The Breast 19 (2010) 33–37

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Original article

Metronomic administration of pegylated liposomal-doxorubicin in extensively pre-treated metastatic breast cancer patients: A mono-institutional case-series report

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ARTICLE INFO

Article history:
Received 5 June 2009
Received in revised form
2 October 2009
Accepted 6 October 2009

Keywords:
Metronomic chemotherapy
Advanced breast cancer
Pegylated liposomal-doxorubicin

ABSTRACT

Background: Metronomic chemotherapy has shown efficacy in patients with metastatic breast cancer. Pegylated liposomal-doxorubicin (PLD) pharmacokinetic characteristics support the rationale for using the drug in a metronomic fashion, potentially able to combine anthracyclines efficacy to a low toxicity profile.
Patients and methods: In a case-series report carried out in both anthracycline-naive and pre-treated metastatic breast cancer patients, we tested feasibility, clinical efficacy and tolerability of PLD administered with a novel metronomic schedule of 20 mg/m^2 i.v. every two weeks.
Results: 52 patients were enrolled and 45 were evaluated. Forty-four patients were assessed for either response or toxicity. Eight patients (18%) had partial responses (PR) and 17 (39%) stable disease (SD), with a clinical benefit (CB) of 45% (95% CI: 30.3%–59.7%). Nineteen patients (43%) had progressive disease (PD). Neither grade 3 nor grade 4 haematological or clinical side effects were recorded, except for 2 patients with grade 3 palmar-plantar erythrodysesthesia (PPE). No cardiac toxicity was recorded.
Conclusion: Metronomic administration of PLD is a feasible and active treatment for extensively pre-treated metastatic breast cancer patients, alternative to classic anthracyclines, balancing clinical efficacy with a good quality of life in terms of reduced side effects and low personal costs for the patient.

Introduction

In the era of novel biologically targeted therapies for advanced breast cancer, cytotoxic chemotherapy can still be considered a mainstay of treatment.[1] The goals of treatment with chemotherapy remain the benefit in survival, the chance of controlling tumor-related symptoms or complications, and quality of life. Nonetheless, when chemotherapeutic drugs are given at maximum tolerated doses (MTD) inevitably carry considerable toxicities that sometimes entail prolonged recovery periods.

Metronomic chemotherapy is a treatment modality characterized by the frequent administration of chemotherapeutic drugs at doses significantly less than the MTD, without prolonged breaks, which in turn are necessary to allow recovery from treatments given at MTD.[2]

Browder et al. have shown that chemotherapeutic drugs given at the MTD can cause apoptosis of tumor-associated vessels in ectopically growing mouse tumors, but this damage can be repaired rapidly during the prolonged recovery periods necessary for myeloid recovery following MTD chemotherapy. Therefore, giving chemotherapy more frequently, daily, weekly or twice weekly, and at a dose lower than MTD, the endothelial cells' repair process can be compromised and the potential effects of chemotherapy enhanced.[3] This suggests that activated endothelial cells may be more sensitive, or even selectively sensitive, to protracted low-dose chemotherapy compared with other types of normal cells, thus creating a potential therapeutic window.

An antiangiogenic activity is prominent with the protracted exposure to low doses of chemotherapeutics, if compared with their cyclic administration at the maximum-tolerated dose.[4]

A number of recent preclinical and clinical studies have exploited conventional chemotherapeutic drugs as angiogenesis inhibitors.[5]

Particularly within our group, the metronomic combinations of conventional cytotoxics such as cyclophosphamide plus methotrexate either given alone or in combination with trastuzumab in Her-2 overexpressing patients, or the combination of cyclophosphamide, capecitabine and bevacizumab have been extensively studied. Results

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doi:10.1016/j.breast.2009.10.003

are promising showing long-term disease control in a high proportion of patients without significant toxicity, supporting their use as additional therapeutic tool in metastatic breast cancer patients.[6–8]

Caelyx® is a pegylated liposomal doxorubicin (PLD), used as single agent in advanced breast cancer at conventional doses ranging from 40 to 50 mg/m^2 every 3–4 weeks, with objective response rates ranging from 31% to 33%.[9]

