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FEC (5-fluorouracil, epidoxorubicin and cyclophosphamide) versus EM (epidoxorubicin and mitomycin-C) with or without lonidamine as first-line treatment for advanced breast cancer. A multicentric randomised study. Final results

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Abstract

From May 1991 to December 1996, 326 patients with advanced metastatic breast cancer were enrolled in a multicentre, randomised, phase III clinical trial with four arms. Patients were randomised to receive chemotherapy according to the FEC regimen (5-fluorouracil (5-FU) 500 mg/m^2, epidoxorubicin (EPI) 75 mg/m^2 and cyclophosphamide (CFA) 500 mg/m^2, intravenously (i.v.). every 3 weeks) or the EM regimen (EPI 75 mg/m^2, i.v. every 3 weeks; mitomycin C (MMC) 10 mg/m^2, i.v. every 6 weeks) or the same regimens with the addition of lonidamine (LND) until disease progression (orally, thrice daily, 150 + 150 + 300 mg); a maximum of eight chemotherapy cycles were planned. The aim of the trial was 2-fold: to compare the EM regimen with the commonly used FEC regimen and to evaluate the possible role of the addition of LND. Patients were eligible if they had histologically proven breast carcinoma, metastatic or locoregional relapse with measurable and/or evaluable disease and were aged between 18 and 70 years: 318 patients were considered eligible. Patients with previous anthracycline-based adjuvant chemotherapy or those who relapsed within 6 months after any adjuvant chemotherapy regimen were excluded. Chemotherapy-related toxicity of grade $\geqslant 3$ was manageable and there was no significant difference between the arms in terms of haematological side-effects. The impact on heart function was mild. No increased toxicity was observed in the LND arms (apart from myalgias in 27–30% of the cases). A significant increase in the complete response rate was observed for the FEC/EM + LND group (20.4%) versus the FEC/EM group (10.8%). The median survival time and the median time to progression for the overall series were 608 days and 273 days, respectively; EM±LND achieved significantly improved survival and time to progression versus FEC±LND ($P = 0.01$). This result was confirmed also when the analysis was restricted to patients previously treated with adjuvant CMF schedules. On the basis of these results, we conclude that EM may represent a valuable alternative to FEC for patients requiring a first-line regimen for advanced/metastatic breast carcinoma, especially in patients previously treated with CMF in an adjuvant setting. Furthermore, we conclude that, in spite of a better complete response rate in the LND arms, as there was no clear advantage in time to progression or survival resulting from the addition of LND to the FEC or EM regimens, the routine use of LND is not warranted outside a clinical trial.

Keywords: Advanced breast cancer chemotherapy; Mitomycin-C drug combination; Epidoxorubicin drug combination; Lonidamine and breast cancer; Lonidamine therapy

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1. Introduction

Metastatic breast cancer is an incurable disease; in spite of high response rates, disease remissions are rarely long-lasting and second-line chemotherapy generally achieves even shorter-lived responses. Several attempts have been made to overcome the multidrug resistance (MDR) that may develop in previously sensitive cells by increasing the dose intensity or alternating non-cross-resistant drugs. A third way is to exploit modulator drugs thereby potentiating the efficacy of established anticancer agents or reverting the acquired MDR; lonidamine (LND) is an agent in this category.

LND is a derivative of indazole-3-carboxylic acid with antispermatogenic properties [1] that acts as an anticancer agent interfering selectively with the energy metabolism of the tumour cells, rather than with the mechanisms of cell division [2,3]. The selective action on neoplastic cells might be ascribed to the inhibition of mitochondrially-bound exokinase, an enzyme that seems to have a role in promoting aerobic glycolysis of rapidly growing tumours, and which is usually absent in normally differentiated cells [4]. Furthermore, LND seems to inhibit the repair processes and more specifically the recovery from potentially lethal damage from radiation and cytotoxic drugs, potentiating the antitumour effect of chemotherapy, radiotherapy and hyperthermia both in simultaneous and sequential combinations [5].

In vivo, LND alone in metastatic breast cancer patients shows a low to moderate anticancer activity (2.6–18.7%) [6–11]. LND seems to have a moderate dose-dependent non-haematological toxicity [12] that is reversible following a dose reduction or treatment discontinuation [13]; with daily doses of LND ranging from 300 to 900 mg, myalgias are the most common (66%) side-effect [13]. When associated with cytotoxic agents no enhanced toxicity is observed, and myelosuppression is never greater than would be expected with chemotherapy alone [13]. In particular, the combination of LND and doxorubicin (ADR) did not enhance ADR-related metabolic cardiac toxicity in the rat heart [14]. In spite of its low activity against breast cancer cells, its low and non-overlapping toxicity makes LND an interesting modulator drug to study in association with established anticancer agents [13].

Anthracyclines, ADR and epidoxorubicin (EPI), are still considered amongst the most active agents against breast cancer and are often included in first-line treatment for advanced disease. Two randomised trials conducted by an Italian and a French cooperative group [15,16] showed that the FEC protocol yields results similar to the 5-fluorouracil, doxorubicin and cyclophosphamide (FAC) schedule and is better tolerated.

