Non-pegylated liposome-encapsulated doxorubicin citrate plus cyclophosphamide or vinorelbine in metastatic breast cancer not previously treated with chemotherapy: A multicenter phase III study

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Abstract. We conducted a phase III multicenter randomized trial to compare the efficacy of the combination of liposome encapsulated doxorubicin (Myocet©) plus either cyclophospha-mide (MC) or vinorelbine (MV). Since July 2006, 233 patients affected with metastatic breast cancer were randomized to receive the combination of Myocet (M) 60 mg/m² i.v. plus cyclo-phosphamide (C) 600 mg/m² on Day 1 of a 21-day cycle (Arm A) or Myocet (M) at 50 mg/m² plus vinorelbine (V) 25 mg/m² i.v. on Day 1 and V 60 mg/m² orally on Day 8 on a 21-day cycle (Arm B). The primary endpoints of the study was time to progression (TTP); secondary endpoints were RR, toxicity and OS. Response was observed in 53/116 (45.7%) evaluable patients of Arm A vs. 51/112 (45.5%) of Arm B, respectively (P=NS). Median TTP was 41 weeks (95% CI, 32-51) and 34 weeks (95% CI, 26-39), for M/C and M/V, respectively (P=0.0234). The difference in median OS was not statistically significant (131 vs. 122 weeks; P=0.107). With regard to toxicity, patients treated with MV showed a slight increase of neutropenia and constipa-tion, as compared to those treated with MC. No clinical signs of cardiotoxicity were observed. The MC combination remains as an unbeaten 'standard' in first line treatment of MBC.

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Introduction

Metastatic breast cancer (MBC) is a chronic and incurable disease, with a median survival of approximately 2-3 years. Although advances have been made in the management of MBC, long-term survivors are rare, with 5-year survival rates varying from 5 to 10% (1,2).

Conventional anthracyclines are among the most widely used agents to treat breast cancer in the adjuvant setting, as well as in metastatic disease (3). In phase II trials the response rate to anthracyclines in patients naïve to chemotherapy is about 50%, however, the clinical use of anthracyclines is limited by dose-related cardiotoxicity, which becomes more relevant with increasing cumulative dose (4-6). The mechanism of anthracycline related cardiotoxicity involves the formation of free radicals that cause lipid perossidation leading to a dose-dependent cardiomyopathy and to congestive heart failure (7-9). Cardiotoxicity can appear during treatment, at the end of therapy, or even years after the end of anthracycline therapy (10). Moreover, doxorubicin associated cardiotoxicity is often unpredictable, because it can happen at lower dose than expected. It was recently reported that this may be related to a genetic predisposition in patients carrying selected poly-morphism of the NAD(P)H oxidase and doxorubicin efflux transporters (11).

Non-pegylated liposome-encapsulated doxorubicin citrate, a liposomal formulation of doxorubicin, was designed to reduce cardiotoxicity while preserving antitumor efficacy (12-15). The formulation consists in encapsulation of water-soluble doxoru-bicin within a phospholipid membrane to prevent doxorubicin from exiting the circulation through the capillary junctions in healthy tissues. Conversely, liposome-encapsulated drug appears to pass easily through the damaged capillaries of

tumor tissues. Therefore, liposome encapsulated doxorubicin does not easily reach heart tissue and a higher cumulative dose of liposome-encapsulated doxorubicin can be delivered to the patient (16,17). Results from phase III trials demonstrated that liposome-encapsulated doxorubicin and doxorubicin are equivalent in terms of antitumor efficacy (18-20). In particular, Myocet in combination with cyclophosphamide showed an efficacy equivalent to doxorubicin, with a better profile in terms of cardiotoxicity and hematological toxicity (20).

Vinorelbine is a semi-synthetic vinca alkaloid, with leukopenia and constipation as the dose limiting toxicities. Phase II studies have shown a response rate ranging from 35 to 50% for vinorelbine as first line chemotherapy for metastatic breast cancer (21-23).

This multicenter randomized phase III trial was designed to compare the efficacy and tolerability of the regimen MV vs. MC. Secondary end-points were ORR, safety and OS.

The principal aim of the study was to assess a difference in time to progression (TTP) between M/C (Arm A) and M/V (Arm B). With the use of a one-sided log-rank test with a type I error of 0.1, we determined that 133 events (disease progression or death from any cause) would be required for an 80% power to detect an expected minimum difference of 2.5 months in PFS between the two arms in favor of vinorelbine containing arm. With a 1:1 randomization of assignment to study groups and considering a total duration of the study of 60 months (48 months of accrual and 12 months of follow-up), we estimated that we would need to enroll 220 patients to observe 133 events.

