Non-pegylated liposomal doxorubicin combined with gemcitabine as first-line treatment for metastatic or locally advanced breast cancer. Final results of a phase I/II trial

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CLINICAL TRIAL

Non-pegylated liposomal doxorubicin combined with gemcitabine as first-line treatment for metastatic or locally advanced breast cancer. Final results of a phase I/II trial

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Abstract Doxorubicin and gemcitabine are active as single agents in breast cancer, have different mechanisms of action, and mainly have non-overlapping side effects. Dose-dependent doxorubicin-related cardiac toxicity is the principal limitation in the metastatic setting. This open, multicenter, single-arm phase I/II study assessed the safety and activity of gemcitabine in combination with non-pegylated liposomal doxorubicin (Myocet®), a more cardiac-friendly anthracycline, in the first-line treatment of patients with advanced breast cancer. We aimed to determine the optimal recommended dose (RD) of gemcitabine combined with Myocet® in a population, with performance status ≥ 2 and LVEF $\geq 50\%$. A formal phase II study was performed afterwards. A total of 53 patients were recruited. Gemcitabine 900 mg/m^2 intravenously day 1 and 8 combined with Myocet® 55 mg/m^2 intravenously day 1, every 21 days, was the final RD. The principal toxicity observed was hematological, and 48% of patients developed grade 3–4 neutropenia. Other toxicities were mild and infrequent, including nausea and vomiting. There were no symptomatic cardiac events despite the fact that 36% of the patients had received prior treatment with adjuvant anthracyclines. Objective responses were observed in 51.1% of 47 evaluable patients (95% CI: 36–66%), including two complete response. In addition, 14 patients (29.8%) demonstrated stable disease. The combination of Myocet® and gemcitabine at the RD is safe and has encouraging clinical activity in patients with advanced breast cancer, without apparent cardiac toxicity in anthracycline-pretreated patients. These data support further development of this combination.

Keywords Liposomal doxorubicin · Gemcitabine · Advanced breast cancer

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Introduction

In 2007, the incidence of this disease reached 180,510 new cases in the USA and 40,910 deaths were attributed to this type of tumor [1]. There have been major advances in the management of breast cancer which have resulted in less aggressive surgery and better overall survival [2–4]. However, there has been less progress in patients who present or develop metastatic disease.

The anthracyclines have been one of the cornerstones in the breast cancer treatment. In the adjuvant setting, there is

evidence of improved time to progression and overall survival in patients treated with regimens involving doxorubicin [5–8]. In patients with metastatic disease, doxorubicin has resulted in response rates of 30–50%. The drug, however, induces a cumulative dose-dependant cardiac toxicity characterized by a progressive myopathy that can lead to fatal congestive heart failure (CHF) [9, 10]. Importantly, the risk of CHF has been found to increase at cumulative doses over 450 mg/m^2 [11]. This finding is of special interest because of the increasing use of doxorubicin in the adjuvant setting, which could lead to limitation of its use in the metastatic disease. One strategy to reduce this problem has been the use of liposomal technology [12, 13].

Non-pegylated liposomal doxorubicin (NPLD) (Myocet®) is a complex of doxorubicin citrate encapsulated in non-pegylated liposomes. Myocet® was developed to selectively reduce the release of active doxorubicin in normal tissues while increasing its concentration in tumor tissues, with the aim of reducing toxicity and increasing efficacy [12, 14–16]. Because of their size, the liposomes do not pass through the capillary beds of normal tissues while they readily diffuse through the chaotic and highly permeable capillaries of tumors. A series of phase II and III studies have shown that NPLD, both as single agent or in combination with other drugs, is effective and safe in patients with breast cancer with an associated reduction in incidence and severity of cardiac events [15, 17–20].

