Cancer Chemother Pharmacol (2009) 64:401–406
DOI 10.1007/s00280-008-0887-3

ORIGINAL ARTICLE

Non-pegylated liposomal doxorubicin and docetaxel in metastatic breast cancer: final results of a phase II trial

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Received: 6 October 2008 / Accepted: 22 November 2008 / Published online: 24 December 2008

Abstract
Background Non-pegylated liposomal doxorubicin (NPLD) has demonstrated equivalent antitumor activity to conventional doxorubicin and a significantly lower risk of cardiotoxicity when given as single agent or in combination with cyclophosphamide, but there is limited experience with the combination of NPLD and taxanes. This phase II study was performed to evaluate the efficacy and safety of the NPLD and docetaxel in patients with metastatic breast cancer.
Patients and methods A total of 51 patients were treated with NPLD (60 mg/m^2) and docetaxel (75 mg/m^2) in 3-weeks intervals for up to eight cycles.
Results The overall response rate was 50% and 78% of patients derived a clinical benefit. Median time to progression and overall survival were 10.0 months (95% CI, 6.9–13.1 months) and 25 months (95% CI, 22.1–29.8 months), respectively. Median duration of response was 12.0 months (95% CI 7.1–16.9). The treatment was generally well tolerated and associated with toxicities that were consistent with the known side-effects of the individual agents and of anthracycline/taxane combinations. There were no symptomatic cardiac averse events and mild asymptomatic LVEF changes were reported in five patients.
Conclusions The combination of NPLD and docetaxel is well tolerated and has high antitumour activity in MBC patients.

Keywords Docetaxel · Non-pegylated liposomal doxorubicin · Cardiotoxicity · Metastatic breast cancer · Chemotherapy

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Introduction

Breast cancer is the most common malignancy affecting women in northern Europe and North America, corresponding to an age-corrected annual incidence of 10–12 per 10,000 females. Approximately 15–20% of all patients treated with curative intent develop metastatic disease. Currently available treatments are unable to eradicate metastatic breast cancer (MBC). Consequently, treatment goals are to prolong survival, prolong disease control, and to provide better palliation for patients.

Anthracyclines and taxanes are among the most active chemotherapeutic agents for the treatment of MBC with response rates ranging from 20 to 40% as single agent therapy [1–5] to 40–70% when used in combination regimens in untreated populations [6–11]. With the increasing use in adjuvant regimens, however, anthracyclines are often not considered for re-treatment in the metastatic setting because of the risk of a cumulative-dose dependent and potentially life-threatening form of cardiotoxicity, despite the fact that they can remain active [12, 13]. The risk of developing congestive heart failure is approximately 5% at a cumulative lifetime doxorubicin dose of 400 mg/m^2 but can be as high as 48% at doses of 700 mg/m^2 [14].

Several strategies have been devised to circumvent these adverse effects. Liposomal encapsulation reduces free drug concentrations in plasma resulting in an improved therapeutic index and a decreased risk of cardiomyopathy [15–18]. Due to an increased intratumoral vascular permeability and a decreased lymphatic clearance from the perivascular space, liposomes can furthermore accumulate in tumour tissue which may enhance the anti-tumour activity.

Non-pegylated liposomal doxorubicin (NPLD; Myocet®), one of two liposomal doxorubicin formulations currently used in breast cancer, has been evaluated in three randomised trials in MBC, comparing NPLD as single agent or in combination with cyclophosphamide to conventional doxorubicin or epirubicin [19–21]. These studies showed that on a milligram per milligram base NPLD exhibits equivalent antitumor activity to conventional doxorubicin and a significantly lower risk of cardiotoxicity. As there is limited experience with the clinically relevant combination of NPLD and taxanes, this phase II study was performed to evaluate the efficacy and safety of the NPLD and docetaxel in patients with MBC.

