PERGAMON

European Journal of Cancer 37 (2001) 1132–1140

European Journal of Cancer

www.ejconline.com

Results of a phase III prospective, randomised trial, comparing mitoxantrone and vinorelbine (MV) in combination with standard FAC/FEC in front-line therapy of metastatic breast cancer

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Received 18 May 2000; received in revised form 17 October 2000; accepted 26 January 2001

Abstract

This comparative phase III trial of mitoxantrone + vinorelbine (MV) versus 5-fluorouracil + cyclophosphamide + either doxorubicin or epirubicin (FAC/FEC) in the treatment of metastatic breast cancer was conducted to determine whether MV would produce equivalent efficacy, while resulting in an improved tolerance in relation to alopecia and nausea/vomiting. This multicentre study recruited and randomised 281 patients with metastatic breast cancer; 280 were evaluable for response survival and toxicity (138 received FAC/FEC, 142 received MV). Patient characteristics were matched in each arm and stratification for prior exposure to adjuvant therapy was made prospectively. The overall response rate (ORR) was equivalent in the two arms (33.3% for FAC/FEC versus 34.5% for MV), but MV was more effective in patients who had received prior adjuvant therapy (13% (95% confidence interval (CI) 3–23) for FAC/FEC versus 33% (95% CI 20–47) for MV $P=0.025$) with a better progression-free survival (PFS) (5 months (range 1–18 months) versus 8 months (range 1–27 months); $P=0.0007$ for FAC/FEC versus MV, respectively) while FAC/FEC was more effective in previously untreated patients (ORR 43% (95% CI 33–53) versus 35% (95% CI 25–45), $P=0.26$; PFS 9 months (range 0–29 months) versus 6 months (range 0–26 months) $P=0.014$). Toxicity was monitored through the initial six cycles

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PII: S0959-8049(01)00093-4

of therapy; febrile neutropenia and delayed haematological recovery was more frequent for MV ($P=0.001$), while nausea/vomiting of grades 3–4 was greater for FAC/FEC ($P=0.031$), as was alopecia ($P=0.0001$), cardiotoxicity was the same for the two regimens. MV represents a chemotherapy combination with equivalent efficacy to standard FAC/FEC and improved results for patients who have previously received adjuvant chemotherapy. Toxicity must be balanced to allow for increased haematological suppression and risk of febrile neutropenia with MV compared with a higher risk of subjectively unpleasant side-effects such as nausea/vomiting and alopecia with FAC/FEC.

Keywords: Metastatic breast cancer

1. Introduction

Metastatic breast cancer (MBC) is an incurable disease and although reasonable response rates can be achieved with chemotherapy, these do not often translate into a major improvement in overall survival [1] which remains around 24 months [2,3]. Neither dose intensification nor combinations with new drugs including paclitaxel and docetaxel have yet produced a significant impact on survival [4]. Nevertheless, meta-analysis has shown that anthracycline-based regimens improve objective response rates, time to progression and survival compared with the cyclophosphamide methotrexate, 5-fluorouracil (CMF) regimen [5], and could therefore be considered as the gold standard for therapy in the metastatic setting. In addition, prior adjuvant chemotherapy adversely affects these efficacy parameters [6,7].

Considering the limited effect of current treatment on survival in MBC, quality of life based on toxicity remains an important goal for therapy and this study was designed to find a regimen with the same efficacy, but a better tolerance profile, than the anthracycline-based regimens.

Mitoxantrone, a topoisomerase II inhibitor, is a dihydroxyanthracenedione derivative which inhibits DNA synthesis by intercalating DNA, inducing DNA strand-breaks and causing DNA aggregation [8]. Thirteen randomised clinical trials in MBC comparing doxorubicin or epirubicin versus mitoxantrone as a single agent or in combination either in first-line [9–18] or in second-line [1,19,20] have shown that the objective response rate and the median duration of response, as well as the median duration of survival, are comparable except in the studies conducted by Leonard and colleagues [9] and Steward and coworkers [18], respectively. With regard to the toxicity profile reported in these studies, mitoxantrone is clearly less toxic than anthracyclines concerning those adverse events which cause most concern to patients, namely alopecia and nausea/vomiting and also the cardiotoxicity of mitoxantrone is mild. Therefore, mitoxantrone is a good candidate for inclusion in treatment schedules for metastatic breast cancer.