Patients and methods

All eligible patients had histological confirmed locally advanced (LABC) or metastatic breast cancer (MBC) Her-2 negative not previously treated with chemotherapy for advanced disease. Previous treatment with an anthracyclines-based chemotherapy regimen in the adjuvant or neo-adjuvant setting was allowed (doxorubicin cumulative dose <240 mg/m^2, epirubicin cumulative dose <360 mg/m^2). Other inclusion criteria were: age 18-70 years; PS (ECOG) ≤2; at least one measurable lesion according to RECIST criteria; previous endocrine therapy allowed; adequate bone marrow, liver and renal function. Main exclusion criteria were: previous chemotherapy for metastatic disease, pregnancy or breast-feeding, serious concomitant systemic disorders, pre-existing sensorial or motor neuropathy, symptomatic brain metastasis, second primary malignancy (except *in situ* carcinoma of the cervix or adequately treated non-melanoma carcinoma of the skin or other malignancies treated at least 5 years previously with no evidence of recurrence). Randomization method 1:1 was performed and any eligible patient was randomized to receive:

Arm A, non-pegylated liposome encapsulated doxorubicin citrate (M) 60 mg/m^2, Day 1 q3w + cyclophosphamide (C) 600 mg/m^2, Day 1 q3w; Arm B, non-pegylated liposome encapsulated doxorubicin citrate (M) 50 mg/m^2, Day 1 q3w + vinorelbine (V) 25 mg/m^2 iv, Day 1 q3w and 60 mg/m^2 orally, Day 8 q3w. Treatment was performed until 6 cycles in case of SD or 8-10 cycles if PR or CR was reached.

Time to progression (TTP) was determined from the date of randomization to the date of assessment of disease progression or death from any cause. TTP curves were calculated by

Table I. Characteristics of the patients.

Characteristics	Arm A no. of patients (%)	Arm B no. of patients (%)
Assessable/entered	116/117	112/116
Median age (range)	59 (37-71)	58 (25-70)
ECOG PS		
0-1	96 (77)	89 (76)
2	21 (23)	27 (23)
Receptor status		
Positive	96 (77)	93 (74)
Negative	22 (17)	26 (20)
Unknown	9 (6)	7 (6)
Her-2 status		
Positive	8 (6)	8 (6)
Negative	101 (80)	105 (84)
Unknown	18 (14)	13 (10)
Prior surgery	92 (74)	104 (83)
Prior adjuvant radiotherapy	46 (37)	42 (33)
Prior hormonal therapy	52 (42)	67 (53)
Prior adjuvant therapy with anthracyclines	98 (84)	103 (89)
Dominant site of disease		
Soft tissue	25 (19)	17 (13)
Bone	12 (10)	17 (13)
Viscera	90 (71)	92 (74)
No. of metastatic sites		
1	44 (35)	39 (31)
2	43 (34)	51 (40)
≥3	40 (31)	36 (29)

Kaplan-Meier method. Toxicity was graduated according to NCI-CTC v. 4.0. Objective response, according to RECIST criteria, was evaluated by a tumor assessment performed every 3 cycles. Survival time was measured from the date of randomization to the date of death or lost to follow-up. Overall survival (OS) curves were calculated by Kaplan-Meier method. Cardiotoxicity was defined as appearance of signs and/or symptoms of CHF and/or a decrease in LVEF below normal limit (<50%) or a decline ≥15% from baseline value. To evaluate Left Ventricular Ejection Fraction (LVEF) an echocardiography was done at baseline and every 3 cycles in all patients entered into the study.

Results

From July 2006 through December 2011, 233 patients with metastatic breast cancer, and no prior chemotherapy for advanced

Table II. Response rate in per-protocol evaluable patients according to dominant site of disease.

Dominant site of disease	No. of patients	CR	PR	SD	PD
Arm A					
Viscera	81	3	31	28	19
Bone	11	0	4	4	3
Soft tissue	24	5	10	8	1
Total (%)	116	8 (7)	45 (39)	40 (34)	23 (20)
Arm B					
Viscera	82	2	37	23	20
Bone	15	0	5	8	2
Soft tissue	15	1	6	6	2
Total (%)	112	3 (3)	48 (43)	37 (33)	24 (21)