Patients and methods

Study design

This phase II study involved nine centres in Germany. The study was conducted in accordance with the Declaration of Helsinki and ICH Harmonized Tripartite Guidelines for Good Clinical Practice, in compliance with local regulations, and with the approval of an independent ethics committee.

The objectives of the trial were to evaluate the efficacy and tolerability of NPLD and docetaxel in patients with MBC. The primary study endpoint was tumour response. Secondary endpoints included time to progression (TTP), overall survival (OS), and safety.

Patient eligibility

Eligible patients had to have histologically confirmed MBC and no prior chemotherapy for metastatic disease. Adjuvant chemotherapy with anthracyclines and/or taxanes was allowed but had to be concluded >12 months prior to enrolment. In case of prior anthracycline-based therapy, the cumulative doxorubicin and epirubicin doses had to be <300 and <480 mg/m^2, respectively. Patients were required to have measurable disease. All patients had to have adequate hematologic, renal, hepatic and cardiac function [ANC $\geq 2.0 \times 10^9$/l; platelets $\geq 100 \times 10^9$/l; haemoglobin ≥ 10 g/dl; bilirubin $\leq 1.25 \times$ upper normal limit (ULN), creatinine level $\leq 1.25 \times$ ULN; left ventricular ejection fraction (LVEF) $\geq 50\%$] and an ECOG performance status of ≤ 2. Written, informed consent was required prior to enrolment.

Exclusion criteria included brain metastases, bone metastases as the only site of disease, a history of other prior malignancies (except for curatively treated non-melanoma skin cancer or carcinoma in situ of the cervix), significant cardiac disease, or any other serious medical or psychiatric conditions which would impair the ability of the patient to receive protocol treatment. Pregnant or lactating women were ineligible.

Treatment plan

Eligible patients were treated with NPLD (60 mg/m^2, intravenous [IV] infusion over 60 min) and docetaxel (75 mg/m^2, IV infusion over 60 min) in 3-weeks cycles. Treatment was planned for six cycles unless there was evidence of unacceptable toxicity or disease progression. Patients could be considered for two additional cycles if a PR or CR was documented for the first time after cycle 6. All patients were given prophylactic oral corticosteroid premedication at 12- and 1-h before docetaxel infusion and at 12, 24 and 36 h after docetaxel. Standard antiemetic therapy was administered in compliance with local standards. Prophylactic use of haematopoetic growth factors was not allowed.

A new treatment cycle was only started if ANC was $\geq 1.5 \times 10^9$/l, platelet count was $\geq 100 \times 10^9$/l and non-haematological toxicity had resolved to grade ≤ 1 (alopecia,

nausea and vomiting excepted). If treatment had to be delayed for >2 weeks, the patient was withdrawn. Doses of NPLD and docetaxel were permanently reduced to 50 and 60 mg/m^2, respectively, in patients who experienced febrile neutropenia, prolonged grade 4 neutropenia (>7 days), grade 4 thrombocytopenia, grade 2 peripheral neuropathy or any grade 3 non-haematological toxicity. In case of symptomatic cardiac events or any given grade 4 non-haematological toxicities, the patient was discontinued. Treatment was discontinued if resting LVEF decreased by ≥20 points from baseline to a final value of ≥50%, or by ≥10 points from baseline to a final value <50%, or by ≥5 points from baseline to a final value <45%.

Assessments

Tumour lesions were measured using WHO Criteria at baseline, at the end of treatment cycles 2, 4 and 6, and every 3 months during follow-up. If response was documented, imaging scans were performed at least 4 weeks later to confirm the response. Adverse events and toxicities were evaluated weekly and recorded for every cycle. They were graded using the NCI Common Toxicity Criteria (CTC; version 2.0, dated April 30, 1999). Cardiac function was monitored by ECG and ECHO at baseline, after cycles 2, 4 and 6, at the end of the study and 3-monthly during follow-up.