One of the newest drugs with activity in breast cancer is gemcitabine. Administered as a single agent to patients with advanced breast cancer, gemcitabine is very well tolerated and results in a 15–46% response rate [21–23]. Gemcitabine has been tested in combination with doxorubicin in a phase II study conducted in Spain [24]. In this trial, gemcitabine was administered at doses of 800–1,000 mg/m^2 and doxorubicin was given at 25 mg/m^2 on a 3-out-of-every-4-weeks basis. However, most patients required either dose reduction or omission of treatment on day 15 due to hematological toxicities. The overall response rate was 55%. The median time to progression was 11.5 months and the overall survival was 27 months. Although only one patient had an asymptomatic decrease in the left ventricular ejection fraction (LVEF), it should be taken into account that only 19% of patients had received previous anthracyclines. Based on these data, the combination of gemcitabine and doxorubicin appears attractive in patients with breast cancer.

Considering the different mechanisms of action and non-overlapping toxicity profiles of NPLD and gemcitabine as single agents, and the activity observed with the combination of conventional doxorubicin and gemcitabine, we designed this open, multicenter, single-arm phase I/II study to test the efficacy and safety of the NPLD (Myocet®) and gemcitabine combination in the first line treatment of patients with advanced or locally advanced breast cancer.

Patients and methods

Patients

Patients with histologically confirmed metastatic or locally advanced breast cancer, with at least one measurable lesion according to the RECIST criteria [25], were enrolled in this study between February 2003 and September 2005 in eight Spanish centers. Other eligibility criteria included age over 18 years; ECOG (Eastern Cooperative Oncology Group) performance status of $\leq$2; life expectancy of >3 months; hemoglobin $\geq$10 g/dl, neutrophils $\geq$2,000/μl, platelets $\geq$100,000/μl, and adequate liver, renal and cardiac (left ventricular ejection fraction (LVEF) $\geq$50%) functions. Patients who had received adjuvant therapy were required to have had a disease-free interval of at least 12 months after completion of therapy, and for those who had received prior adjuvant anthracycline-based treatment, the total cumulative dose had to be <300 mg/m^2 for doxorubicin and 450 mg/m^2 for epirubicin; previous hormonal treatment and radiotherapy (provided it had not affected more than 30% of the bone marrow reserve) were permitted.

Patients were excluded if they had received previous chemotherapy treatment for advanced disease or were pregnant; patients with severe comorbid conditions or a history of further malignancy, other than basal or squamous cell carcinomas of the skin, carcinoma in situ of the cervix, or contralateral breast cancer, in the last 5 years were not eligible. No other restrictions due to age or extent of disease were used. All patients signed an informed consent form before the study entry. The study protocol was approved by the institutional review board of each participating institution and the studies were conducted in accordance with the principles of the Declaration of Helsinki and the applicable guidelines for Good Clinical Practice.

Drugs administration

In the dose escalation part of the study, patients were treated in cohorts with escalating doses of gemcitabine. All patients received a fixed dose of NPLD (60 mg/m^2, 1 h infusion) administered on day 1. The starting dose of gemcitabine was 1,000 mg/m^2, administered i.v. for 30 min on days 1 and 8, every 21 days. The dose of gemcitabine was scheduled to be escalated up to 1,200 mg/m^2 in the subsequent cohort. The maximum total number of cycles was 6. The RD was defined as the highest dose at which less than one-third of patients developed DLT during the first two courses.

Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria, version 2. Intrapatient dose escalation was not permitted. DLT was defined as the following: (a) delay in treatment of more than 7 days due to hematological toxicity; (b) febrile neutropenia; (c) thrombocytopenia with bleeding of grade $\geq$3, and (d) non-hematological toxicity of grade $\geq$3, except for nausea and/or vomiting in the absence of an appropriate anti-emetic regimen.

Patients received anti-emetic treatment at the physician's discretion. The use of prophylactic colony-stimulation factors was not allowed.

Study design

This was an open, multicenter, single-arm phase I/II study. Pretreatment examination included a complete medical history and physical examination with ECOG performance status, complete blood cell (CBC) count, standard biochemistry including the tumor marker CA 15.3, electrocardiogram and an analysis of the LVEF, and clinical tumor assessment (if possible, computed tomography (CT) scans of the chest and abdomen, and bone scan). Physical examination, monitoring of toxic effects, and a CBC were performed at the beginning of each cycle. A CBC was also obtained on day 8 before the administration of gemcitabine. Response was evaluated after every three cycles of chemotherapy and every 3 months thereafter. An electrocardiogram was performed before each course. LVEF analysis was repeated at least at off-study.