disease, were enrolled at 18 Italian centers: 117 patients were randomized to receive MC and 116 patients to receive MV. The results are reported on the basis of data collected on all 233 patients with follow-up through December 2012. The two treatment groups were equally distributed for baseline characteristics with respect to age, disease-free interval, ECOG performance status, estrogen/progesterone receptor status and visceral involvement (Table I). Prior therapies were well matched between the two groups: 84% in group A vs. 89% of group B had received anthracyclines as adjuvant therapy, respectively. Up to two lines of previous hormonal treatment were allowed. A median of 6 cycles (range 2-10) of therapy was performed in both arms. With regard to response rate, 116/117 patients in Arm A and 112/116 in Arm B were evaluable per protocol, however, responses were also assessed on intention to treat basis. In fact, 1 patient and 4 patients for Arms A and B, respectively, were not evaluable for early drop out (1 refused to continue, 3 lost to follow-up, 1 drug related death after the first cycle in Arm B). Overall response rate (Table II), per protocol, was 53/116 [45.7% (95% CI, 36.5-54.7%)] for Arm A and 51/112 [45.5% (95% CI, 36.3-54.7%)] for Arm B, respectively (P=NS). On intent to treat basis, responses were 53/117 [45.29% (95% CI, 36.6-54.3%)] and 51/116 [44% (95% CI, 35.3-53.0%)] for Arms A and B, respectively. The response rate by prognostic factors showed a high degree of comparability between the two treatment groups (Table III). The duration of response was longer for MC treated patients as compared to MV (26 vs. 19 weeks; P=0.327). Median TTP (Fig. 1) was 41 (95% CI, 32-51) and 34 (95% CI, 26-39) weeks, respectively (P=0.0234). With a median follow-up of 36 months, there was little difference in the overall survival curves. The median survival was 131 weeks in the MC patients vs. 122 weeks in the MV treated patients (P=0.107) (Fig. 2).

Safety. Therapy was generally well tolerated in both groups (Table IV). Myelosuppression was the most frequent and severe adverse side effect on both arms, and was the most common cause of dose reduction and delay. Still, dose reductions and delays were not common: median duration of cycles was 21 days on both arms, and patients achieved 90% of the planned dose intensity. Grade 3 or 4 thrombocytopenia was observed in 2% of the MC vs. 3% of MV patients. Grade 3-4 neutro-

Table III. Results with regard to prognostic factors.

	Percentage of responding patients	
	MC (N=116)	MV (N=112)
Age (years)		
<50	52	54
50-59	45	43
>60	35	32
Disease-free interval		
<2 years	44	45
>2 years	42	43
ECOG PS		
0	48	47
1	47	45
2	25	24
Receptor status		
Positive	44	43
Negative/unknown	46	46
Prior radiotherapy	43	42
Prior hormonal therapy	44	45
Prior adjuvant therapy with anthracyclines	43	40
Dominant site of disease		
Soft tissue	75	80
Bone	35	38
Viscera	45	44
No. of metastatic sites		
1	45	45
2	45	45
≥3	38	40

penia, however, was significantly lower in the MC arm: 16% of MC patients as compared to 32% of MV patients (P=0.008).
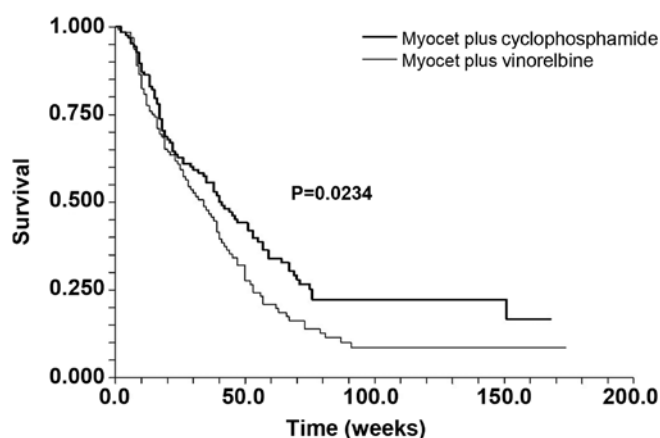
Figure 1. Time to progression (TTP) of patients treated with Myocet plus cyclophosphamide vs. those treated with Myocet plus vinorelbine.
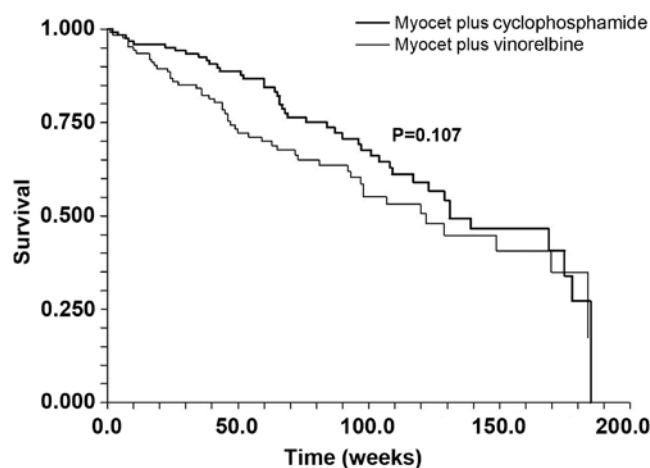