The pharmacokinetics of Caelyx® is mainly due to the polyethylene-glycol-coated liposomic coat surrounding the molecule. Liposomes markedly prolong circulation and enhance drug accumulation inside the tumour, retarding uptake by mononuclear phagocytes; PLD achieves a longer half-life than non-pegylated liposomal doxorubicin, as the polyethylene glycol liposome interacts with plasma proteins and inhibits mononuclear phagocytes, consequently prolonging circulation time.[10] Caelyx® is also characterized by a reduced volume of distribution, a long intravascular circulating half-life and a slow plasma clearance compared with free doxorubicin. Seventy-two hours after administration, doxorubicin levels observed in lesions of patients receiving PLD were 5.2 to 11.4 times greater than those found in patients given comparable doses of standard doxorubicin.[11]

These pharmacokinetic characteristics supported the rationale for using PLD in a metronomic fashion.

Based on these considerations, we treated a series of both anthracycline-naive and anthracycline pre-treated consecutive metastatic breast cancer patients within an institutional guide-line to determine the feasibility, the clinical efficacy and tolerability of PLD, with a metronomic schedule of 20 mg/m^2 iv administered every two weeks.

Patients and methods

Patients were treated at the European Institute of Oncology, Milan, Italy.

Female patients aged 18 to 80 years, with histologically confirmed metastatic breast cancer and at least one measurable lesion according to RECIST criteria[12] or with bone lesions, lytic or mixed, in the absence of measurable disease as defined by RECIST criteria, were eligible to receive the study treatment. Other selection criteria were: adequate cardiac function documented by personal history negative for heart events (arrhythmias, ischemic disease, heart failure) and by cardiac US (LVEF $\geq$ 50%); prior chemotherapy with anthracycline-based treatment with a disease-free interval of at least 12-months in the adjuvant setting and 6 months for metastatic disease, and a total cumulative dose of 300 mg/m^2 for doxorubicin and 600 mg/m^2 for epidoxorubicin; at least one treatment for metastatic disease, presence of brain metastasis was allowed if stable brain disease and well-controlled by the concomitant symptomatic treatment; life expectancy longer than 3 months; ECOG (Eastern Cooperative Oncology Group) Performance Status equal or less than 2, adequate bone marrow function (Hemoglobin $\geq$ 10 gr/dl; WBC $\geq$ 3500/μl; Neutrophils $\geq$1500/μl, Platelets $\geq$ 100 000/μl), hepatic function (AST and ALT $\leq$ 2,5 upper limit of normal and bilirubin $\leq$ 3 mg/100 ml) and renal function (creatinine within normal institutional limits); negative pregnancy test for potential child bearing patients. Written informed consent according to institutional requirements was obtained before the treatment was started.

Treatment plan

Patients received pegylated liposomal-doxurubicin (Caelyx®; Schering-Plough Europe, Brussels, Belgium) 20 mg/m^2 diluted in 250 ml of 5% dextrose, every 14 days by a 60 min i.v. infusion. Antiemetic prophylaxis included dexametazone 4 mg i.v., alizapride 50 mg iv, chlorphenamine 10 mg i.v. administered 30 minutes before treatment.

Each treatment administration was repeated every 14 days until disease progression or any toxicity warranting discontinuation.

Toxicity was documented and graded for intensity according to NCIC-CTG criteria on day 1 of each administration. Dose modification at 75% of scheduled dose was allowed or therapy could be delayed 1 week, when grade 4 neutropenia, febrile neutropenia, grade 3 thrombocytopenia or grade 3 anaemia was present. Grade 3 palmar-plantar-erythrodysesthesia (PPE) or cardiotoxicity with LFEV $<$ 50% or neutropenia $\geq$ Grade 3 that persisted for longer than 4 weeks represented criteria to stop the treatment. Treatment administration was discontinued in case of neutropenia $\geq$ 3 persisting for longer than 4 weeks.

