Improved anti-tumor response rate with decreased cardiotoxicity of non-pegylated liposomal doxorubicin compared with conventional doxorubicin in first-line treatment of metastatic breast cancer in patients who had received prior adjuvant doxorubicin: results of a retrospective analysis

Gerald Batist, Lyndsay Harris, Nozar Azarnia, Lily Waiyee Lee and Pascual Daza-Ramirez

Our objectives were to ascertain the safety (cardiotoxicity) and efficacy of non-pegylated liposomal doxorubicin [Myocet (M)] compared with conventional doxorubicin (A) in patients with metastatic breast cancer (MBC) who had received adjuvant anthracycline treatment and were at high risk of developing iatrogenic cardiomyopathy. This retrospective analysis is based on data pooled from two prospective phase III comparative randomized clinical trials comparing Myocet versus conventional doxorubicin in combination with cyclophosphamide and as single agents, respectively, for the treatment of MBC. The outcome measures reviewed in this analysis were overall response, time to treatment failure, time to disease progression, overall survival and cardiotoxicity. The analysis was carried out by strata according to patients' previous exposure to adjuvant anthracyclines. Kaplan–Meier, log-rank χ^2-test, Cox proportional-hazards and Cochran–Mantel–Haenszel statistics were used for the analysis. Sixty-eight patients were included in this analysis: 29 and 39 patients from Studies 1 and 2, respectively, had received adjuvant anthracycline treatment. Study 1, with $n=297$, compared M 60 mg/m^2 (M60) plus cyclophosphamide (C) 600 mg/m^2 (C600) versus A 60 mg/m^2 (A60) plus C600 as first-line treatment for MBC. Twenty-nine patients had received prior adjuvant doxorubicin, of whom, after randomization, 14 received M60 + C600 and 15 received A60 + C600 for the treatment of MBC. Study 2, with $n=224$, compared M 75 mg/m^2 (M75) with A 75 mg/m^2 (A75) as first-line treatment for MBC disease. Thirty-nine patients had received prior adjuvant doxorubicin, of whom, after randomization, 18 received M75 and 21 received A75 for their MBC. Hence, 32 patients received M-containing regimens and 36 received A-containing regimens for the treatment of MBC. Median age in both groups was 54 years. The groups were well balanced in terms of demographic characteristics. Overall response rates were 31% and 11% for M-treated patients and A-treated patients, respectively (Cochran–Mantel–Haenszel $P=0.04$, odds ratio = 4.0). Median time to progression was 4.5 versus 3.4 months [log-rank $P=0.66$, hazard ratio (HR) = 1.14], median time to treatment failure was 4.2 versus 2.1 months (log-rank $P=0.01$, HR = 2.06) and median survival time was 16 versus 15 months (log-rank $P=0.71$, HR = 1.12). Cardiac events occurred in 22% of M-treated patients [one congestive heart failure (CHF)] versus 39% of A-treated patients (three CHFs) (log-rank, $P=0.001$). Median lifetime dose at onset of cardiotoxicity was 780 mg/m^2 for M versus 580 mg/m^2 for A (log-rank $P=0.001$, HR = 4.8). This retrospective analysis shows that treatment based on non-pegylated liposomal doxorubicin (Myocet) significantly reduced the risk of cardiotoxicity in patients with MBC who had received prior adjuvant doxorubicin. Furthermore, anti-tumor activity and time to treatment failure were significantly improved compared with patients who received treatment based on conventional doxorubicin for their MBC. This analysis revisits the therapeutic option of including doxorubicin in the treatment of MBC patients who have had prior adjuvant anthracycline exposure. *Anti-Cancer Drugs* **17:587–595 © 2006 Lippincott Williams & Wilkins.**

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Jewish General Hospital, McGill University Department of Oncology, Montreal, Quebec, Canada, Duke University Medical Center, Durham, North Carolina, USA and Sopherion Therapeutics, Princeton, New Jersey, USA.