Statistical analysis

The primary efficacy endpoint, objective response rate, was defined as the percentage of patients with CR or PR. The sample size was estimated at 46 evaluable patients assuming an objective response rate ≤30% as null hypothesis, a true response rate of ≥50%, a power of 80% and a significance level of 5%.

TTP was defined as the time from registration until disease progression. Death was regarded as a progression event in those who died before disease progression. Subjects whose disease had not progressed at the time of analysis were censored using the last assessment date. Duration of response (DR) was defined, for responding patients only, as the period of time from registration to the first observation of disease progression. OS was calculated from the date of registration to the date of death for any reason.

Standard descriptive methods were applied. Analyses were performed on an intent-to-treat population including all patients without major violation of eligibility criteria. OS and TTP were estimated by the Kaplan–Meier method. Categorical variables were described by contingency table methods and percentages. Continuous variables were described by mean and median values, standard deviations and minimum and maximum values.

Results

Patient characteristics

A total of 51 patients with MBC were enrolled between March 2003 and January 2005. All patients were assessable for safety analysis, and 50 patients were assessable for efficacy. Patient characteristics at the time of study registration are listed in Table 1. The median age was 51 years. More than 80% of patients had visceral-dominant disease and 35% had ER-negative disease or unknown ER status. Twenty-eight percent of patients had received neoadjuvant or adjuvant chemotherapy including anthracyclines in 20%.

Chemotherapy administration

A total of 272 cycles were administered throughout the study. The mean number of cycles per patient was 5.3 (range, 1 to 8). Thirty-eight patients (75%) completed 6 cycles of chemotherapy and 13 patients completed eight cycles (25%). Most treatment cycles (246; 90%) were

Table 1 Patient baseline characteristics

	All patients (n = 51)
Age [median (range)]	55 (35–69)
ECOG Performance Status [n (%)]	
0	22 (45.8%)
1	25 (52.1%)
2	1 (2.1%)
Hormone receptor status [n (%)]	
ER/PgR positive	33 (64.7%)
ER and PgR negative	13 (25.5%)
Unknown	5 (9.8%)
Her2/neu status [n (%)]	
Overexpression (IHC 3+ or FISH+)	8 (15.7%)
No overexpression/unknown	43 (84.3%)
Metastatic sites [n (%)]	
Visceral	39 (81.3%)
Lung	22 (45.8%)
Liver	30 (62.5%)
Bone	30 (62.5%)
Soft tissue	14 (29.2%)
Number of metastatic sites [n (%)]	
1	15 (29.4%)
2	25 (49.0%)
≥ 3	11 (21.6%)
(Neo)Adjuvant treatment	
Chemotherapy	14 (27.5%)
Anthracyclines	10 (19.6%)
Endocrine Therapy	21 (41.2%)

administered every 3 weeks as planned. Twenty-six cycles had to be delayed, mainly due to logistical reasons/patient request (81%) or prolonged neutropenia (15%). Dose reductions were required in four patients. The median relative dose intensity was 0.98 for both NPLD and docetaxel.

The median cumulative doxorubicin dose was 374 mg/m^2 (range, 60 to 600 mg/m^2) with 482 mg/m^2 (range, 300–600 mg/m^2) for anthracycline-pretreated women, and 348 mg/m^2 for women without prior neoadjuvant or adjuvant anthracycline therapy (range, 60 to 480 mg/m^2).

Efficacy

Complete and partial responses were observed in 6 (12%) and 19 (38%) of the 50 evaluable patients accounting for an objective response rate (ORR) of 50% (Table 2). Seventeen additional women (34%) had stable disease (SD; 2 unconfirmed), and 14 had SD ≥6 months, for a clinical benefit rate (CBR; CR + PR + SD ≥ 6 months) of 78%.

Median TTP based on Kaplan-Meier estimate was 10.0 months (95% CI, 6.9–13.1 months. The median duration of objective response and clinical benefit were 12.0 months (range, 4–63 months; 95% CI, 7.1–16.9 months) and 14.0 months (range, 4–63 months; 95% CI, 10.3 to 17.7 months), respectively. Median survival was 25.0 months (95% CI, 22.1–29.8 months).