Mitomycin C (MMC) is not often used in first-line chemotherapy regimens; however, MMC-containing regimens have often been used as second-line chemotherapy; in fact, as the choice of a salvage combination depends also on the previous treatments, patients failing regimens based on cyclophosphamide, methotrexate, 5-fluorouracil (CMF) are more often treated with combinations incorporating drugs not included in CMF [17]. Although the benefit of the addition of MMC to ADR has been questioned [18], the use of combination chemotherapy with ADR and MMC is documented as both first-line and second-line treatments [17,19,20] with objective response rates ranging from 25 to 73%. From December 1988 to February 1991, our group treated 112 consecutive patients with visceral metastases from breast cancer or with relapse occurring within 1 year with a combination of EPI and MMC (EM) as first-line treatment [21]. Complete responses were 21.6% and partial responses were 49%; median values of time to progression and survival were 42 and 79.4 weeks, respectively; toxicity was generally mild. We concluded that EM is an active and safe combination for advanced breast cancer and that further evaluation in a randomised trial against FEC was warranted.

The aim of the present paper is to report the results of a randomised trial comparing EM to FEC with or without the addition of LND in advanced/metastatic breast cancer patients that were not previously treated with chemotherapy for advanced disease.

2. Patients and methods

From May 1991 to December 1996, 326 patients with advanced metastatic breast cancer were consecutively enrolled to enter one of the four arms of this trial in eight different institutions of the Tuscany Oncology Group (Table 1).

2.1. Trial design

This was a multicentre, randomised, phase III clinical trial with four arms and a two-by-two factorial design. Patients were stratified by participating centre, dominant site of disease (viscera versus bone versus soft tissues); skeletal metastases alone were stratified separately. The four treatments were randomly assigned according to a

Table 1
Participating centres and accrued patients ($n = 326$)

Centre	No. of patients
Florence 1	186
Arezzo	40
Grosseto	33
Siena 1	31
Siena 2	14
Lucca	8
Florence 2	7
Leghorn	7

computer-generated randomisation list. The data were collected centrally by the Radiotherapy and Oncology Department of the Hospital of Careggi, Florence, Italy. The trial was preliminarily approved by the ethics committee of the co-ordinating centre.

2.2. Trial objectives

These were: to evaluate the efficacy of the FEC regimen in comparison with the EM regimen with or without lonidamine in terms of objective response rate, overall survival and time to progression; to evaluate the side-effects in terms of acute tolerance with a special focus on cardiac function.

2.3. Eligibility criteria

These were the following: histologically proven breast carcinoma; metastatic or locoregional relapse with measurable or evaluable disease according to the WHO criteria [22]; age between 18 and 70 years; performance status $\leqslant 2$ according to the WHO guidelines; adequate bone marrow reserve (leucocytes $\geqslant 4000/\mu l$, platelets $\geqslant 100\,000/\mu l$); adequate renal and liver function (serum creatinine < 175 μmol/l, bilirubin < 3.5 μmol/l, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) < 3 times the normal values), oral and/or written informed consent.

2.4. Exclusion criteria

These were as follows: patients with osteoblastic bone metastases, ascites and/or pleural effusions as the only indicators of disease; breast relapse alone after conservative treatment; patients with advanced, inoperable, locoregional disease without evidence of distant metastases; previous palliative radiotherapy with irradiation of $> 25\%$ of the bone marrow; previous irradiation of the mediastinum or of the internal mammary chains with high-energy photons; history of myocardial infarction or active angina pectoris; cardiac arrhythmias requiring continuous therapy and/or hypertension uncontrolled with medical treatments; previous adjuvant chemotherapy with anthracycline-based regimens, or relapse within 6 months after any adjuvant chemotherapy; previous chemotherapy for advanced disease (hormonal therapy for advanced disease was permitted); history of previous cancer (with the exclusion of *in situ* carcinoma of the cervix and basal cell carcinoma of the skin, radically treated).

2.5. Patient prerandomisation evaluation

This included medical history and physical examination, chest X-ray, liver ultrasound, isotope bone scan with radiographs of suspicious areas, measurement of white blood cell count (WBC), differential and platelets, serum bilirubin, AST, ALT, lactate dehydrogenase (LDH), gamma-glutamyltransferase (GGT), alkaline phosphatase, serum creatinine and serum electrolytes, an electrocardiogram (ECG), a left ventricular ejection fraction (LVEF) determined with isotope cardiac scan or echocardiography. All other examinations were at the investigator's discretion.

2.6. Trial treatment

Patients were randomised to receive chemotherapy according to the FEC or EM regimens (Table 2) or the same regimens with LND (EM + LND = LEM; FEC + LND = LFEC); a maximum of eight cycles were planned. Full chemotherapy dose delivery was planned for patients with $\geqslant 3500/\mu l$ leucocytes, $\geqslant 90\,000/\mu l$ platelets and a differential count of $\geqslant 1500/\mu l$ granulocytes. No dose reduction was permitted; in case of contraindications to the cycle delivery, a maximum delay of 2 weeks was allowed; the treatment was stopped in patients with a longer delay or with two consecutive 2-week delays. Patients who discontinued the study treatment in the FEC/EM + LND arms (LFEC, LEM), because of chemotherapy toxicity, were planned to continue the LND intake until disease progression.