Correspondence to G. Batist, Jewish General Hospital, 3755 Cote St Catherine, Montreal, PQ H3T 1E2, Canada.
Tel: +1 514 340-7915; fax: +1 514 340-7916;
e-mail: gbatist@onc.jgh.mcgill.ca

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Introduction

For three decades, doxorubicin (Adriamycin; Pharmacia, Peapack, New Jersey, USA) has been the most active chemotherapeutic agent in the treatment of advanced breast cancer [1–5]. Its anti-tumor activity is further enhanced when used in combination with cyclophosphamide. Unfortunately, little change in overall survival has been observed with currently available chemotherapeutic agents used in metastatic disease [6–9]. In terms of tolerability, doxorubicin is often limited by cardiomyopathy [10–12]. The risk of developing congestive heart failure (CHF) increases sharply with increasing total cumulative doses higher than 450 mg/m^2 [13]. The use of anthracycline-containing regimens in adjuvant therapy has therefore limited the use of doxorubicin administered to patients with advanced or metastatic disease.

Liposome-encapsulated doxorubicin (Myocet; Elan, Princeton, New Jersey, USA) is a non-pegylated formulation designed to reduce the risk of cardiotoxicity associated with doxorubicin while preserving its anti-tumor efficacy [14,15]. Two randomized phase III trials, in combination with cyclophosphamide (Study 1 [16]) and as a single agent (Study 2 [17]), respectively, showed that liposomal doxorubicin was significantly less cardiotoxic than conventional doxorubicin in the first-line treatment of metastatic breast cancer (MBC) [16,17].

This analysis aims to ascertain the safety (cardiotoxicity) and efficacy of non-pegylated liposomal doxorubicin [Myocet (M)] compared with conventional doxorubicin (A) in patients with MBC who had received adjuvant anthracycline treatment and were at higher risk of developing iatrogenic cardiomyopathy.

Patients and methods

Patient population

The present analysis was based on all evaluable patients from the two studies [16,17] who had received prior adjuvant doxorubicin. The original entry criteria in both studies permitted enrolment of patients who had received adjuvant doxorubicin up to a maximum lifetime dose of 300 mg/m^2. For both studies, patients were eligible if they were 18 years and older, and had proven breast cancer, performance status of ≤ 2 (WHO criteria) and life expectancy of at least 3 months. Patients were required to have a resting left ventricular ejection fraction (LVEF) $\geq 50\%$. All patients gave written, informed consent before randomization. Full patient eligibility criteria are provided in the original reports [16,17]. Table 1 summarizes the study design and main outcomes of the studies. The median dose of adjuvant doxorubicin that had been received was 240 mg/m^2 (range 63–360) in the AC group and 240 mg/m^2 (range 100–300) in the MC group. The median time from the last adjuvant doxorubicin dose was 28 months (7–96) for the AC group and 28 months (6–72) for the MC group (Table 2).

Drug regimens

At each center participating in the original studies, patients were stratified by prior adjuvant anthracycline therapy and randomized to one of the two treatment groups using a balanced block design. In Study 1 [16], patients received either non-pegylated liposomal doxorubicin (M) 60 mg/m^2 or conventional doxorubicin (A) 60 mg/m^2, each in combination with cyclophosphamide (C) 600 mg/m^2. In Study 2 [17] patients received either M 75 mg/m^2 or A 75 mg/m^2. Dose reduction was required for a platelet nadir less than 50 000 cells/μl, absolute neutrophil count nadir less than 500 cells/μl, grade 3/4 vomiting or mucositis, or serum bilirubin ≥ 2 mg/dL on repeat testing.

Clinical setting

For both studies [16,17], patients were treated on an outpatient basis in specialist cancer centers or in hospital oncology departments.

Disease assessments

Details of disease assessments (both studies followed the same procedure) are described in the reports of Studies 1 and 2 [16,17].

Efficacy and safety assessment

All randomized patients in the original studies [16,17] were assessed for efficacy. An independent committee, blinded to treatment assignment, assessed tumor measurements and other efficacy data. All treated patients were evaluated for safety, including cardiac toxicity. All clinical and laboratory toxicities were graded by the National Cancer Institute Common Toxicity Criteria.

Retrospective assessment of outcome measures

This retrospective analysis was based on data collected during two randomized controlled clinical trials [16,17] in patients treated for MBC who had received anthracyclines as part of their adjuvant therapy. The analysis presented here examines the cardiotoxicity and efficacy of non-pegylated liposomal doxorubicin (M) versus conventional doxorubicin (A).

Cardiotoxicity was defined as the lifetime dose of doxorubicin to a cardiac event (reduction in LVEF). Efficacy was measured as the overall response rate [complete response (CR) + partial response (PR)] to treatment, time to treatment failure, time to disease progression and overall survival.