Before the start of a cycle, an ANC of >1,500/μl and platelets >100,000/μl were required. The presence of anemia did not required dose modification. All non-hemato logical toxicities were required to return to grade 1, excluding alopecia and/or vomiting, before treatment. Adjustments of dose were based on the nadir hematological values for the preceding cycle. Dose reductions were maintained for all subsequent cycles. Treatment was delayed for a maximum of 3 weeks to allow recovery.

Study endpoints

The primary endpoint of the phase I study was to determine the RD of the combination of non-pegylated liposomal doxorubicin and gemcitabine as first-line treatment of patients with metastatic or locally advanced breast cancer. The primary objective of the phase II study was to determine the overall response rate (ORR) to the combination, which was defined as complete response and partial response in patients treated with the RD.

Secondary aims included determining time to progression, time to response, response duration, time to treatment failure, 1-year survival, overall survival, and safety.

Statistical analysis

All patients were assessable for response and toxicity according to the intention-to-treat principle. Progression-free survival was measured from the date of initial treatment to the date of disease progression. Overall survival was measured from the date of the first course of chemotherapy to the date of death or to the last follow-up examination. Time-to-event distributions were estimated by Kaplan–Meier analysis [26]. 95% Confidence intervals for response rate were calculated using methods for exact binomial confidence interval estimation [27]. Qualitative factors were compared using Pearson χ^2 contingency table analysis.

A sample size of 48 patients in the phase II study was planned on the basis of 80% power to demonstrate a 55% response rate, assuming a lower level of interest of 30% with a one-sided test of 0.05.

All endpoints were also analyzed in the subgroup of patients that had received previous anthracycline treatment, and compared using the log-rank method. The SAS statistics program, version 8.2, was used for all statistical analyses.

Results

Patient characteristics

A total of 53 patients with metastatic or locally advanced breast cancer were included in the study. Of those patients, 20 received NPLD 60 mg/m^2 and gemcitabine 1,000 mg/m^2 or dose level 1 (DL-1) (60/1,000 regimen) and 33 received NPLD 55 mg/m^2 and gemcitabine 900 mg/m^2 or dose level 2 (DL-2) (55/900 regimen) (see below). All 53 patients were included in the safety population. However, six of these patients withdrew from the study without any post-basal tumor assessment. One patient withdrew because of a protocol deviation, one patient withdrew consent, one patient due to an adverse event (hidroneumothorax), two patients due to grade 4 treatment-related toxicity (the first one developed grade 4 emesis and the second one developed grade 4 diarrhea, grade 4 febrile neutropenia, and grade 4 plaquetopenia) and one because of rapid progression with CNS metastasis and exitus. Thus, the efficacy population only included 47 patients. Patient characteristics of the efficacy population are summarized in Table 1. Median age was 59 years (range 32–79) and 29% of the patients had hormone receptor positive cancers; the majority of tumors were ductal infiltrating carcinoma (92%) and 37% of patients had visceral (lung or liver) metastatic disease.