2.7. LND

LND (Doridamina®, tablets 150 mg; Angelini-Acraf, Rome, Italy) was administered orally three times daily (150 mg + 150 mg + 300 mg), for a total dose of 600 mg/day until disease progression. The LND dose was reduced to 450 mg, and then to 300 mg in case of moderate (grade 3) drug-related side-effects; an interruption no longer than one week in the LND intake was allowed. LND was stopped in cases of patient refusal due to severe, unacceptable (grade 4) drug-related toxicity. NSAIDs (non-steroidal anti-inflammatory drugs) were recommended to alleviate the side-effects of LND, whilst it was recommended to limit the use of steroids in this setting as much as possible. The recommended antiemetic therapy was methylprednisolone (Solumedrol®) 250 mg i.v. + alizapride (Limican®) 2 vials i.v. immedi-

Table 2
Treatment regimens

FEC	
5-Fluorouracil	500 mg/m^2/i.v. day 1, every 21 days
Epidoxorubicin	75 mg/m^2/i.v. day 1, every 21 days
Cyclophosphamide	500 mg/m^2/i.v. day 1, every 21 days
EM	
Epidoxorubicin	75 mg/m^2/i.v. day 1, every 21 days
Mitomycin-C	10 mg/m^2/i.v. day 1, every 42 days

i.v., intravenous.

ately before chemotherapy; Alizapride i.v. was repeated at the end of chemotherapy, and then given intramuscularly (i.m.) 4 and 8 h after the treatment. The use of new antiemetic drugs was allowed.

2.8. Concomitant treatments

Concomitant treatments with drugs potentially active in the disease were not allowed until disease progression was documented. Concomitant palliative radiotherapy was permitted but the irradiated sites were excluded from response evaluation.

2.9. Visit procedures

A complete physical examination, haematology and blood chemistry were performed before each cycle and at the termination visit. Weekly blood counts were not requested by protocol. Chest X-ray, liver ultrasound and whatever evaluation method selected for tumour assessment at baseline had to be used for all subsequent tumour evaluation after the third, the sixth administration and at the termination visit. A repetition of the bone scan was not planned before the sixth cycle. ECGs were performed after the third and the sixth cycle, whilst the LVEF was examined with cardiac scan or ultrasound at the termination visit. Only the patients showing objective response or stable disease at the third and at the sixth cycle evaluation continued treatment.

2.10. Toxicity evaluation

The evaluation of toxicity was performed according to the WHO recommendations for grading of acute and subacute toxicity [22]; as for the cardiac toxicity the LVEF changes were considered in addition to the WHO criteria [23]. As for LND, an arbitrary 4-grade scale was adopted (due to the lack of a specific scoring system): grade 0 (no toxicity); grade 1 (very mild toxicity — no therapy required); grade 2 (mild toxicity — medical therapy required); grade 3 (moderate toxicity — dose reduction required); grade 4 (severe toxicity — discontinuation required). Patients developing $\geqslant$grade 3 WHO toxicity (with exclusion of hair, nausea and vomiting and LND toxicity) discontinued the study treatment. As for the haematological toxicity the recommended guidelines are mentioned previously.

2.11. Adverse experiences

All adverse experiences had to be recorded in the case report form. Adverse experiences were defined as serious if they fulfilled at least one of the following criteria: death, life-threatening condition, permanent disability/incapacity and/or hospitalisation required. For all serious adverse events the investigator was asked to record start/end date, severity, duration, evolution and the adopted measures; furthermore, trial drug relationship had to be determined. Serious adverse events had to be reported to the coordinating centre within 24 h, and a specific, more detailed report had to be sent within 15 days.

2.12. Response evaluation

Patients were considered eligible for response if they were evaluated (as indicated before) after the third cycle; however, any disease progression within the third cycle, i.e. before a formal re-evaluation, were considered as a treatment failure. The guidelines for reporting response proposed by Miller and colleagues [22] were followed for definitions of objective response in measurable, non-measurable disease and bone metastases, and for determination of response and overall response in solid tumours. The period between two consecutive observations for the definition of response was reduced from 4 to 3 weeks. Other parameters were considered for the evaluation of the treatment efficacy: time to progression: interval between the date of the first cycle and the date when diagnosis of progressive disease was first diagnosed after the end of chemotherapy; survival: interval between the date of the first cycle and the date of death or last follow-up.

2.13. Statistical analysis

At least 280 patients were considered necessary to validate the hypothesis of equivalence between the two chemotherapy regimens (i.e. FEC versus EM) and the significant increase of response with the addition of LND, assuming an objective response rate of at least 50% in the two arms treated with chemotherapy alone and a 20% increase of this rate with the addition of LND (with an α value of 5%, and a β value of 20%). The accrual of at least 300 patients was planned over 3 years. Time to progression and overall survival analysis were performed with the Kaplan–Meier product-limit method with time being the number of days from the start of treatment. The level of significance of differences in terms of survival rates was assessed using the log-rank test method; the P level of differences between percentages of response rates was calculated with the Quick Calculator facility of the Statistica 97® (Statsoft) package that was used for all analyses. Corrections of P values were not made for multiple comparisons of the secondary endpoints and the subgroup analysis.