Statistical analysis

Distribution of time-to-event was estimated by the Kaplan–Meier product-limit method and curves were

Table 1 Summary of design and results of Study 1 [16] and Study 2 [17]

	Study 1		Study 2	
Objectives	to determine if M + C results in significantly less cardiotoxicity than the same dose and schedule of A + C while providing comparable anti-tumor activity		to determine if single-agent M results in significantly less cardiotoxicity than the same dose and schedule of A while providing comparable anti-tumor activity	
Setting	first-line treatment of MBC			
Study design	randomized, multicenter, controlled clinical trial			
Treatment schedule	every 3 weeks until disease progression or unacceptable toxicity (including cardiotoxicity)			
Drug regimen	M60 mg/m^2 + C600 mg/m^2	A60 mg/m^2 + C600 mg/m^2	M75 mg/m^2	A75 mg/m^2
Outcome measures				
overall response (%)	43	43	26	26
time to treatment failure (months)	4.6	4.4	2.8	2.8
time to disease progression (months)	5.1	5.5	2.9	3.2
overall survival (months)	19.0	16.0	15.7	21.2
cardiotoxicity (%)	6[a]	21	17[a]	37
lifetime dose of doxorubicin at onset of first cardiotoxic event (mg/m^2)		480	785[a]	533
Sample size	142	155	108	116
No. of patients who received adjuvant anthracyclines	14 (10%)	15 (10%)	18 (17%)	21 (8%)

[a]$P = 0.001$ versus doxorubicin (A)-based regimen.

compared using the log-rank χ^2-test. The Cox proportional-hazards model was employed to estimate the hazard ratio (HR). Two-sided confidence intervals (CIs) were applied to all time-to-event variables.

Cochran–Mantel–Haenzsel statistics were used in comparing the rates of protocol-defined cardiac events in the two treatment groups. Kaplan–Meier curves were used to plot the lifetime cumulative doxorubicin dose at the onset of cardiac events (i.e. dose of prior adjuvant doxorubicin plus on-study cumulative dose of liposomal or conventional doxorubicin); curves were compared by log-rank test and a HR was estimated by the Cox regression.

Results

This report is based on prospectively collected data on 68 patients who participated in either Study 1 [17] or Study 2 [16], both randomized controlled trials of treatment of patients with MBC. All 68 patients had received adjuvant anthracycline treatment before enrolling to participate in the randomized controlled trial. Two hundred and ninety-seven patients entered Study 1 [16], of whom 29 patients had received prior adjuvant doxorubicin: 14 were randomized to receive M60 + C600 and 15 to receive A60 + C600. Two hundred and twenty-four patients entered Study 2, of whom 39 had received prior adjuvant doxorubicin: 18 were randomized to receive M75 and 21 to receive A75. The two studies included in this analysis are described in Table 1.

Demographics

Median age was 54 years in both treatment groups. All relevant pre-treatment characteristics were balanced between the two treatment groups (Table 2).

Table 2 Characteristics of the 68 patients assessed in the analysis

	M ± C (n=32)[a]	A ± C (n=36)[b]
Median age [years (range)]	54 (36–73)	54 (29–65)
Median adjuvant doxorubicin [mg/m^2 (range)]	240 (100–300)	240 (63–360)
Median time from the last dose of adjuvant doxorubicin [months (range)]	28 (6–72)	28 (7–96)
WHO performance status [n (%)]		
0	15 (47)	15 (42)
1	15 (47)	19 (52)
2	2 (6)	2 (6)
Estrogen receptor-positive [n (%)]	14 (44)	23 (64)
Progesterone receptor-positive [n (%)]	14 (44)	22 (61)
Visceral involvement [n (%)]	24 (75)	27 (75)
Prior radiation therapy [n (%)]	21 (66)	23 (64)
Prior hormonal therapy [n (%)]	24 (75)	26 (72)

[a]Group comprises 14 patients from Study 1 treated with M60 + C600 and 18 patients from Study 2 treated with M75.
[b]Group comprises 15 patients from Study 1 treated with A60 + C600 and 21 patients from Study 2 treated with A75.

Study drug exposure

The median number of cycles was 4.5 in the liposomal doxorubicin-treated group compared with 3 in the doxorubicin-treated group, resulting in a higher median cumulative dose on liposomal doxorubicin (308 versus 225 mg/m^2) (Table 3). A delay in dosing was rather infrequent, resulting in an overall median of 21 days per cycle.