Figure 2. Overall survival of patients treated with Myocet plus cyclophosphamide vs. those treated with Myocet plus vinorelbine.

Table IV. Toxicity.

Toxicity	Arm A (N=117)		Arm B (N=116)	
	Grade I-II (%)	Grade III-IV (%)	Grade I-II (%)	Grade III-IV (%)
Leucopenia	25 (21)	19 (16)	23 (20)	37 (32)
Febrile neutropenia	-	8 (7)	-	18 (16)
Anemia	40 (34)	3 (3)	39 (34)	7 (6)
Thrombocytopenia	10 (9)	2 (2)	9 (8)	4 (3)
Nausea/vomiting	49 (42)	2 (2)	30 (26)	3 (3)
Mucositis	20 (17)	3 (3)	19 (16)	9 (8)
Diarrhoea	4 (3)	1 (1)	13 (11)	1 (1)
Asthenia	17 (15)	2 (2)	15 (13)	1 (1)
Constipation	3 (3)	1 (1)	10 (9)	8 (7)
Hair loss	43 (37)	73 (62)	42 (36)	70 (60)
Neuropathy	3 (3)	-	4 (3)	1 (1)
Cardiac toxicity	8 (7)	-	9 (8)	-

G-CSF was administered in 35% of MV cycles vs. 19% of MC cycles. Eight patients (7%) on the MC arm compared with 18 patients (16%) on the MV arm developed neutropenic fever requiring IV antibiotics and/or hospitalization. Additionally, fewer RBC transfusions were required with MC (5 transfusions to 3 patients) relative to MV (10 transfusions to 7 patients). The incidence of all grade mucositis/stomatitis was comparable in both arms although a slight increase in percent of grade 3-4 mucositis was observed in MV arm (8 vs. 3%). With regard to gastrointestinal toxicity, incidence of grade 3-4 diarrhea was negligible in both arms (1%). However, grade 1-2 diarrhea was more frequent on MV as compared to MC (11 vs. 3%; P=0.042). Conversely, constipation was significantly higher on MV arm (16 vs. 4%; P=0.003), with 7% of grade 3-4.

With regard to cardiotoxicity, overall 17/233 (7%) patients after 6-8 cycles of either arm, developed a decrease of LVEF below 50%, or showed >15% decline of LVEF below basal examination, without any clinical sign of or symptom. Most

of these patients (75%) were previously treated with anthra-cyclines. All patients recovered after appropriate treatment. The median dose of non-pegylated liposomal doxorubicin administered was 420 mg (range 120-660). No patient developed palmar-plantar erythrodisesthesia which is a common side effect with pegylated liposomal doxorubicin. Moreover, we observed only one treatment related death in Arm B, because of sepsis.

Discussion

Doxorubicin is a mainstay in the treatment of breast cancer. In fact, this drug is generally included in the treatment of early as well as of advanced/metastatic disease. However, the most important drawback in its use is the development of cardiotoxicity, which is fatal in more than 5% of the patients when cumulative dose of 450 mg^2 is reached (4-6). This risk is particularly high when patients with advanced disease have

been already treated with anthracyclines as a component of their adjuvant treatment of early disease. Thus, doxorubicin cardiac toxicity can limit patient ability to receive further potentially active therapy, in particular when the tumor is responding to the current treatment including anthracyclines.