3. Results

8 patients out of 326 (2%) randomised patients were excluded from the following analysis because they were considered ineligible for the trial before the start of

chemotherapy: there were no data available for 1 patient, 1 patient had no evidence of metastatic disease, 2 patients showed evidence of cerebral metastases, 1 patient died of cerebral ictus and 3 patients refused treatment (Fig. 1). The patients' characteristics are reported in Table 3; the four treatment arms were well balanced in terms of age, performance status, menopausal status, receptor status, time to first disease relapse, involved sites and number of involved sites. Similarly there were no major imbalances in terms of previous treatments in the adjuvant setting (chemotherapy, hormonal therapy and radiotherapy) or treatment for advanced disease (hormonal therapy and radiotherapy).

The compliance to chemotherapy is shown in Table 4. The mean number of administered cycles was 6 (range: 6.2–6.7); the median number of administered cycles was 8 for the EM and LEM arms, 7 for the LFEC arm and 6 for the FEC arm. No reduction of drug dose was performed. The pattern of treatment delays was similar for all arms with an overall rate of delays ranging from 18.2 to 21%; delays for FEC/EM (19.9%) versus LFEC/LEM (18.8%) and FEC/LFEC (18.5%) versus EM/LEM (20.2%) were not significantly different.

The compliance to LND intake is reported in Table 5. A similar number of patients reduced the LND dose to 450 mg daily (first reduction level), 300 mg daily (second reduction level) or stopped the treatment (no LND intake) in the two LND arms during treatment. The dose reduction was considered as moderate toxicity (score 3 of an arbitrary scale), whilst the treatment interruption of LND intake was considered as severe toxicity (scale 4 of an arbitrary scale). Moderate to severe toxicity from LND leading to dose reduction/treatment interruption was observed in 27% (LFEC arm) to 30% (LEM arm).

The grade 3–4 toxicity (according the WHO/UICC grading system) by treatment arm is reported in Table 6. As for haematological grade $\geqslant 3$ side-effects, leucopenia was similar for all four arms, anaemia was uncommon (1% in all arms) and platelet toxicity was not observed. In spite of supportive therapy, nausea and vomiting of grade $\geqslant 3$ were observed fairly frequently; the difference in the incidence of nausea and vomiting between the FEC arm and the LEM arm was significantly ($P = 0.01$) in favour of the latter arm; the difference between the FEC/EM and the LFEC/LEM arms was also significant ($P = 0.03$). Alopecia was common ($> 90\%$ in all arms) as expected; the occurrence of infection was rarely reported ($\leqslant 1\%$). Severe cardiac toxicity was found in 2 patients in the FEC arm; in general the impact on heart function was mild; median pretreatment values ranged from 61.5 to 63.5% and median post-treatment values ranged from 56 to 59% with a difference of 4–5.5%. No specific toxicity seemed to be increased in the LND arms (apart from myalgias).

3.1. Response rate

In the analysis of the whole series, the difference in the complete responder (CR) rate achieved a significant P level only when the LFEC + LEM combined arm was compared with FEC + EM (20.4 versus 10.7%, $P = 0.01$). When the four arms were compared separately the complete response (CR) rate was significantly