Response rates

The objective response rates (CR + PR) were 31% ($n = 10$) in the subgroup of patients who received liposomal doxorubicin compared with 11% ($n = 4$) in the group receiving conventional doxorubicin [Cochran–Mantel–Haenszel $P = 0.04$, odds ratio (OR) = 4.0] (Table 4).

Table 3 Exposure to study drug of 68 patients included in the analysis

	M ± C (n=32)[a]	A ± C (n=36)[b]
Median no. of cycles (range)	4.5 (1–9)	3.0 (2–6)
Median total cumulative dose [mg/m^2 (range)]	308 (60–540)	225 (100–495)
Median total lifetime dose [mg/m^2 (range)]	548 (160–785)	460 (183–750)
Total no. of cycles	139	120
cycles with dose reduction (%)	17	15
for myelosuppression (%)	16	14
for other toxicity (%)	1	1
cycles delayed by $\geq$ 7 days (%)	15	11
cycles with granulocyte colony-stimulating factor use (%)	47	61
cycles with blood transfusion (%)	3	14
Reason patients off-study		
cardiotoxicity	13	28
risk of cardiotoxicity	6	3
other adverse events	0	8
disease progression	47	36
response/stable disease	31	6
other reasons	3	19

[a]Group comprises 14 patients from Study 1 treated with M60 + C600 and 18 patients from Study 2 treated with M75.
[b]Group comprises 15 patients from Study 1 treated with A60 + C600 and 21 patients from Study 2 treated with A75.

Table 4 Efficacy assessment (response) of 68 patients included in this analysis

	M ± C (n=32)[a]	A ± C (n=36)[b]
Complete response [n (%)]	2 (6)	1 (3)
Partial response [n (%)]	8 (25)	3 (8)
Stable disease [n (%)]	11 (35)	17 (47)
Progressive disease [n (%)]	9 (28)	12 (34)
Not evaluable [n (%)]	2 (6)	3 (8)
Overall response (complete + partial) [n (%)] [95% CI]	10 (31) [16–50]	4 (11) [3–26]
OR (M ± C/A ± C) [95% CI]	4.00 [1.07–15.0]	
Cochran–Mantel–Haenszel stratified χ^2P	0.04	

[a]Group comprises 14 patients from Study 1 treated with M60 + C600 and 18 patients from Study 2 treated with M75.
[b]Group comprises 15 patients from Study 1 treated with A60 + C600 and 21 patients from Study 2 treated with A75.
The definitions of response were according to WHO criteria.

Time to treatment failure

There was a significant difference in the median time to treatment failure in favor of the subgroup receiving liposomal doxorubicin (4.2 versus 2.1 months, log-rank $P = 0.01$, HR = 2.06) (Fig. 1).

Time to progression

The median time to progression was 4.5 months for the liposomal doxorubicin subgroup compared with 3.4 months for conventional doxorubicin (log-rank $P = 0.66$, HR = 1.14) (Fig. 2).

Overall survival

There was no difference in the median survival time between the two treatment groups (16 versus 15 months, log-rank $P = 0.71$, HR = 1.12) (Fig. 3).

Cardiotoxicity

Cardiac events leading to removal from the original studies occurred in seven patients (22%) treated with liposomal doxorubicin and 14 patients (39%) treated with conventional doxorubicin (Table 5). A Kaplan–Meier estimate of the probability of the first onset of a cardiac event, as related to the lifetime cumulative dose of doxorubicin, shows that risk of cardiotoxicity was much higher with conventional doxorubicin treatment than with liposomal doxorubicin in this subgroup of patients (log-rank $P = 0.001$, HR = 5.4) (Fig. 4).

There were four cases of CHF among the whole subgroup. One case was in a patient from the liposomal doxorubicin group, but occurred 11 months after the last dose of study drug treatment, during which time she had been subsequently treated with 5 cycles of mitomycin plus mitoxantrone. This patient had received a prior adjuvant doxorubicin dose of 290 mg/m^2 and prior chest wall irradiation, and received 5 cycles of liposomal doxorubicin for a total lifetime doxorubicin dose of 785 mg/m^2. Four months after the last dose, a MUGA scan showed that LVEF was 46% (a 16-point decrease from baseline). Three patients on conventional doxorubicin developed clinical CHF at lifetime doses of 480–750 mg/m^2. All three cases occurred within 3 months of the last dose of doxorubicin and were attributed to the study-drug treatment.