Table 1 Baseline patient characteristics

Characteristics	DL-1 ($n = 19$)	DL-2 ($n = 28$)	Total ($n = 47$)
Age in years, mean (range)	58 (42–73)	61 (32–79)	60 (32–79)
Postmenopausal, *N* (%)	17 (90)	23 (82)	40 (85)
Functional stage performance status (ECOG)			
0	10 (53)	18 (64)	28 (60)
1	8 (42)	9 (32)	17 (36)
2	1 (5)	1 (4)	2 (4)
Prior cardiovascular events, *N* (%)	4 (21)	9 (32)	13 (28)
Controlled hypertension	3	8	11
Peripheral arteriopathy	1	0	1
Prior CVA	0	1	1
LVEF ≥50%	19 (100)	28 (100)	47 (100)
Tumor histology, *N* (%)			
Ductal	17 (90)	26 (93)	43 (92)
Lobular	0	2 (7)	2 (4)
Tumor stage, *N* (%)			
I	3 (16)	1 (4)	4 (9)
II	7 (37)	7 (25)	14 (30)
III	3 (16)	6 (21)	4 (9)
Hormone receptors, *N* (%)			
Positive	14 (74)	15 (54)	29 (62)
Negative	4 (21)	9 (32)	13 (28)
Unknown	1 (5)	4 (14)	5 (10)
Serum HER2 determination, *N* (%)			
Positive	2 (10)	2 (7)	4 (8)
Negative	15 (79)	23 (82)	38 (81)
Unknown	2 (10)	3 (11)	5 (11)
Previous treatments, *N* (%)			
Surgery	17 (89)	18 (64)	35 (74)
Radiotherapy	15 (79)	12 (43)	27 (57)
Adjuvant chemotherapy	14 (74)	12 (43)	26 (55)
Adjuvant hormonotherapy	12 (63)	12 (43)	24 (51)
Previous chemotherapy, *N* (%)			
No	5 (26)	16 (57)	21 (45)
Anthracyclines	12 (63)	5 (18)	17 (36)
Metastatic sites, *N* (%)			
Lymph nodes	9 (47)	14 (50)	23 (49)
Liver	8 (42)	13 (46)	21 (45)
Lung	9 (47)	7 (25)	16 (34)
Bone	3 (16)	7 (25)	10 (21)
Soft tissue	3 (16)	3 (11)	6 (13)
Others	0	2 (7)	2 (4)

CVA Cerebrovascular accident

Phase I: determination of the recommended dose

Three patients were treated at the first dose level (60/1,000 regimen). One patient developed a DLT consisting of grade 3 mucositis in cycle 1, after day 8. For that reason, four more patients were included in this cohort. All seven patients finalized the first two cycles of treatment. Although no other DLTs were observed in these patients, the dose of gemcitabine on day 8 had to be reduced (between 25 and 50% of the dose) in four of the 14 cycles administered (28.5% of the cycles) due to neutropenia. Moreover, in three out of the seven patients the administration of cycle 2 was delayed between 4 and 7 days due to neutropenia on day 1 of cycle 2. For safety and feasibility reasons, 60/1,000 was considered

the RD for the phase II part, without a subsequent further increase in dose to the next level.

Phase II: efficacy and toxicity

During the phase II study, thirteen more patients received the 60/1,000 regimen, so a total of 20 patients were treated with the RD. A total of 14 severe adverse events were registered for nine patients. Most of the adverse events were hematological toxicity, including seven cases of febrile neutropenia (10% of the cycles) and five cases of grades 3 and 4 thrombocytopenia (7% of the cycles). Given that the dose of the combination (liposomal doxorubicin 60 mg/m^2 and gemcitabine 1,000 mg/m^2) was jeopardizing the safety or intensity of the total dose received, a 10% reduction in the dose of both drugs was subsequently used for the new patients enrolled in the study ($n = 33$) (55/900 regimen).

A total of 235 cycles (101 in DL-1 and 134 in DL-2) were administered, with a median of five cycles per patient (range 2–6). Delay in treatment administration was reported in 61 cycles (30 in DL-1 and 31 in DL-2). The most common reason for delay was hematological toxicity (40 cycles, 17%). Dose reduction related to hematological toxicity was done in 81 cycles (34%) (Table 2). Mean dose intensity administered was 52.33 mg/m^2 for liposomal doxorubicin and 1,524.71 mg/m^2 for gemcitabine. The relative dose intensity was 91.94% for gemcitabine and 81.26% for liposomal doxorubicin.

In the total population, 35.8% of patients experienced some treatment-related adverse events (10 patients in DL-1 and 9 in DL-2). Grade 3 and 4 hematological and non-hematological toxicities are summarized in Table 3. It is noteworthy that a total of five patients (one in DL-1 and four in DL-2) withdrew from the study due to treatment-related toxicity: in the DL-1 group, one patient developed pneumotoxicity related to gemcitabine treatment after cycle 5. This patient required symptomatic treatment and continued monotherapy treatment with NPLD. In the DL-2 group, one patient developed mielotoxicity, one patient developed grade 4 emesis, another patient developed grade 4 diarrhea and febrile neutropenia after dose 8 of the first cycle, and another developed grade 4 neutropenia.