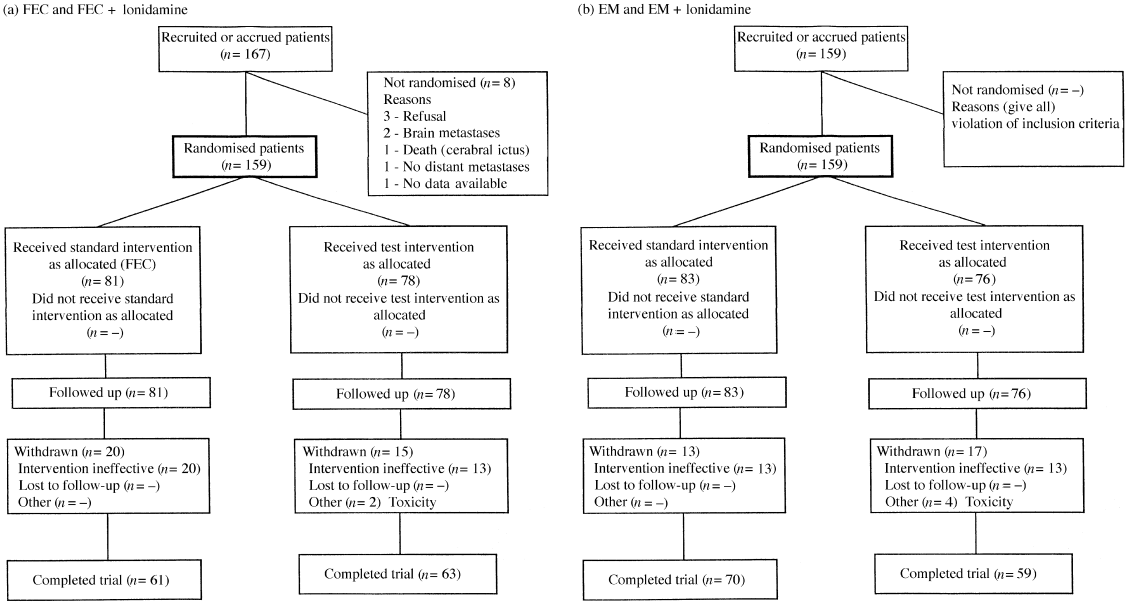

Fig. 1. Flow chart of the progress of patients through the trial. (Adapted from Begg C, Cho M, Eastwood S, *et al.* Improving the quality of reporting of randomized controlled trials: the CONSORT statement. *JAMA* 1996, **276**, 637–639.) Withdrawn, < 6 cycles of chemotherapy; intervention ineffective, progressive disease (as best response); completed trial, $\geqslant 6$ cycles of chemotherapy.

Table 3
Patient characteristics

Arm	FEC *n* (%)	EM *n* (%)	LFEC *n* (%)	LEM *n* (%)
Randomised pts $n=326$	81 (25)	83 (25)	86 (26)	76 (23)
Eligible pts $n=318$	81 (25)	83 (26)	78 (25)	76 (24)
Age (years)				
Mean (range)	56.5 (33–70)	57.2 (35–70)	57.2 (36–70)	56 (24–69)
PS (WHO/UICC)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
0	48 (59)	56 (67)	55 (64)	46 (61)
1	28 (35)	21 (25)	21 (24)	21 (28)
2	5 (6)	6 (7)	9 (10)	9 (12)
Menopause				
Premenopausal	13 (16)	13 (16)	9 (10)	11 (14)
Menopausal	62 (77)	64 (77)	73 (85)	64 (84)
Hysterectomy	6 (7)	6 (7)	3 (3)	1 (1)
ER				
Positive	21 (26)	22 (27)	27 (31)	27 (36)
Negative	12 (15)	20 (24)	15 (17)	13 (17)
Not available	48 (59)	41 (49)	43 (50)	36 (47)
PgR				
Positive	19 (23)	26 (31)	20 (23)	25 (33)
Negative	13 (16)	16 (19)	21 (24)	13 (17)
Not available	49 (60)	41 (49)	44 (51)	38 (50)
Time to first relapse				
<1 year	23 (28.3)	17 (20.4)	20 (26.3)	14 (18.4)
<2 years	62 (76.5)	64 (77.1)	61 (78.2)	65 (85.5)
No. of involved sites				
1 site	22 (27)	22 (27)	26 (33)	19 (25)
2 sites	30 (37)	28 (34)	29 (37)	34 (45)
3 sites	21 (26)	24 (29)	17 (22)	13 (17)
>3 sites	8 (10)	9 (11)	6 (8)	10 (13)
Sites				
B	8 (10)	7 (8)	6 (8)	7 (9)
ST	8 (10)	10 (12)	15 (19)	11 (14)
B + ST	9 (11)	7 (8)	11 (14)	10 (13)
V	12 (15)	10 (12)	12 (15)	8 (11)
V + B	27 (33)	34 (41)	21 (27)	26 (34)
V + ST	17 (21)	15 (18)	13 (17)	14 (18)
Adjuvant treatments				
Chemotherapy				
Yes	22 (27)	23 (28)	18 (21)	26 (34)
No	59 (73)	60 (72)	67 (78)	50 (66)
Hormonal therapy				
Yes	29 (36)	26 (31)	31 (36)	35 (46)
No	52 (64)	57 (69)	54 (63)	41 (54)
Radiotherapy				
Yes	54 (67)	54 (65)	55 (64)	59 (78)
No	27 (33)	29 (35)	30 (35)	17 (22)
Treatments for advanced disease				
Hormonal therapy				
Yes	52 (64)	57 (69)	54 (63)	41 (54)
No	29 (36)	26 (31)	31 (36)	35 (46)
Radiotherapy				
Yes	52 (64)	57 (69)	54 (63)	41 (54)
No	29 (36)	26 (31)	31 (36)	34 (45)
(Any) previous systemic treatment				
No treatment	22 (27)	28 (34)	25 (29)	16 (21)

Pts, patients; PS, performance status; ER, oestrogen receptors; PgR, progesterone receptors; B, bone; ST, soft tissues; V, viscera.

Table 4
Compliance to chemotherapy: delays for each cycle and number of patients for administered cycles according to CHT arm

CHT arm	Total no. of cycles	Total no. of delays (%)	>7 day delays	% of delay before each CHT cycle									
				Overall	2nd cycle	3rd cycle	4th cycle	5th cycle	6th cycle	7th cycle	8th cycle	9th cycle	10th cycle
FEC	505	95 (18.8)	16	18.8	12.9	18	26.3	25.7	15.2	9	14.2	–	–
LFEC	499	91 (18.2)	6	18.2	10.9	10.9	23	19	23	24	12	–	–
EM	563	118 (21)	12	20.9	12.7	19	31.7	21.6	29.2	22.8	22.8	1.2	–
LEM	491	95 (19.3)	7	19.3	13.4	17.7	19.2	16.2	28	28.4	16.5	1.4	–
		Mean no. of cycles	No. of patients for no. of administered CHT cycles										
			0 cycle	1 cycle	2 cycles	3 cycles	4 cycles	5 cycles	6 cycles	7 cycles	8 cycles	9 cycles	10 cycles
FEC	505	6.2	–	5	3	5	3	4	20	3	37	–	1
LFEC	499	6.3	6	7	1	4	3	2	21	6	36	–	–
EM	563	6.7	–	3	1	5	–	4	16	8	44	2	–
LEM	491	6.4	–	3	1	6	3	4	19	1	37	1	1