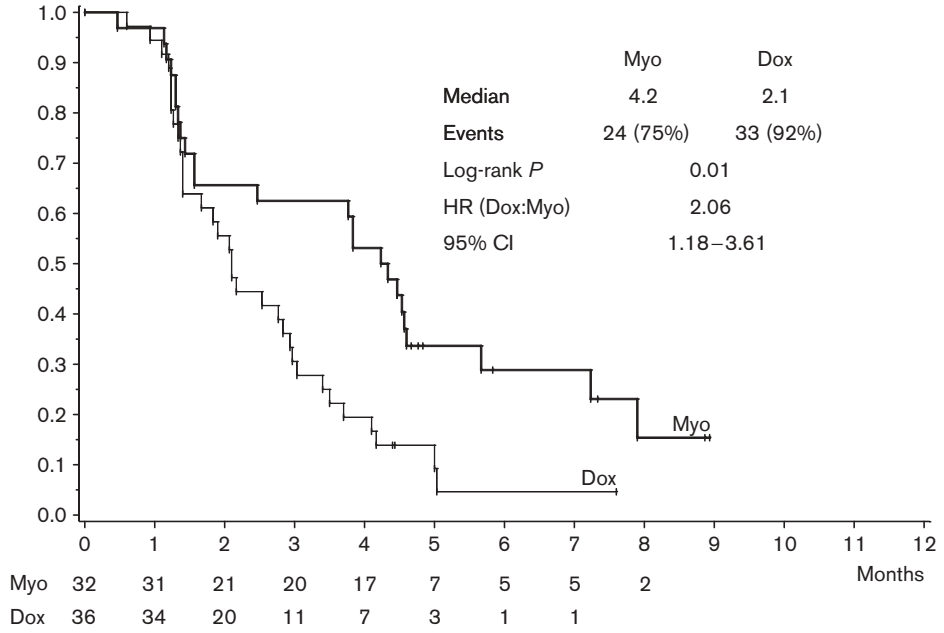
Safety and tolerability

There were no new or unexpected toxicities in the liposomal doxorubicin group and there was no increase in incidence or severity of known doxorubicin toxicities. There was no drug-related death. Myelosuppression was the most frequent and severe toxicity, with neutropenia (ANC $< 500/\mu l$) affecting approximately 60% of patients in both groups. There was little difference between the two treatment groups in incidence of grade 3/4 toxicities. There was no report of palmar–plantar erythrodysesthesia (PPE; hand–foot syndrome) with this non-pegylated liposomal formulation of doxorubicin.

Discussion

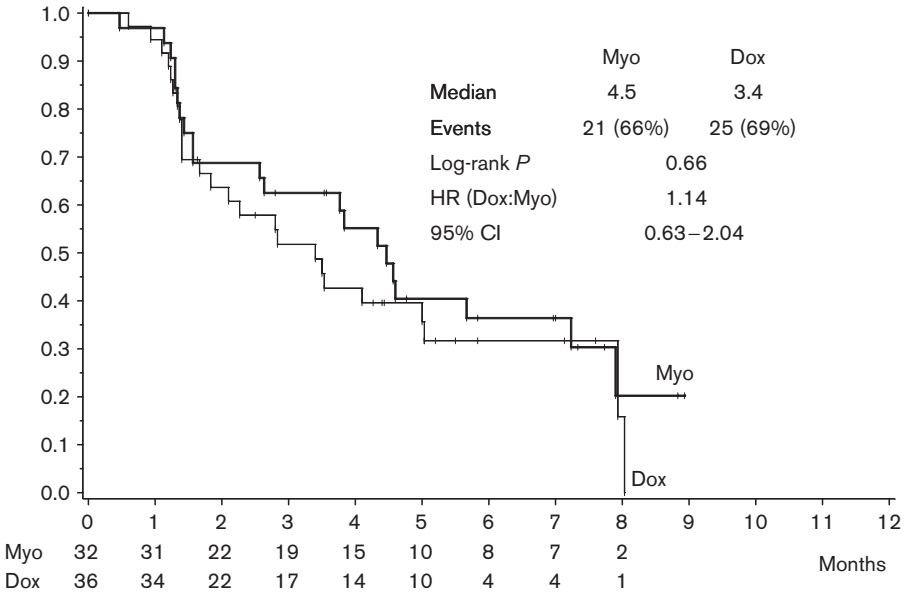
The results of this analysis suggest that patients with breast cancer who relapse later than 6 months after anthracycline treatment in the adjuvant setting may respond to anthracycline-based treatment of metastatic disease and, furthermore, that there may be greater benefit from non-pegylated liposomal doxorubicin, either alone or in combination with cyclophosphamide, as first-line treatment in the metastatic setting compared with conventional doxorubicin. The benefits demonstrated in this analysis include a significantly higher overall response rate and a significantly prolonged time to treatment failure. The patients receiving liposomal doxorubicin were four times more likely to achieve a CR or PR (OR 4.0, Myocet:doxorubicin), while the risk of treatment