A total of 17 patients (36.1%) had received prior adjuvant treatment with anthracyclines [10 patients had received

Table 2 Characteristics of treatment administration (efficacy population, $n = 47$)

	DL-1 (101 cycles)	DL-2 (134 cycles)	Total (235 cycles)
Delay in cycle administration, *N* (%)	30 (30)	31 (23)	61 (26)
Delay due to hematological toxicity, *N* (%)	21 (21)	19 (14)	40 (17)
Dose reduction, *N* (%)			
The whole cycle	19 (19)	14 (10)	33 (17)
Day 8	39 (39)	39 (39)	72 (36)
Dose reduction due to hematological toxicity, *N* (%)	44 (43)	37 (10)	81 (34)

Table 3 Grade 3 and 4 hematological and non-hematological toxicity according to NCI criteria (safety population, $n = 53$)

	DL-1 ($n = 20$)		DL-2 ($n = 33$)		*P*-value
	Grade 3	Grade 4	Grade 3	Grade 4	
Leukopenia, *n* (%)	8 (40)	7 (35)	10 (30)	6 (18)	0.0576
Neutropenia, *n* (%)	0	11 (55)	8 (24)	8 (24)	0.0608
Thrombocytopenia, *n* (%)	7 (35)	2 (10)	4 (12)	1 (3)	0.0169
Anemia, *n* (%)	3 (15)	0	6 (18)	0	1
Febrile neutropenia, *n* (%)	4 (20)	2 (10)	2 (6)	1 (3)	0.0896
Non-hematological toxicity					
Nausea, *n* (%)	2 (10)	0	1 (3)	1 (3)	0.62
Vomiting, *n* (%)	3 (15)	0	1 (3)	1 (3)	0.35
Stomatitis, *n* (%)	5 (25)	0	4 (12)	0	0.27
Asthenia, *n* (%)	2 (10)	0	3 (9)	1 (3)	1
Liver enzymes: ↑ ALT and/or AST and/or GGT, *n* (%)	1 (5)	0	7 (21)	0	0.52
Alopecia, *n* (%)	5 (25)	0	1 (3)	1 (3)	0.08
Diarrhea, *n* (%)	0	0 (0)	1 (3)	1 (3)	0.52
Anorexia, *n* (%)	0	0	1 (3)	0	1

Table 4 Overall response rate and the best response rate (efficacy population and DL-2 population)

		Efficacy population ($n = 47$)		DL-2 population ($n = 30$)	
Best response rate	CR	2	(4.3%)	0	(0.0%)
	PR	22	(46.8%)	13	(43.3%)
	SD	14	(29.8%)	12	(40.0%)
	PD	9	(19.1%)	5	(16.7%)

epirubicin (median dose 419.65 mg/m^2, range 282–540 mg/m^2) and seven patients had received doxorubicin (median 282.33 mg/m^2, range 200–300 mg/m^2)]. All patients presented a normal LEVF baseline value (≥50%) according to the protocol inclusion criteria. A total of four patients (8.5%) (3 in DL-1 and 1 in DL-2) had an asymptomatic decrease in the LVEF at the end of the study (range 44.5–49%). Of these, three had received prior adjuvant treatment with epirubicin.

Forty-seven patients were evaluable for response ($n = 47$). Two of them (4.3%) had a complete response (CR) and 22 patients (46.8%) had a partial response (PR), thus the overall response rate was 51.1% ($n = 24$, 95% CI: 36–66%). A total of 14 patients (29.8%) had stable disease and nine patients (19%) progressed. The overall response rate and the best response rate of the efficacy population are summarized in Table 4. Median time to response was 2.53 months (95% CI: 2.07–3.72). No statistical differences in overall response rate were observed between those patients who had received adjuvant anthracycline treatment and those who had not (64.7% vs. 43.3%, $P = 0.16$). According to the intention-to-treat analysis, the overall response rate was 45.3%.