Outcome was better for patients without prior anthracycline therapy with an ORR of 50%, a CBR of 83% and a median TTP of 12 months (95% CI, 7.0–17.0 months), as compared to an ORR of 40%, a CBR of 50% and a median TTP of 5 months (95% CI, 4.2–13.3 months) for women with prior anthracycline exposure.

Table 2 Treatment efficacy results

Outcomes	ITT-analysis
Objective response [*n* (%)]	
CR	6 (12)[b]
PR	19 (38)[c]
SD	17 (34)[d]
SD ≥ 6 months	14 (28)
PD	8 (16)
NE	1 (2)
Clinical benefit	39 (78)
Time to progression[a] (months)	
Median (95% confidence interval)	10.0 (6.9–13.1)
Median duration of response[a] (months)	
Median (95% confidence interval)	12.0 (7.1–16.9)
Median duration of clinical benefit[a] (months)	
Median (95% confidence interval)	14.0 (10.3–17.7)
Median overall survival[a] (months)	
Median (range, 95% confidence interval)	25.0 (22.1–29.8)

[a] Intent-to-treat analysis based on all patients

[b] Unconfirmed in 3 patients

[c] Unconfirmed in 3 patients

[d] Unconfirmed in 2 patients

Safety

Treatment related adverse events are summarized in Table 3. Most common grade 3/4 adverse events were leukopenia ($n = 40$), neutropenia ($n = 37$), infection ($n = 14$), fatigue ($n = 6$), diarrhea ($n = 4$), and nausea ($n = 4$). All other treatment related adverse events occurred in ≤3 women. PPE was observed in only one patient.

No symptomatic cardiac events were recorded throughout the study. Nine patients had minor changes in the LVEF (grade 1, $n = 5$; grade 2, $n = 1$) or signs of left diastolic ventricular dysfunction (grade 1, $n = 5$) on echocardiogram, but remained asymptomatic during study and follow-up and did not require any diagnostic or therapeutic intervention. None of the patients with cardiac events met the protocol-defined criteria for discontinuation.

Table 3 Treatment-related adverse events ($n = 51$ patients enrolled and treated)

Body system and adverse event	Grades 1 and 2		Grades 3 and 4	
	No. of patients	%	No. of patients	%
Haematologic				
Anaemia	36	72.0	8	16.0
Leukopenia	8	16.0	40	80.0
Neutropenia	6	13.0	34	73.9
Thrombocytopenia	16	32.0	2	4.0
Infection (including FN)	11	21.6	14	27.5
Febrile Neutropenia	–	–	12	23.5
Gastrointestinal				
Nausea	35	68.6	4	7.8
Vomiting	17	33.3	2	3.9
Diarrhea	20	39.2	4	7.8
Stomatitis	26	51.0	0	0
Skin reaction				
Hand-foot skin reaction	1	2.0	0	0
Alopecia	47	92.2	–	–
Nail changes	11	21.6	0	0
Sensory neuropathy	11	21.6	0	0
Fatigue	36	70.6	6	11.8
Cardiac				
LVEF	6	11.8	0	0
CHF	0	0	0	0
LV diastolic dysfunction	5	9.8	0	0
Conduction abnormality	3	5.9	0	0

Discussion

Doxorubicin is one of the most active agents against breast cancer, even in the context of newer agents such as the taxanes. Cardiotoxicity from doxorubicin continues to be an ongoing medical concern and ultimately is the cumulative toxicity that is dose-limiting. NPLD offers an alternative to doxorubicin for women with MBC. As first line treatment NPLD has demonstrated a similar efficacy to conventional doxorubicin when given alone or in combination with cyclophosphamide with a significantly reduced risk of cardiotoxicity and an improved safety profile [19–21]. This is the first published study in MBC that evaluated the safety and efficacy of NPLD in combination with docetaxel.