Fig. 1



Time to treatment failure in the 68 patients included in the analysis. Time to treatment failure was defined as the time from day 1 of treatment to removal from study for an adverse event, the onset of cardiac toxicity, lack of efficacy, patient intolerance, first evidence of progressive disease or death.

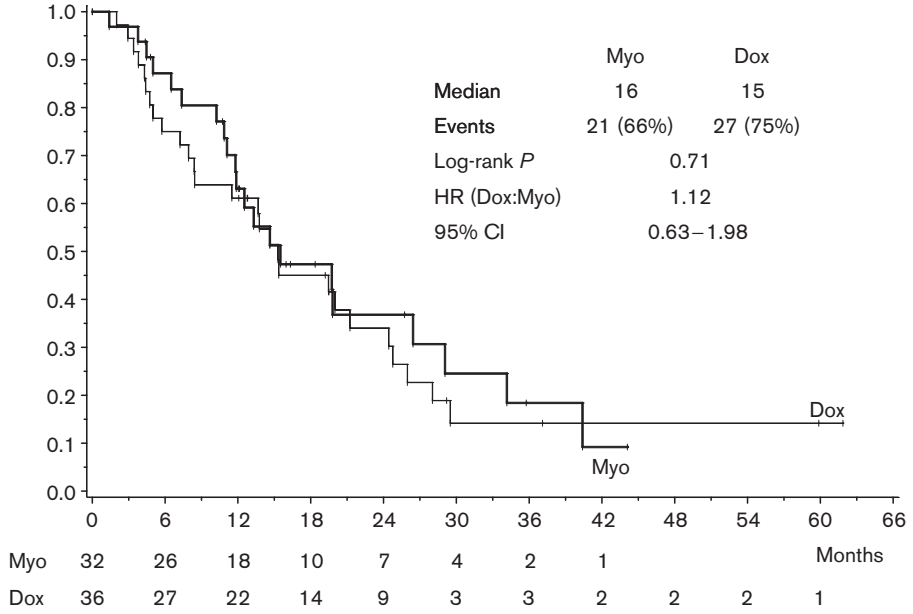
Fig. 2



Time to disease progression in the 68 patients included in the analysis. Time to progression was defined as the time from day 1 of treatment to the first evidence of progressive disease or death.

failure was half that for patients receiving conventional doxorubicin (HR 2.06, doxorubin:Myocet). While these data are quite interesting, we are cautious in their interpretation in the absence of a difference in time to disease progression. It is, however, important to include in this analysis the fact that treatment with

Fig. 3



Overall survival time in the 68 patients included in the analysis. Overall survival was defined as the time from day 1 of treatment to death.

non-pegylated liposomal doxorubicin significantly reduced the risk of cardiotoxicity in this group of patients who were at high cardiac risk. The incidence of cardiotoxic events was halved and patients were able to achieve a 37% greater lifetime cumulative dose of doxorubicin before reaching a cardiotoxicity endpoint. In the only case of CHF on liposomal doxorubicin, the onset of CHF occurred at a higher cumulative dose than the three cases on doxorubicin. Furthermore, this patient had received 290 mg/m^2 of adjuvant doxorubicin and 5 cycles of mitoxantrone as third-line treatment of her MBC before the onset of CHF.