Study evaluation

Before starting treatment, patients underwent a complete medical history and physical examination, including evaluation of performance status, body weight and vital signs. Radiological assessment was performed to determine the extent of disease and an echocardiography to evaluate LVEF was performed at baseline or within the first month of treatment. At baseline and every 4 weeks, complete medical history, blood cell count, hepatic and renal functions were performed. In addition CEA and Ca 15.3 were measured. Every 2 weeks, only blood tests were performed. Heart-US and LEVF evaluation were performed every 3–4 months.

Tumour responses were evaluated every 3 months.

Responses were evaluated according to both radiological and clinical evaluation and graded according to standard RECIST criteria.[12]

Statistical analysis

The primary aim of this consecutive case-series analysis was to assess the activity of PLD given with a metronomic schedule in terms of overall clinical benefit (CB) which was defined as the objective RR (CR plus PR) plus the rate of SDs at 24 weeks after treatment initiation.

Time to disease progression (TTP) was defined as the time from the first day of treatment to disease progression or relapse. Overall survival (OS) was defined as the time from the first day of treatment to death and was censored at the date of last contact for subjects who were alive.

Frequencies distributions of clinically relevant patients' characteristics were tabulated. Number of metastases per patient and clinical benefit were cross-tabulated with previous treatment of antracyclines and the association has been tested by Fishers' two-sided exact test. Time to disease progression and the overall survival were estimated using the Kaplan-Meier method.

Results

Patients characteristics

Between January 2005 and November 2006, 52 consecutive patients were treated with PLD metronomic schedule. Seven patients were not eligible, because of major entry criteria violations (PS $>$ 3 in 4 patients, addition of another drug in 2 patients, presence of symptomatic brain metastasis in 1 patient) and were not included in the analysis. Forty-four patients were assessable for both response and CB (1 patient continued treatment in another hospital). Two patients had bone metastasis only and one patient received PLD as first line treatment for metastatic disease. Patients' characteristics are summarized in Table 1.

Table 1
Patients characteristics at baseline.

Characteristics	No. of patients	%
No. enrolled	52	
No. assessable	45	
Median Age (range)	57 (35-78)	
Menopausal status		
Premenopausal	24	53
Postmenopausal	21	47
Hormone Receptor status		
ER+/PgR+	28	60
ER+/PgR−	7	15
ER−/PgR− or +	10	25
HER-2/neu status		
0	36	80
1+	3	7
3+	6	13
N metastatic sites		
1	9	20
2	19	42
≥3	17	38
Predominant Metastatic site		
Viscera	26	58
Bone	10	22
Soft Tissue	6	13
CNS	3	7
Prior anthracycline	23	51
No. of prior metastatic CT regimens		
0	1	2
1	10	22
≥2	34	76

Efficacy

Of 44 patients assessable for response 8 patients (18%) had partial responses (PR) and 17 (39%) stable disease (SD), 19 patients (43%) progressed for an overall response rate (RR) of 18% (95% CI, 8.2%–32.7%). The clinical benefit calculated as % of SDs longer than 24 weeks ($n = 12$) plus PRs ($n = 8$) was observed in 20 patients (45%, 95% CI: 30.3%–59.7%).

Median time to progression (TTP) was 4.2 months (95% CI 3.4–6.2) and median overall survival (OS) was 17.6 months (95% CI 14.0–23.0). Median OS in patients pre-treated with anthracycline was 21.2 months and 15.5 months in the not anthracycline pre-treated cohort (Log-Rank *p*-value: 0.132; Fig. 1).

Treatment compliance and toxicity

A total of 342 treatment administrations were performed, with a median of 5 treatments per patient, ranging from 2 to 17 administrations. Delay in treatment administration occurred 19 times. The most common reason for delay was grade 2 PPE (7 treatments), concomitant radiotherapy (3 treatments) or fever (3 treatments).

In the total population, a dose reduction was performed in 15 treatments. In 10 out of 15 treatments a 25% dose reduction was performed due to mild PPE, conjunctivitis, dermatitis, nausea-asthenia or haematological toxicity. Only in one cycle, a 40% dose reduction was necessary because of grade 3 skin rash and asthenia.