Our results demonstrate that NPLD 60 mg/m^2 and docetaxel 75 mg/m^2 can be combined safely. In spite of the slightly higher relative doses compared to standard doxorubicin/docetaxel combinations with 60/60 or 50/75 mg/m^2 doxorubicin and docetaxel, respectively, the study treatment was generally well tolerated and associated with toxicities that were consistent with the known side-effects of other anthracycline/taxane combinations [1, 6–11]. More than 90% of treatment cycles were given at the planned dose and schedule, and the relative DIs for NPLD and docetaxel were 98%, in spite of the fact that prophylactic use of haematopoetic growth factors was not allowed.

As expected, the incidence of cardiac side effects was low. All reported cardiac events were mild and were not associated with any clinical symptoms. Even among patients who had received anthracyclines as part of their adjuvant treatment and/or received a cumulative doxorubicin dose of ≥480 mg/m^2 (n = 18; mean, 510 mg/m^2; range, 480–600 mg/m^2), only three patients met the protocol-defined LVEF criteria for cardiac toxicity. Apart from one patient who was inadvertently enrolled despite a baseline LVEF of 40%, all LVEF changes were <10% from baseline and none of the patients developed any clinical signs of cardiomyopathy. Interestingly, even in the patient with the initial LVEF of 40%, no decline in LVEF was observed with NPLD therapy, and instead LVEF had improved by >10 points at follow-up. These date underline the cardiac safety of this regimen even at higher cumulative anthracycline doses.

One adverse effect frequently associated with liposomal anthracyclines is a specific form of skin toxicity generally referred to as PPE or hand–foot syndrome. In reported breast cancer studies, almost half of patients treated with pegylated liposomal doxorubicin (PLD) experienced PPE (17–18% grade 3), and PPE resulted in treatment discontinuation in 7–8% of patients [22, 23]. The mechanism of this skin toxicity is thought to be the result of microtrauma to the vasculature that leads to leaky blood vessels and subsequent extravasation of the cytostatic compound into these tissues. In contrast to PLD, NPLD is not associated with an increased risk of skin toxicity compared to conventional doxorubicin. There was only one report of PPE (grade 1) in this study with NPLD and docetaxel. This compares favourably with the data reported for NPLD single agent or in combination with cyclophosphamide [19–21].

With an objective response rate of 50%, a clinical benefit of 78% and a median PFS of 10 months, NPLD/docetaxel demonstrated the expected high anti-tumour activity in this prognostically unfavourable cohort of women with either ER-negative and/or visceral disease. Substantial antitumour activity was seen in both anthracycline-pretreated and naïve patients, although the efficacy was expectedly somewhat higher in women without prior anthracycline exposure. In similar clinical settings, several randomized trials have demonstrated comparable efficacy for anthracycline/taxanes combinations with response rates ranging from 47 to 68% and median PFS ranging from 7 to 9 months [6–11]. These data were confirmed in a recent meta-analysis with more than 3,000 patients from eight randomised trials which demonstrated a response rate of 57% for anthracycline/taxane combinations, a median PFS of 7.7 months (95% CI, 7.2–8.0 months) and a median OS of 19.8 months (95% CI, 18.7–20.6) [24]. Although comparing trials can be problematic, it is relatively clear given the results from these studies that NPLD/docetaxel have a similar efficacy compared to other anthracycline/taxanes combinations.

In conclusion, we were able to demonstrate that NPLD and docetaxel is a highly effective combination with a favourable safety profile. This combination might be considered as an alternative to conventional anthracycline/taxanes combinations, particularly in patients with an increased risk of experiencing cardiotoxicity or anthracycline pre-treated women.

Acknowledgments This study was supported by grants from Cephalon Pharma, Germany, Aventis Pharmaceutical, Germany and Amgen Pharmaceutical, Germany.

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