These results were obtained by the method of retrospective analysis, the findings of which may be open to criticisms of introduction of bias and confounding factors. We believe that the present analysis can withstand these criticisms, since it based on data collected prospectively in two randomized controlled studies conducted according to protocols that were identical apart from whether doxorubicin was administered alone or in combination with cyclophosphamide. The addition of cyclophosphamide to either Myocet or doxorubicin did result in increased efficacy as well as toxicity compared to Myocet/doxorubicin alone. However, in either setting, the Myocet-based regimen resulted in equivalent anti-tumor efficacy and dramatically reduced cardiotoxicity compared to doxorubicin-containing treatment [16,17]. The proportion of patients who had cyclophosphamide was very similar in each of the groups analyzed in this study and the conclusion is the same when these patients were analyzed separately. The retrospective analysis was performed in order to answer the specific question of safety and efficacy of doxorubicin treatment in patients at high cardiac risk, and the two randomized controlled trials provided a well-matched and sufficiently large population of patients in whom this question could be addressed.

In the two randomized controlled trials, there were no differences in response and time-to-event variables between the liposomal and conventional doxorubicin treatment groups. The retrospective analysis showed that, similarly, the time to disease progression and overall survival did not differ for high-risk patients treated with liposomal or conventional doxorubicin. However, the 3-fold higher response rate and doubling of time to treatment failure with liposomal doxorubicin are of sufficient interest to warrant further exploration in a future prospectively conducted clinical trial.

The pharmacological characteristics of liposomal doxorubicin can account for improved efficacy and reduced cardiotoxicity compared with conventional doxorubicin. Liposomal formulation was developed with the objective of improving the therapeutic index of the active drug. The microscopic lipid vesicles are designed to be retained in the circulation at sites of intact vasculature serving healthy tissues such as the heart, thus reducing the toxicity of the active drug. In contrast, the liposomes will be more readily taken up into tissues with leaky

vasculature, such as tumor sites, areas of inflammation and organs rich in reticuloendothelial system tissue. As reviewed recently [18,19], high concentrations of drug within the liposome and a low rate of drug leakage in the circulation are achieved by loading the doxorubicin via a pH gradient and forming a complex with citrate within the vesicle. All these characteristics should result in reduced drug distribution to the myocardium, while drug delivery to tumor sites is maintained or even increased. Thus, administering a less-toxic drug with improved therapeutic index may allow patients to respond better. Our retrospective analysis showed that patients treated with a non-pegylated liposomal doxorubicin-based regimen fared better in terms of overall response and time to treatment failure. It is possible that these patients, who had responded to doxorubicin in the adjuvant setting, were obtaining more benefit from liposomal doxorubicin for their metastatic disease because of the preferential distribution of the active drug to the tumor sites.

Table 5 Changes in cardiac function by total lifetime doxorubicin dose in the 68 patients included in this analysis

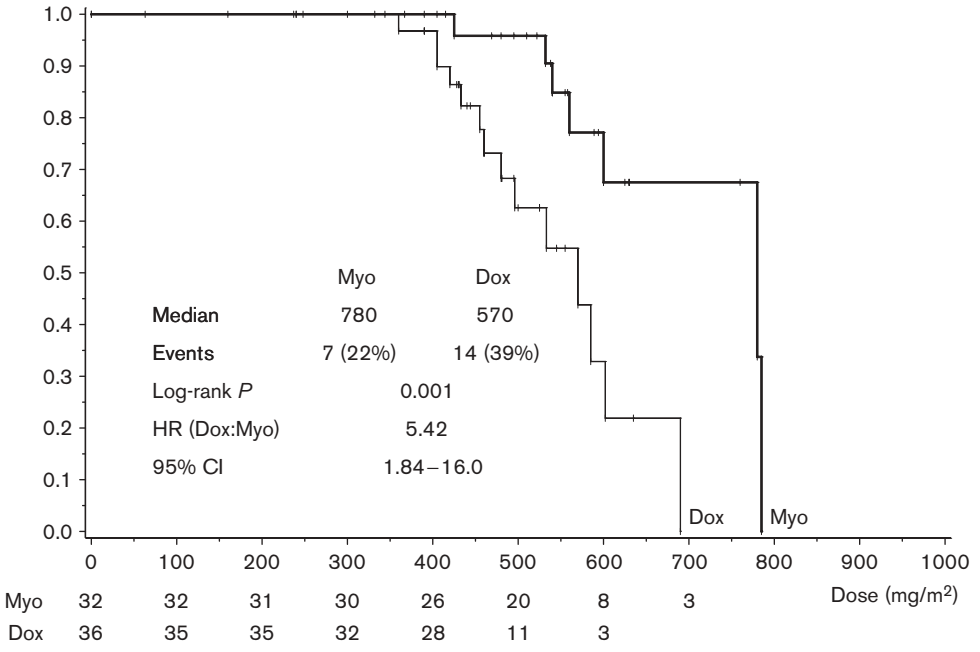
Lifetime dose (mg/m^2)	Patients at risk (*n*)		EF change[c](%)	
	M±C (*n*=32)[a]	A±C (*n*=36)[b]	M±C (*n*=32)[a]	A±C (*n*=36)[b]
0–199	32	36	2	0
200–299	31	35	0	0
300–399	30	32	−2	−6
400–499	26	28	−4	−8
500–599	20	11	−8	−7
600–699	8	4	−2	−31
≥ 700	3	1	−12	−26