Vinorelbine is a semi-synthetic vinca-alkaloid which inhibits the polymerisation of tubulin into functional microtubules. Its chemical structure and pharmacokinetic profile differ from earlier vinca-alkaloids. As a result of catharanthine moiety modifications, vinorelbine displays lower neurotoxicity and better clinical activity than the other compounds of its class. Vinorelbine is one of the most active new drugs for the management of MBC, and when given as first-line monotherapy for MBC, leads to response rates in the range from 35 to 57% [21]. Two phase II trials combining mitoxantrone and vinorelbine have been reported in first-line treatment of MBC [22,23] and this combination can achieve a response rate of around 50% even in patients who had received a prior adjuvant anthracycline regimen [23].

In order to compare the combination of vinorelbine and mitoxantrone to the classical FAC (5-fluorouracil, doxorubicin, cyclophosphamide) or FEC (5-fluorouracil, epirubicin cyclophosphamide) regimen, a phase III study was initiated in first-line MBC with a stratification on the basis of prior exposure to adjuvant/neoadjuvant chemotherapy.

2. Patients and methods

2.1. Patients

To be eligible for inclusion in this open labelled multicentre randomised trial, women were required to have: histologically documented carcinoma of breast with locally advanced or metastatic disease; at least one bidimensionally measurable lesion (previously irradiated lesions were not considered as measurable); age between 18 and 75 years old; performance status $\leqslant 2$ according to the Eastern Cooperative Oncology Group (ECOG); life expectancy $\geqslant 3$ months; neutrophils count $\geqslant 2000\times10^6$/l, platelets count $\geqslant 100\times10^9$/l creatinine concentration $\leqslant 130$ μmol/l; serum bilirubin less than 1.25 the normal upper limits and liver function tests alanine aminotransferase (ALAT) aspartate aminotransferase (ASAT) $\leqslant 2.5$ times normal (unless abnormal liver function results were due to involvement of liver); left ventricular ejection fraction (LVEF) measurement $\geqslant 50\%$ using radionuclide cardioangiography or $\geqslant 40\%$ using echocardiography.

Patients were not eligible for the study for the following reasons: patients who had received prior chemotherapy for unresectable locally advanced or

metastatic disease (patients with prior adjuvant or metastatic hormonal therapy and palliative radiation for metastatic disease were allowed); patients with pleural effusion, ascites, lymphangitis and bone metastasis as the sole lesion; patients who relapsed within 12 months of completing adjuvant chemotherapy; patients who had previously received greater than 300 mg/m^2 of doxorubicin or 400 mg/m^2 of epirubicin or 72 mg/m^2 of mitoxantrone; patients with clinical or electrocardiogram (ECG) signs of heart disease or congestive heart failure; patients with brain involvement or a history of other malignancy (except for basal cell carcinoma or carcinoma *in situ* of the cervix).

The study was designed according to the recommendations of the Helsinki declaration and approved by the Ethics Committee of Nice (France). Written informed consent was obtained from all patients.

2.2. Pretreatment evaluation

Prior to therapy, all patients underwent evaluation that included medical history, physical examination, performance status determination, haematological and biochemical profile, ECG, measurement of LVEF, chest X-ray, ultrasound or computerised tomographic (CT) scan of the liver, a radionuclide bone scan, and other relevant tests if clinically indicated.

2.3. Treatment and dose modification

Patients were stratified according to the participating institution and to prior neoadjuvant/adjuvant chemotherapy or none, and were registered at the coordinating study centre via a network computer which provided centralised randomisation. Patients were randomly allocated to one of the two regimens (FAC/FEC or mitoxantrone–vinorelbine (MV)) that are shown in Table 1. Both regimens were repeated at intervals of 21 days. The choice of the FAC or FEC regimen at each centre was decided by centre preference. However, all patients treated in each centre received the same regimen, either FAC or FEC as previously determined at the start of the study.