CHT, chemotherapy.

better for the LFEC arm versus the FEC arm ($P=0.03$) (Table 7). Furthermore, seven disease sites were considered for analysis of response in specific subgroups: bone (375), lymph nodes (342), liver (230), lung (219), chest wall (158), pleural effusions (139) and breast (89). A significant increase in terms of overall (CR + PR) objective response rate was observed in all disease sites, when considered individually, for the EM/LEM group compared with the FEC/LFEC group in favour of the first group: bone $P=0.02$, lymph nodes $P=0.00001$, liver $P=0.0009$, lung $P=0.00001$, chest wall $P=0.0009$, pleural effusions $P=0.0001$ and breast $P=0.001$.

3.2. Survival

The median survival for the overall series was 608 days. There was no statistically significant difference in terms of overall survival between the single arms, whether with or without the addition of LND. In the composite groups, survival of EM + FEC was similar to that of LEM + LFEC ($P=0.44$), whereas EM±LND achieved significantly improved survival versus FEC±LND ($P=0.01$) (Fig. 2). The median time to progression (TTP) in the overall series was 273 days. The TTP was significantly better for EM versus FEC ($P=0.015$), and EM±LND in comparison with FEC±LND ($P=0.015$), whilst there was no significant difference between EM + FEC and the same regimens with LND (Fig. 3). TTP and overall survival were significantly increased for EM±LND in comparison with FEC±LND ($P=0.02$ and $P=0.01$, respectively) when the comparison was performed by restricting the analysis to the subgroups treated with adjuvant chemotherapy (CMF schedules; patients previously treated with anthracycline-based adjuvant schedules were excluded from the trial). The two subgroups were comparable in terms of number of patients relapsing within 1 year after the adjuvant chemotherapy (1/49 and 2/40 patients, respectively). In postmenopausal patients TTP, but not overall survival, was significantly better ($P=0.02$) for the LFEC + LEM group (137 patients) versus the FEC + EM group (126 patients). The significance level was maintained also including patients with hysterectomy ($P=0.01$).

Table 5
Compliance to lonidamine intake during and after chemotherapy

Trial arm	LFEC	LEM
Evaluable pts	74	74
Dose reduction during CHT	*n* (%)	*n* (%)
600→450 mg	13 (18)	12 (16)
600→300 mg	1 (1)	3 (4)
600→0 mg	6 (8)	7 (9)
After CHT		
600→450 mg	2 (3)	4 (5)
600→300 mg	–	1 (1)
600→0 mg	5 (7)	7 (9)

Pts, no. of patients; No., number of cases with LND reduction or interruption; CHT, chemotherapy.

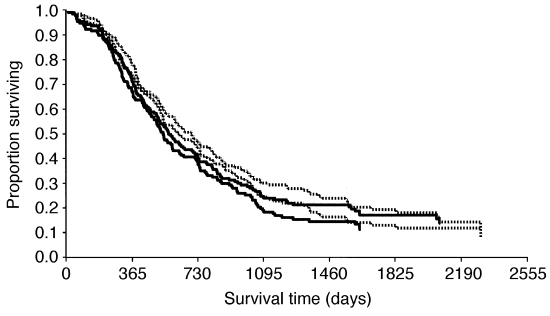

Fig. 2. Overall survival (Kaplan–Meier). FEC and EM without LND (lower dotted line) versus FEC and EM + LND (upper continuous line): $P=0.44$; FEC±LND (lower continuous line) versus EM±LND (upper dotted line): $P=0.01$.

Table 6
Grade 3–4 toxicity (WHO/UICC grading system) according to treatment arm

Treatment arm	Pts (*n*)	Leucocytes (%)	Haemoglobin (%)	Oral (%)	Liver[a] (%)	Nausea/ vomiting (%)	Cardiac function (%)	Hair loss (%)	Infection (%)
FEC	79	7 (9)	1 (1)	1 (1)	2 (3)	30 (38)	2 (3)	72 (91)	1 (1)
LFEC	74	2 (3)	1 (1)	3 (4)	–	21 (28)	–	72 (97)	–
EM	81	4 (5)	1 (1)	1 (1)	–	26 (32)	–	78 (96)	1 (1)
LEM	74	2 (3)	1 (1)	1 (1)	–	14 (19)	–	71 (96)	–
FEC/EM	160	11 (7)	2 (1)	2 (1)	2 (1)	56 (35)	2 (1)	150 (94)	2 (1)
LFEC/LEM	148	4 (3)	2 (1)	4 (3)	–	35 (24)	–	143 (97)	–
FEC/LFEC	153	9 (6)	2 (1)	4 (3)	2 (1)	51 (33)	2 (1)	144 (94)	1 (1)
EM/LEM	155	6 (4)	2 (1)	2 (1)	–	40 (26)	–	149 (96)	1 (1)

Pts, patients evaluable for toxicity.
[a] Bilirubin, ALT/AST, alkaline phosphatase.