After a median follow-up of 19.64 months (range 3–45.5 months), the median time to progression was 12 months (95% CI: 7.8–19.6 months). Median time to treatment failure was 8.3 months (95% CI: 3.2–13.8 months). Median response duration was 11.9 months (95% CI: 5.9–25.3) and median overall survival was 25.4 months (95% CI: 16.8–31.18 months) (Fig. 1). It is noteworthy that the median time to progression was 15.4 months (95% CI: 5.3–25.5 months), of those 14 patients who had stable disease as the best response. Eight of them had progressed and six had stable disease at the last follow-up visit.

Discussion

This phase I/II clinical trial was performed to determine the RD of gemcitabine administered on days 1 and 8 every 21 days in combination with Myocet® administered on day 1, to patients with advanced breast cancer. Although the RD was established in the 60/1,000 regimen, a protocol amendment was approved to reduce the dose of both agents by 10% for feasibility and safety reasons. The study shows that at a dose of 900 mg/m^2 gemcitabine and 55 mg/m^2 Myocet®, the combination is well tolerated and has encouraging clinical activity in this group of patients.

As expected, the principal toxicity observed was hematological. The frequency and severity of hematological events precluded the conduction of the study according to the initial protocol and required protocol amendments, to permit the assessment of doses that were lower than initially planned. Overall, approximately 50% of the patients developed grade 3,4 neutropenia. Other toxicities were mild and rare, including a low incidence of nausea and vomiting, which are common in doxorubicin-containing regimens. Importantly, there were no symptomatic cardiac events despite the fact that 36% of the patients had received prior treatment with anthracyclines. This is particularly important because those patients who have progressed after previous anthracycline-based therapy, and still have potentially sensitive disease, should not be treated with standard doxorubicin due to the potential of cardiac failure—but they could receive NPLD. This was also observed in a retrospective analysis by Batist et al. [15]. In that study, thirty-nine patients who had previously received adjuvant doxorubicin were treated with NPLD 75 or conventional doxorubicin 75 for their metastatic disease. Cardiac events occurred in 22% of NPLD-treated patients [one congestive heart failure (CHF)] as opposed to in 39% of conventional doxorubicin-treated patients (three CHFs) (log-rank, $P = 0.001$).

The results of our study must be analyzed in the context of other similar studies. Rivera et al. [28] conducted a phase II clinical trial to determine the clinical efficacy and safety of pegylated liposomal doxorubicin in combination with gemcitabine in patients with metastatic breast cancer. Patients were eligible if they had measurable disease and had had no prior chemotherapy for metastatic disease, and they received pegylated liposomal doxorubicin 24 mg/m^2 intravenously on day 1 plus gemcitabine 800 mg/m^2 intravenously on days 1 and 8 of each 21-day cycle. Of 49 patients enrolled, 27 had received prior adjuvant chemotherapy (19 with an anthracycline). The previous median cumulative anthracycline dose was 240 mg/m^2. Three complete responses and 21 partial responses were achieved in 46 assessable patients, for an overall response rate of 52% (95% CI: 37–67%). Responses were observed in 11 (58%) of 19 patients with previous anthracycline exposure.

