorelbine regimen is within the range observed with other chemotherapy regimens in a similar patient population. Indeed, docetaxel monotherapy as second-line treatment of metastatic breast cancer patients refractory or resistant to anthracyclines demonstrated an objective response rate of 68.9% with a median survival time of 11.5 months [30]. Similar results were obtained with weekly docetaxel in patients pre-treated with anthracyclines [31]. Moreover, the combination of docetaxel and gemcitabine in anthracycline-pretreated patients with metastatic breast cancer revealed an objective

Table 4 Efficacy of anthracycline plus vinorelbine combinations in MBC

Study (ref)	Chemotherapy regimen	Number of patients	Line of therapy	Response rate (%)
Spielmann et al. [35]	Doxorubicin 50 mg/m^2 d1 Vinorelbine 25 mg/m^2 d1+8	97	1st	ORR 74 CR 21, PR 53
Baldini et al. [36]	Epirubicin 90 mg/m^2 d1 Vinorelbine 25 mg/m^2 d1+8	51	1st	ORR 70 CR 8, PR 62
Nistico et al. [37]	Epirubicin 25 mg/m^2/week Vinorelbine 25 mg/m^2/week G-CSF support	52	1st	ORR 77 CR 19, PR 58
Vici et al. [38]	Epirubicin 100 mg/m^2 d1 Vinorelbine 25 mg/m^2 d1+5 G-CSF support	97	1st	ORR 70
Pawlicki et al. [39]	Doxorubicin 25 mg/m^2 d1+8 Vinorelbine 25 mg/m^2 d1+8	38	1st	ORR 78
Gebbia et al. [40]	PLD 20 mg/m^2 d1+15 Vinorelbine 30 mg/m^2 d1+15	18	1st	ORR 63
Serin et al. [41]	Epirubicin 90 mg/m^2 d1 Vinorelbine IV 25 mg/m^2 d1 Vinorelbine oral 60 mg/m^2 d8	49	1st	ORR 51
Martin et al. [21]	PLD 35 mg/m^2 d1 Vinorelbine 30 mg/m^2 d1	13 21	1st 2nd	ORR 31 ORR 38
Rimassa et al. [29]	PLD 40 mg/m^2 d1 Vinorelbine 20 mg/m^2 d1+8	23	2nd	ORR 17

response rate of 54% and a median time to tumor progression of 8 months [32]. Other studies evaluating the combination of vinorelbine with gemcitabine resulted in objective responses ranging from 25.5 to 42% with a median survival higher than 15 months [33, 34].

The above results were obtained with an acceptable toxicity profile which was similar with that observed in other studies [26, 34]. Indeed, the main adverse event observed with the pegylated liposomal doxorubicin and vinorelbine combination was myelosuppression with grade 3 and 4 neutropenia occurring in 58% of the patients; in addition, three episodes of febrile neutropenia were observed. However, myelosuppression was easily manageable with growth factor support. In addition, prophylactic administration of recombinant human G-CSF support was required in 10% of the chemotherapy cycles. Other clinically severe toxicities were rare. It is interesting to note that the incidence of cardiotoxicity was very low and mainly limited to a decrease of the LVEF without clinical symptoms of cardiac failure.

Although combinations of an anthracycline plus vinorelbine have been extensively evaluated in the first-line setting with promising results, there are few published data in pretreated patients with MBC (reviewed in Table 4). The results of the present study indicate that the combination of pegylated liposomal doxorubicin and vinorelbine is an active and relatively well tolerated chemotherapy regimen, especially for patients who progress after an initial response to front-line chemotherapy. This regimen merits further comparison in randomized studies with single agent pegylated liposomal doxorubicin.

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