[a]Group comprises 14 patients from Study 1 treated with M60+C600 and 18 patients from Study 2 treated with M75.
[b]Group comprises 15 patients from Study 1 treated with A60+C600 and 21 patients from Study 2 treated with A75.
[c]Median change from baseline to off study.
EF, ejection fraction.

Another potential explanation may lie in the imbalance in hormone receptor status between the two groups, with the Myocet-containing group more frequently both estrogen and progesterone receptor-negative. While negative receptor status may be associated with a more aggressive natural history of breast cancer, recent analyses of large clinical trials in breast cancer suggest that hormone receptor-positive patients benefit less from adjuvant chemotherapy [20].

Varying the physical characteristics of the liposome will alter the pharmacokinetics, e.g. pegylated liposomal doxorubicin has a much longer half-life than non-pegylated liposomal doxorubicin and a smaller volume of distribution [21,22], suggesting that clinical effects of one liposomal formulation cannot be extrapolated to another. Pegylated liposomal doxorubicin has indeed been shown to be effective in treating MBC and to have lower cardiac toxicity than free doxorubicin, and there have been no studies comparing the pegylated versus non-

Fig. 4



Lifetime dose of doxorubicin to a cardiotoxicity endpoint in the 68 patients included in the analysis.

pegylated liposomal doxorubicin formulations [23,24]. Of note, the non-pegylated formulation is associated with a very low incidence of skin toxicity as PPE, with only one case of grade 2 PPE among the 250 patients (0.4%) treated with liposomal doxorubicin in the two randomized studies [16,17]. The pegylated liposome, probably because of its prolonged half-life, is commonly associated with PPE which may limit dose intensity of treatment [25].

There have been many attempts to modify the cardiac toxicity while retaining the efficacy of anthracyclines. In fact, the iron-chelating drug dexrazoxane was approved for concomitant use with doxorubicin and has proven effective without compromising the anti-tumor efficacy of the anthracyclines [26,27]. There are no data comparing the combination of dexrazoxane plus anthracycline to non-pegylated liposomal doxorubicin, although it may be the case that an additional drug is a more cumbersome therapy for administration. In conclusion, non-pegylated liposomal doxorubicin improved the therapeutic index of doxorubicin in this cohort of high-risk patients receiving first-line treatment for MBC. Cardiotoxicity was significantly reduced ($P = 0.001$), and significant improvements in anti-tumor activity ($P = 0.04$) and time to treatment failure ($P = 0.01$) were demonstrated with treatment based on liposomal doxorubicin.

Given the risk of cardiac toxicity from accumulated doxorubicin dose, it has become less common to re-treat MBC patients with doxorubicin if they had received it as part of their adjuvant chemotherapy. The selection has therefore often turned to a taxane as a single agent, even though taxanes in combination with doxorubicin are more efficacious [28]. The data derived in this analysis add to the case for further study of liposomal doxorubicin in patients in this setting. Recent studies combining Myocet with both taxanes and with trastuzumab provide an important context in which to appreciate the possibility of using this anthracycline formulation in patients who have received prior anthracyclines [29]. In this clinical trial, the investigators observed a greater than 90% overall response rate and a greater than 20% CR rate in patients with both metastatic and locally advanced breast cancer. The median survival is not reached and the time to tumor progression for the group of 54 patients exceeds 24 months. While this certainly does not prove enhanced survival times, these data are certainly impressive. Cardiac toxicity was below 5% in these patients, suggesting that trastuzumab can be safely combined with the Myocet formulation of doxorubicin, in combination with taxol. A randomized trial comparing taxol/trastuzumab to taxol/trastuzumab plus Myocet will determine the feasibility of re-using doxorubicin in the metastatic setting, even if patients had received prior adjuvant doxorubicin.

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