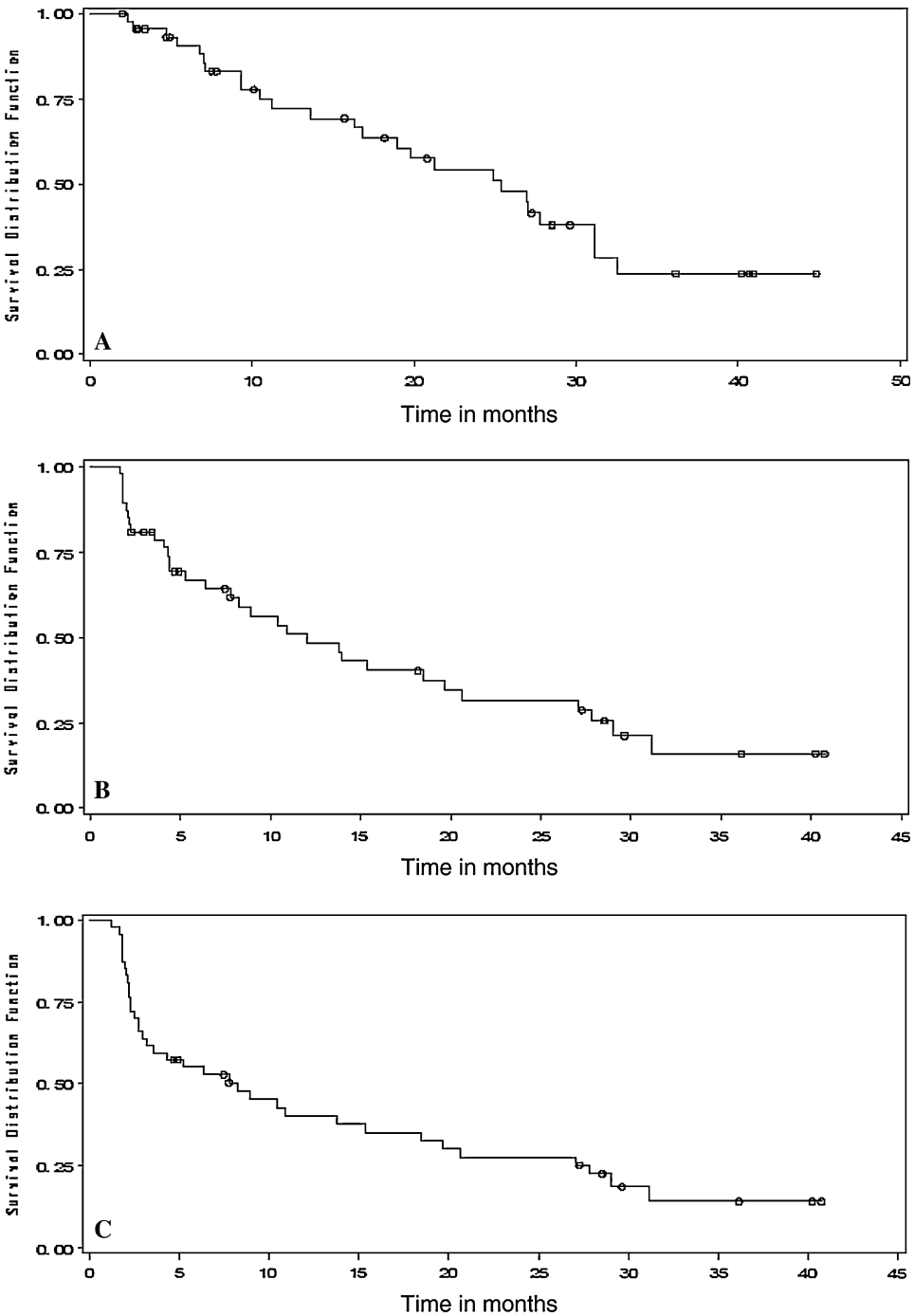

Fig 1 Overall survival (**a**), time to progression (**b**), and progression-free survival (**c**)

Although these results are very similar to those observed in our study, the median time to progression of 12 months observed with our combination appears to compare very favorably with the 5.6 months obtained with PLD and gemcitabine.

Likewise, Fabi et al. [29] reported a 47.8% response rate and a median time to progression of 7 months with the same combination of PLD and gemcitabine. Once again, the median time to progression appears to have been lower than that observed in our study. Response rates were similar in patients with and without prior anthracycline treatment. No neutropenic complications were observed, but one patient had a 26% reduction in LVEF. Other studies have tested gemcitabine in combination with conventional anthracyclines. These studies, including both epirubicin and doxorubicin, showed similar response rates but higher hematological toxicities than the results reported here [24, 30]. The outcomes of the present study, with a 51% response rate and a time to progression of 12 months, compare very satisfactorily with the results of these other

studies, although this might be due, at least in part, to the intrinsic biases of non-comparative phase II trials. In addition, this combination was well tolerated at the recommended phase II dose.

In conclusion, the results of this study show that the combination of Myocet® at a dose of 55 mg/m^2 and gemcitabine at a dose of 900 mg/m^2 is safe and effective in patients with advanced breast cancer. The reduced dose resulted in less thrombocytopenia and manageable neutropenia. The efficacy data support further investigation of this combination in a phase III clinical trial.

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