Table 1
FAC or FEC and MV regimens

Agents	Doses		
FAC 50 or FEC 50			
5-Fluorouracil	500 mg/m^2	i.v.	Day 1
Doxorubicin or epirubicin	50 mg/m^2	i.v.	Day 1
Cyclophosphamide	500 mg/m^2	i.v.	Day 1
MV			
Mitoxantrone	12 mg/m^2	i.v.	Day 1
Vinorelbine	25 mg/m^2	i.v.	Days 1 and 8

FAC, 5-fluorouracil, doxorubicin, cyclophosphamide; FEC, 5-fluorouracil, epirubicin, cyclophosphamide; MV, mitoxantrone–vinorelbine; i.v., intravenously.

For both regimens, if the neutrophil count and platelet count were $<1500\times10^6$/l and $<100\times10^9$/L respectively at time of retreatment, the cycle was delayed 1 week, and the counts were re-checked until the neutrophil count and platelet count reached respectively 1500×10^6/l and 100×10^9/l. If these values were not reached after a 2 week delay, the patient was removed from protocol therapy and monitored for survival. For the MV arm, vinorelbine was administered at day 8, only when the neutrophil count was $\geqslant1000\times10^6$/l. No dose reductions were permitted.

Toxicities were graded according to World Health Organization (WHO) criteria [24].

Reasons for removing patients from the study were: disease progression, severe toxicities, treatment refusal, use of growth factors, maximum cumulative dose administered of doxorubicin, epirubicin or mitoxantrone respectively of 550, 850 and 160 mg/m^2; patients could be removed from the study if they had stable disease after at least four cycles of therapy had been administered.

2.4. Study assessments

Tumour responses were assessed every two cycles according to WHO criteria [25]. The first evaluation was performed at least 15 days after the second cycle. For responding patients, three additional cycles were mandatory after the best response was observed, for a minimum of six cycles. In each cycle, blood cells counts were performed at day 1 for the standard regimen FAC/FEC and days 1 and 8 for MV. Beyond the sixth cycle, LVEF had to be estimated after every two further cycles.

2.5. Endpoint and statistical considerations

The primary endpoint of this study was to establish the equivalence in terms of response rate between the standard regimen FAC/FEC and the tested MV regimen. The secondary endpoints were to assess the tolerance of both regimens and to assess the other efficacy criteria of this study: duration of response, progression-free survival (PFS) and overall survival (OS).

The initial required sample size of the study was 400 patients (200 per arm) based on an assumed response rate of 55% for the FAC/FEC regimen [26,27]. After 2 years recruitment, an interim analysis was performed. The unexpectedly low objective response rate (ORR) (31% for both arms together) (95% CI: 24.6–37.4%) led to a reassessment of the sample size. The assumed response rate was then set at 35% for FAC/FEC and the equivalence interval was set to 15% in a one-sided design (type I error rate α was set at 0.05 and type II error rate β at 20%) [28]. This new assessment led to the

conclusion that only a total population of 280 patients was needed and recruitment was stopped as 281 patients had already been enrolled. To ratify the decision, the approval of the 22 investigators was obtained after the recommendation of two independent experts in statistics.

Characteristics of the patients were compared using the appropriate tests in order to ensure they were well balanced. Efficacy criteria were analysed both on an 'intention to treat' and a 'per protocol' analysis. The response rate was defined as the ratio of best OR to the total number of treated patients. The 90% confidence interval (CI) of the difference of the OR was calculated and the significance limit was determined by using the Dunnett and Gent Chi-square test as a means of establishing equivalence between the two arms. The OR and their 95% CI were also assessed in each strata and arm, and compared by the Chi-square test as an exploratory analysis. Duration of partial and complete responses were assessed from the start of treatment and from the first documentation of a complete response to the first documentation of tumour progression, respectively [29]. Duration of response, PFS and OS were estimated by Kaplan–Meier method and compared in each strata and arm (log-rank test) [30]. PFS and OS in each arm were also compared adjusted to the stratification for prior chemotherapy (proportional hazards model of Cox) [31].