With this regard, considerable research has been undertaken to reduce the potential cardiotoxicity of this drug. Drugs having potential protective effect as dexrazoxane (24,25) or the administration of doxorubicin as continuous infusion (26), have been proposed as tools able to reduce risk of hearth damage, but none has been considered really effective. Non-pegylated liposomal doxorubicin (Myocet©) is a unique formulation of doxorubicin, able to alter the tissue distribution of this doxorubicin. Pharmacokinetic studies have demonstrated that doxorubicin in Myocet is bioavailable, metabolized and excreted in a manner similar to that of conventional doxorubicin, but in a slower rate sparing myocardial cells. Moreover, a number of clinical studies (18-20) have demonstrated comparable activity and lesser toxicity of Myocet vs. conventional doxorubicin. In addition, data from a phase III randomized controlled clinical trial, comparing Myocet plus cyclophosphamide (MC) vs. adriamycin plus cyclophosphamide (AC) in advanced breast cancer, demonstrated that Myocet significantly reduced the cumulative cardiac toxicity, while providing comparable antitumor efficacy. In fact, in this study which enrolled 296 patients, an objective response of 43% was observed in both arms, with a significant reduction of cardiotoxicity (6 vs. 21%; P=0.0002) in favor of MC patients (20). A further phase III study (19) randomized 160 patients to receive cyclophosphamide 600 mg/m^2 plus either epirubicin 75 mg/m^2 or liposomal doxorubicin 75 mg/m^2. No significant differences were observed in the rate of asymptomatic reduction in LVEF (11 vs. 10%). In this study, no patient developed clinical heart failure. In 2010, the Cochrane Library reported a systematic review of the different anthracycline compounds and their cardiotoxicity (27). Studies by Harris et al (18) and Batist et al (20) were analyzed together, and authors concluded that non-pegylated liposomal anthracyclines did reduce the overall risk of cardiotoxicity (RR=0.38, P<0.0001) and the risk of clinical heart failure (RR=0.20, P=0.02).

The aim of the present study was to compare the efficacy of the regimen Myocet plus vinorelbine (MV) vs. the standard MC in a population mostly pretreated with anthracyclines as adjuvant treatment. Secondary end-points of the study were ORR, safety and OS.

The rationale of the choice of the association of Myocet and vinorelbine as comparator of the standard Myocet-cyclophosphamide was the synergism observed in breast cancer cell lines between doxorubicin and vinorelbine (28). In cell lines, an increased p38 activity was demonstrated following vinorelbine, with unchanged mitogen-activated protein kinase (MAPK) activity and p53 expression. On the other hand, doxorubicin treatment resulted in increased p53 expression, without changes in MAPK or p38 activity. This different mechanism of action may result in increased cell apoptosis in vitro as well as in vivo. Nevertheless, the first randomized trial of the combination of doxorubicin plus vinorelbine vs. doxorubicin alone, reported disappointing results (29) with no difference in response rate as well as in overall survival between doxorubicin alone and the combination with vinorelbine. However,

following this study, Pawlicki et al (30) reported an objective response rate of nearly 80%, in 38 chemotherapy naïve metastatic breast cancer treated with doxorubicin plus vinorelbine, and Lorvidhaya et al showed an overall response of 67% in 27 patients (31) with this combination. In addition, few years later, a Scandinavian group reported the results of a phase III study of 387 patients who were randomly assigned to receive IV epirubicin 90 mg/m^2 on Day 1 plus vinorelbine 25 mg/m^2 on Days 1 and 8 or epirubicin alone at dosage of 90 mg/m^2 IV on Day 1 (32). Both regimens were given every 3 weeks for a maximum of 1 year but discontinued prematurely in the event of progressive disease or severe toxicity. In addition, epirubicin was discontinued at a cumulative dose of 1000 mg/m^2 (950 mg/m^2 from June 1999). It is noteworthy that prior anthracycline-based adjuvant chemotherapy and prior chemotherapy for metastatic breast cancer was not allowed. Overall response rates to vinorelbine and epirubicin, and epirubicin alone, were 50 and 42%, respectively (P=0.15). The complete response rate was significantly superior in the combination arm (17 vs. 10%; P=0.048) as was median duration of progression-free survival (10.1 vs. 8.2 months; P=0.019). Median survival was similar in the two arms (19.1 vs. 18.0 months; P=0.50). Leukopenia related complications, stomatitis and peripheral neuropathy were more common in the combination arm. The incidences of cardiotoxicity and constipation were similar in both arms. The Authors concluded that addition of vinorelbine to epirubicin conferred a significant advantage in terms of complete response rate and progression-free survival, but not in terms of survival.

The results of the present study demonstrate that the combination of Myocet plus cyclophosphamide had a significantly longer TTP compared to Myocet plus vinorelbine while the two combinations showed similar response rate and overall survival. Also safety of the two combination was comparable, except for a higher incidence of leukopenia and neurotoxicity in MV arm.

In conclusion, the combination of Myocet plus cyclophosphamide showed a good profile of efficacy and safety in a population with previous exposure to anthracyclines in the early phase of the disease and remains an unbeaten standard in the treatment of advanced/metastatic breast cancer.

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