Treatment was well tolerated. Main adverse events are listed in Table 2. Neither grade 3 nor grade 4 haematological or clinical side effects were recorded, except for 2 patients with grade 3 PPE. Grade 1–2 anemia, leukocytopenia and neutropenia were the most common haematological toxicity accounting for 11%, 25% and 16% of patients, respectively. Among the clinical side effects, grade 1 PPE was the most common occurring as a grade 1or 2 in 23 patients (52%). Mucositis, asthenia and nausea were recorded in 43%, 41%, and 36% of patients, respectively.

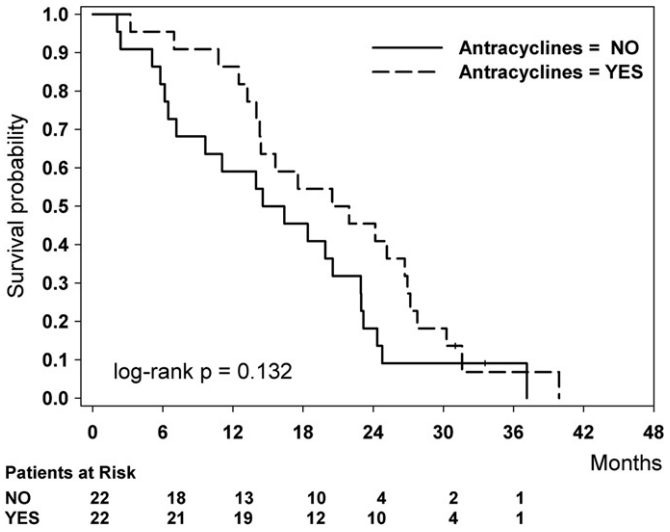

Fig. 1. Overall Survival by previous treatment with antracyclines.

A total of 23 pts had received a previous treatment with anthracyclines: all patients showed a normal LEVF (≥50%) at baseline and no significant clinical changes were observed during the treatment with pegylated liposomal doxorubicin.

Discussion

Metastatic breast cancer has been recognized as a chronic disease requiring various strategies to delay disease progression and related symptoms, thus treatments aimed at inhibition of tumor progression, long-term stabilization and acceptable quality of life are warranted.

The present case-series was conceived to determine feasibility, tolerability and toxicity of Caelyx® administered according to a novel metronomic schedule.

The pharmaceutical formulation and the pharmacokinetics of Caelyx® support its repeated low-dose administration, aiming to produce an anti-angiogenic effect on the tumour rather than cell killing. Thanks to the small molecule size (ca. 100 nm) and to the

Table 2
Main adverse events.

	No. of Patients (%)	
Adverse effect	All grades	>Grade 3
Palmar-Plantar- Erythrodysesthesia	23 (52)	2 (5)
Mucositis	19 (43)	0
Asthenia	18 (41)	0
Nausea	16 (36)	0
Constipation	12 (27)	0
Skin rash	12 (27)	0
Leucopenia	11 (25)	0
Neutropenia	7 (16)	0
Fever	6 (14)	0
Vomiting	5 (11)	0
Anemia	5 (11)	0
Inappetence	4 (9)	0
Conjunctivitis	4 (9)	0
Diarrhea	3 (7)	0
Abdominal pain	3 (7)	0
Epigastric pain	2 (5)	0
Dyspnea	2 (5)	0
Alopecia	2 (5)	0
Headache	2 (5)	0
Onychopathy	2 (5)	0

persistence in the circulation, PLD can penetrate tumour microvessels and be delivered directly and continuously at the tumour site.[10]

A bi-weekly metronomic administration of PLD at lower doses represents a potentially successful approach as previously demonstrated in patients affected by Kaposi's sarcoma[12–16] and recurrent platinum-sensitive and platinum-refractory ovarian cancer.[17–19]

The metronomic schedule targeting genetically stable cells, such as local and circulating endothelial cells, theoretically circumvents two of the major mechanisms of drug resistance in oncology, namely genetic instability of tumour cells and insufficient drug penetration in the tumour mass. Subsequently, a strategy targeting both tumour vasculature and tumour cells by means of one drug might be potentially more effective than the single strategies taken alone.