Tolerance was assessed in all treated patients. Nausea, vomiting and alopecia were compared in the two arms by selecting the worst WHO grade observed per patient. The assessment was limited to the first six cycles in order to avoid bias due to any differences in the number of cycles in the two arms and according to Kisner's recommendations [32]. Nevertheless, all cardiac toxicity and febrile neutropenia (temperature $\geqslant 38.5^{\circ}C$, neutrophils count $< 500 \times 10^6/l$) from any cycle have been taken into account.

3. Results

3.1. Patients characteristics

Between April 1993 and December 1995, 281 patients were entered into this study by the 22 participating centres and were stratified according to previous neoadjuvant/adjuvant chemotherapy, no previous neoadjuvant/adjuvant chemotherapy and by centre. One patient was enrolled, but never treated after withdrawal of informed consent. 280 patients were evaluable for tumour response, survival and toxicity. 138 and 142 patients were randomly assigned to the FAC/FEC or to MV regimens, respectively (Fig. 1). 13 patients (5%) did not meet all the eligibility criteria of the study (5 in the FAC/FEC arm and 8 in the MV arm), but were included in the analysis performed on an 'intent-to-treat basis'. 9 patients (3%) were randomised in the wrong stratum: 5 in the FAC/FEC arm and 4 in the MV arm.

Patients characteristics were well balanced between the FAC/FEC and MV regimens (Table 2); the population had an overall median age of 60 years old (range 33–75 years), 82% of patients had visceral metastases and 49% liver metastases. 89 patients had received previous adjuvant therapy; 76 of these patients had received an anthracycline/anthracenedione-containing regimen (doxorubicin: 43 patients, epirubicin: 26 patients; pirarubicin: 1 patient, mitoxantrone: 6 patients).

3.2. Treatment

A total of 1539 cycles were administered, 841 (median 6; range 1–18) of FAC/FEC regimens and 698 (median 5; range 1–12) of the MV combination. The percentage of patients treated with six cycles was 65% in the FAC/FEC arm and 49% in the MV arm. Among the FAC/FEC group, 88% of patients received FEC.

The mean relative dose intensity (administered/planned doses) of FAC/FEC combination was 96, 95 and 96% for 5-fluorouracil, anthracycline and cyclophosphamide, respectively, and 92 and 77% for mitoxantrone and vinorelbine, respectively. Omission of vinorelbine at day 8 due to haematological toxicity, mainly neutropenia, occurred in 29% of the cycles. Treatment was delayed in 28 and 38% of the cycles in the FAC/FEC and MV regimens, respectively. Neutropenia was responsible for delaying treatment in 58 and 71%

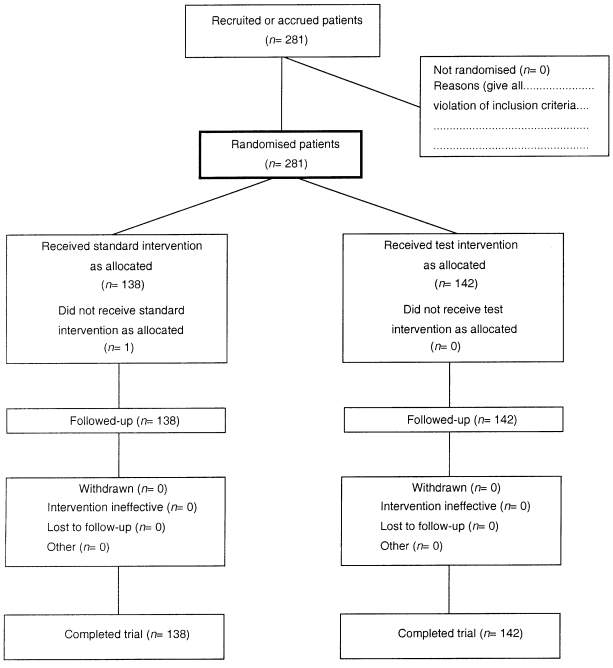

Fig. 1. Flow chart of the progress of patients through the trial (adapted from Begg C, Cho M, Eastwood S, *et al.* Improving the quality of reporting of randomized controlled trials: the CONSORT statement. *JAMA* 1996, **276**, 637–639).