4. Discussion

The combination of LND and anthracyclines has been investigated in several pilot studies and phase II trials: there is evidence from these studies that LND may be able to reverse resistance to ADR *in vivo* [24,25]; promising results were obtained when LND was used in combination with EPI [26], EPI + CFA [27] and EPI + cisplatin (CDDP) [28,29] in metastatic breast cancer patients. A pilot study on EPI, CDDP and LND as first-line chemotherapy for anthracycline-naive metastatic breast cancer was performed by Dogliotti and colleagues [29] in 28 patients. The overall response rate was 81.8% (31.8% CR) in 22 evaluable patients. The association, however, resulted in substantial toxicity with a cumulative haematological toxicity. They are testing the combination in a four-arm randomised trial, versus EPI + CDDP (with a reduced dose of CDDP), EPI + LND and EPI.

The role of the addition of LND to ADR or EPI was investigated in two randomised trials (Table 8). 137 patients with metastatic breast cancer and with objective response or stable disease after three cycles of induction ADR were randomised in a two-arm trial (ADR 75 mg/m^2 i.v. versus ADR + LND 600 mg/day orally) by Amadori and colleagues [30]. Toxicity was not increased by LND, except myalgia (WHO grade $\geqslant$2: 57%). Overall response rate was higher for LND (50 versus 38%) but statistical significance was not achieved. A statistically significant difference in favour of ADR + LND was observed in the subgroup of patients with liver metastases (68 versus 33%, $P = 0.03$) a subset which the authors suggest focusing upon in further clinical trials with LND. Dogliotti and associates [31] enrolled 207 patients with advanced breast cancer in a randomised trial to receive EPI (60 mg/m^2 i.v. days 1 and 2, every 21 days) with or without LND (450 mg orally). The response rate was significantly higher for the combination regimen (60 versus 39.8%, $P < 0.01$) in 193 evaluable patients, 55.3 versus 37.5% in all randomised patients according to an intention-to-treat analysis). A significant improvement of overall response was observed in patients with liver metastases (13.6 versus 31.2%). No adjunctive side-effects were observed, except myalgia (grade $\geqslant$2: 41%). Overall survival and time to progression were similar in both groups. The authors concluded that the efficacy of EPI *in vivo* is enhanced by concomitant LND administration.

Apart from the present study, two further randomised trials have investigated the possible role of LND addition to anthracycline-based chemotherapy. Lorusso and colleagues [32] enrolled 206 patients (190 were evaluable) to compare the effectiveness of CNF versus CNF + LND (450 mg 3 times daily) as first-line treat-

Table 7
Objective response rate by arm

Arm	Pts	CR (%)	PR (%)	CR + PR (%)	NC (%)	PD (%)
1. FEC	78	5 (6)	42 (54)	47 (60)	8 (10)	23 (29)
2. EM	80	12 (15)	46 (58)	58 (73)	7 (9)	15 (19)
3. LFEC	73	17 (23)	38 (52)	55 (75)	5 (7)	13 (18)
4. LEM	74	13 (18)	43 (58)	56 (76)	7 (9)	11 (15)

Pts, number of patients evaluable for response; CR, complete response; PR, partial response; NC, no change; PD, progressive disease; CR (arm 1 versus arm 3): $P = 0.03$; CR (arm 1 versus arm 4): $P = 0.02$; CR + PR (arm 1 versus arm 3): $P = 0.051$; CR + PR (arm 1 versus arm 4): $P = 0.03$.

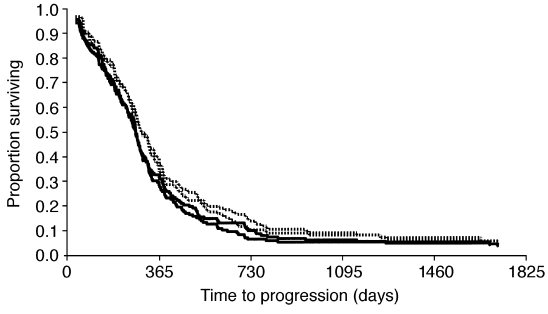

Fig. 3. Time to progression (Kaplan–Meier). FEC and EM without LND (lower dotted line) versus FEC and EM + LND (upper continuous line): $P = 0.15$; FEC±LND (lower continuous line) versus EM±LND (upper dotted line): $P = 0.015$.