Previous murine experiments demonstrated that repeated administration of PLD using short dose intervals of 1 week resulted in an accumulation of doxorubicin in the cutaneous tissue of mice developing PPE-like lesions.[20] These results confirm many clinical observations that too short dose-intervals in humans may increase the incidence and the severity of PPE.

The metronomic schedule of PLD used in the present group of patients showed a good tolerability profile with a clinical relevant proportion of patients achieving a control of the disease (CB: 45%; 95% CI 30.3%–59.7%), although most patients were extremely pretreated for metastatic disease (76% had received $\geq$2 pervious lines of chemotherapy for metastatic disease) or had an extended visceral metastatic disease (58% of pts) at the time of study entry (80% of pts $>$ 1 metastatic site). This result compare favourably with those observed in the literature achieving similar CB rates of 24–64% with different and more intensive schedules of treatment.[21–25]

The TTP observed in the present study was 4.2 months (95% CI 3.4–6.2), with an OS of 17.6 months (95% CI 14.0–23.0). In a phase III study involving 301 patients with advanced breast cancer who had failed a prior first or second-line taxane-containing regimen, Keller and colleagues compared PLD, 50 mg/m^2 every 4 weeks, with the European standard of treatment, either vinorelbine, 30 mg/m^2 once weekly, or mitomycin C, 10 mg/m^2 on days 1 and 28, plus vinblastine, 5 mg/m^2 on days 1, 14, 28, and 42 every 6-8 weeks.[26] Progression-free survival was similar for PLD and for the control arm (2.86 months versus 2.53 months, respectively). Overall survival was slightly higher with PLD (11.0 months versus 9.0), although this difference was not statistically significant. The objective response rate was 9% for PLD and 12% in the control arm. More recently, maintenance PLD 40 mg/m^2 q4wk for 6 cycles after the completion of six cycles of conventional anthracycline and taxane chemotherapy resulted in a prolonged TTP. Median TTP increased from 9.96 months in the observation arm to 16.04 months in the PLD arm with a negligible toxicity profile.[27] These results compare favourably with those obtained with the metronomic schedule reported in the present paper.

A slightly better OS was observed in favour of patients previously treated with anthracycline with respect to those not pretreated; although this difference was not statistically significant (21.2 months vs 15.5 months; log-rank p-value = 0.132). These data support the fact that the previous exposure to conventional anthracyclines was not harmful for patients.

The favourable CB obtained in our series of patients was free from major toxicities, as neither grade 3 nor grade 4 haematological toxicity was recorded, despite the fact that patients were mostly heavily pre-treated for metastatic disease. Importantly, there were no symptomatic nor asymptomatic cardiac events.

In the management of metastatic endocrine non-responsive breast cancer patients, anthracyclines still represent a mainstay of treatment. Patients who received anthracycline-based treatments in the adjuvant setting and relapsed, but cannot be considered "refractory" to anthracyclines, might benefit from anthracycline re-exposure.[28] However, anthracyclines-related cardio-toxicity influences its use in the event of recurrence. Furthermore, conventional anthracyclines are usually not recommended in patients with higher cardiac risks (e.g., pre-existing cardiac disease, history of mediastinal irradiation) and in elderly patients with endocrine non-responsive disease, where the appropriate use of chemotherapy remains controversial, being dose reducing or modified schedules the most used habits. In these settings, PLD represent a good alternative to conventional anthracyclines. Furthermore, according to the evidence of this case series report, PLD administered metronomically at 20 mg/m^2 every 2 weeks represents a good treatment, which can be used as an alternative to classic anthracyclines, if they are contra-indicated or following anthracyclines in not refractory patients with metastatic breast cancer, balancing clinical efficacy with a good quality of life in terms of reduced side effects and low personal costs for the patient.

Conflict of Interest Statement

All authors have no conflict of interest to disclose.

Funding Source

The study had no sponsor or funding source.

Ethical Approval

Written informed consent according to institutional requirements was obtained before the treatment was started.

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