for FAC/FEC and MV, respectively; the most frequent duration of delay was 1 week (approximately 90% for both arms).

3.3. Response

The OR rate was 33.3% for FAC/FEC and 34.5% for MV, a difference in response rate of 1.2%, however when the test of equivalence was applied, the 90% CI of the difference is −8% to +11% and the MV combination is therefore demonstrated to be at least as effective as FAC/FEC ($P=0.014$). The objective response rates, according to the localisation of the disease (visceral and non-visceral), are shown in Table 3.

Tumour response calculation according to stratification by prior adjuvant therapy (Table 4) showed that the ORR in the group of patients previously treated with adjuvant chemotherapy was higher for those who subsequently received the MV combination: 33% (95% CI 20–47) versus 13% (95% CI 3–23), $P=0.025$, while in patients who had not received prior adjuvant chemotherapy, the ORR was 35% (95% CI 25–45) for MV versus 43% (95% CI 33–53) for FAC/FEC, $P=0.26$. The median duration of objective response was 10 months (range 1–29 months) and 7 months (range 1–27 months) for the FAC/FEC and MV combinations, respectively. 12 patients in each arm had not progressed at the time of the analysis. These are 'intention-to-treat' analysis, but the same results were obtained in the 'per protocol' analysis.

3.4. Survival

At the time of this analysis, median time of follow-up was 24 months (range: 8.66–40.8). The median overall survival (range) was similar: 20 (0–38.5) and 17 (0–35.5) months for the FAC/FEC and MV regimens, respectively ($P=0.27$). The median PFS was 7 months for

Table 2
Pretreatment characteristics of all treated patients

Characteristics	FAC or FEC No. (%)	MV No. (%)	*P* value
Total treated	138 (100)	142 (100)	
Age (years)			
Median (range)	60 (33–75)	60 (35–75)	0.63
Pre-menopausal	22 (16)	23 (16)	0.93
Post-menopausal	116 (84)	119 (84)	
Performance status (ECOG)			
0	82 (59)	75 (53)	0.41
1	43 (31)	55 (39)	
2	13 (9)	12 (8)	
Metastatic disease at diagnosis	24 (17)	27 (19)	0.70
Prior adjuvant chemotherapy[a]	41 (30)	48 (34)	0.57
With anthracycline/anthracenedione	36	40	0.57
Previous hormonal therapy for metastasis	43 (31)	55 (39)	0.18
Two or three lines of hormonal therapy	13	13	
Dominant site of disease			
Visceral	112 (81)	118 (83)	
Liver	70	67	
Lung	36	43	0.78
Other visceral	6	8	
Non-visceral	26 (19)	24 (17)	
Number of visceral sites per patient			
1	83	95	
2	20	20	0.43
⩾3	9	3	
Number of disease sites per patient			
Median (range)	2 (1–7)	2 (1–7)	0.68
Disease-free interval[b] (months)			
Median (range)	34 (0–362)	37 (0–288)	0.47

FAC, 5-fluorouracil, doxorubicin, cyclophosphamide; FEC, 5-fluorouracil, epirubicin, cyclophosphamide; MV, mitoxantrone–vinorelbine; ECOG, Eastern Cooperative Oncology Group.

[a] 46 in FAC or FEC/46 in MV (intention-to-treat), 41/48 (per protocol: error stratum in randomisation).

[b] Months from the end of initial treatment and first metastasis.