Table 8
Randomised studies of anthracycline-based chemotherapy with and without lonidamine in metastatic breast cancer

Author [Ref.]	Treatment arms	Pts no.	% OR	*P* value	MTTP months	*P* value	MST months	*P* value
Amadori [30]	ADR	68	38	n.s.	6.5	n.s.	24	n.s.
	ADR + LND	69	50		6		23	
Dogliotti [31]	EPI	98	39.8	$P < 0.01$	10.6	n.s.	25.3	n.s.
	EPI + LND	95	60		10.5		25	
Calabresi [33]	FAC	124	46.7	$P = 0.002$	6.3	$P = 0.003$	17.9	n.s.
	FAC + LND	116	62.1		9.2		18.7	
Lorusso [32]	CNF	96	39.5	n.s.	5	$P = 0.04$	~20	n.s.
	CNF + LND	94	47.8		8		~20	
Pacini (this study)	EM/FEC	158	66.3	n.s.*	9	n.s.	19	n.s.
	EM/FEC + LND	147	75.5		10		21	

Pts, number of patients; % OR, percentage of objective response (complete + partial responses); MTTP, median time to disease progression; MST, median survival time; n.s., non significant; *with two-sided test; $P = 0.039$ with one-sided test. 5-FU, 5-fluorouracil; CFA, cyclophosphamide; ADR, doxorubicin; EPI, epidoxorubicin; NOV, mitoxantrone; MMC, mitomycin C; LND, lonidamine; ADR = 75 mg/m^2 day 1, every 3 weeks; EPI = 60 mg/m^2 i.v. days 1 and 2, every 21 days; FAC = 5-FU 500 mg/m^2 days 1, 8; ADR 50 mg/m^2 day 1; CFA 500 mg/m^2 day 1; every 3 weeks; FEC = 5-FU and CFA as above; EPI 75 mg/m^2 day 1; every 3 weeks; EM = EPI 75 mg/m^2 day 1, every 3 weeks; MMC 10 mg/m^2 every 6 weeks; CNF = CFA 600 mg/m^2 day 1; NOV 10 mg/m^2 day 1; 5-FU 600 mg/m^2 day 1; every 3 weeks; LND (see text).

ment for metastatic breast cancer. Specific grade $\geqslant 2$ toxicity related to LND administration (myalgia/gastric pain) was uncommon. The overall response rate was similar in the two arms but more CRs were observed in the LND group, especially in patients with soft tissue lesions, although the level of significance was not reached. Median time to progression was significantly longer in the LND arm, whilst overall survival did not significantly differ between the two groups. The second randomised trial was conducted by Calabresi and associates [33,34] to verify whether LND (600 mg orally thrice daily) can potentiate the antineoplastic effects of FAC chemotherapy in advanced breast cancer. 265 patients with metastatic breast cancer were included; 240 patients were evaluable for response (124 FAC, 116 FAC + LND): the objective response rate was significantly better in the FAC + LND arm: 62.1% versus 46.7% of the FAC-treated patients. Median time to progression was also significantly different (6.3 versus 9.2 months in favour of the LND arm), whilst median survival was not significantly different (17.9 versus 18.7 months) except in the group of postmenopausal patients. Group B (the LND arm) showed no increase of toxicity, except myalgia (24.8% WHO grade $\geqslant 2$) and abdominal pain. They concluded that LND can potentiate the FAC regimen.

Taken together, the available data from randomised trials indicate that the administration of LND with ADR or EPI alone or combination chemotherapy protocols containing anthracyclines is able to increase the complete and the overall response rate by approximately 10–15%. Two out of five trials have found a significant *P* value [31,33]. Amongst the 1065 patients evaluated in the five trials, the overall (complete + partial) response rate was 61.2% in 521 patients treated with the addition of LND versus 48.8% of 544 patients treated without LND, with a statistically significant 12.4% mean increase in the LND arms. The difference in response rate observed in our trial (9.1%) is not significant: considering our initial optimistic hypothesis of a potential 20% increase in objective responses with LND, a larger sample might have been necessary to detect a clear statistical significance. The data of the present study cannot support the statement of the trials of Amadori and associates [30] and Dogliotti and colleagues [31] about the particular efficacy in the subset of patients with metastatic liver disease who received EPI or ADR + LND versus EPI or ADR alone; this effect was not reported in patients treated with combination chemotherapy ([32,33] and the present trial). Whether the increase in overall response rate can be translated into a correspondingly significant increase in time to progression is unclear: a significant improvement in terms of median time to progression was reported by Lorusso and coworkers [32] and Calabresi and coworkers [33] but not by the other three studies. Furthermore, the time to progression reported for the arms without LND in these two trials are definitely shorter (5–6.3 months) than the corresponding values in similar arms of other trials (current trial: 9 months; Dogliotti and colleagues [31]: 10.6 months). A possible interference of menopausal status with the TTP was observed in the present study but excluded by Calabresi and coworkers [33]. A significant improvement in median survival time was not observed in any of the five trials. In conclusion, it is our opinion that LND should not be used routinely, outside a clinical trial. A meta-analysis of the existing data might be warranted.

The present paper confirms the preliminary analysis [35] regarding the efficacy of the EM combination as an alternative to FEC. EM is not more toxic than FEC and the overall incidence rate of treatment delay is only 2.2% higher than FEC, mainly due to haematological reasons. EM is at least as good as FEC in terms of TTP

and survival; there may be a possible advantage in choosing this protocol when CMF was delivered previously in an adjuvant setting, although the conclusions drawn from the analysis of small subsets should always be considered with caution.

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