Table 3
Tumour response (according to the localisation)

	FAC/FEC					MV				
	Visceral				Non-visceral	Visceral				Non-visceral
	Liver ($n=70$)	Lung ($n=36$)	Other ($n=6$)	Total ($n=112$)	($n=26$)	Liver ($n=67$)	Lung ($n=43$)	Other ($n=8$)	Total ($n=118$)	($n=24$)
CR	4	1	0	5	5	2	2	2	6	7
PR	19	8	4	31	5	19	12	1	32	4
OR	23 (33%)	9 (25%)	4 (67%)	36 (32%)	10 (38%)	21 (31%)	14 (33%)	3 (38%)	38 (32%)	11 (46%)

FAC, 5-fluorouracil, doxorubicin, cyclophosphamide; FEC, 5-fluorouracil, epirubicin, cyclophosphamide; MV, mitoxantrone–vinorelbine; CR, complete response; PR, partial response; OR, objective response.

both regimens (ranges 0–29 months for FAC/FEC and 0–27 months for MV ($P=0.79$). The OS and PFS curves are shown in Figs. 2 and 3. The median PFS was better with MV in patients who had received prior adjuvant chemotherapy: 8 months (range 1–27 months) versus 5 months (range 1–18 months) ($P=0.0007$). The median PFS was better in the FAC/FEC group in patients who had not received prior adjuvant chemotherapy: 9 months (range 0–29 months) versus 6 months (range 0–26 months) ($P=0.014$). The PFS curves according to the stratification are shown in Figs. 4 and 5. The trend was similar for the overall survival, but did not reach significance for MV: the median survival was 20 months (range 0–35.5 months) in the MV group and 16 months (range 0–33 months) in the FAC/FEC group for patients previously treated with adjuvant chemotherapy ($P=0.25$); and it was 16 months (range 0–31 months) in the MV group versus 22 months (0–38.5 months) in the FAC/FEC group for the other strata ($P=0.027$).

3.5. Toxicity

During the first six cycles, at day 21, WHO grade 3 or 4 neutropenia was observed in 8% of cycles of FAC/FEC versus 15% of cycles of MV. Thrombocytopenia and anaemia were rare in both arms.

Febrile neutropenia with hospitalisation was reported in 2% of patients ($n=3$) (three cycles) in the FAC/FEC arm and in 15% of patients ($n=21$) (26 cycles) in the MV arm ($P=0.001$). This toxic event was responsible for the death of one patient in each arm; the patient who died in the MV arm experienced febrile neutropenia which was associated with cor pulmonale (the combined effect of which was the cause of death). Other deaths reported were not related to the study and consisted of: one pulmonary embolism, one sudden cardiac arrest, 1 patient who committed suicide and another who developed septic shock after withdrawal from the study.

The most frequent toxicities — nausea, vomiting and alopecia — were among the secondary endpoints of this study. We compared the non-haematological toxicities which occurred in the two treatment arms by using the worst grades experienced during the first six cycles. The results are shown in Table 5. The ratio of patients presenting with grade 3 or 4 of nausea/vomiting in the FAC/FEC arm was statistically higher than in MV arm: 16% versus 8% ($P=0.031$). This result was confirmed even when adjusted for preventive treatment with anti-5-HT3 antagonists at the first cycle. Concerning alopecia, the ratio of patients presenting with a grade 3 in the FAC/FEC arm was also statistically higher than in MV arm: 30% versus 7% ($P=0.0001$).

Table 4
Tumour response (according to prior adjuvant/neoadjuvant therapy or no adjuvant/neoadjuvant therapy)

	FAC or FEC			MV		
	Adjuvant/neoadjuvant chemotherapy ($n=46$) *n* (%)	No adjuvant/neoadjuvant chemotherapy ($n=92$) *n* (%)	Total ($n=138$) *n* (%)	Adjuvant/neoadjuvant chemotherapy ($n=46$) *n* (%)	No adjuvant/neoadjuvant chemotherapy ($n=96$) *n* (%)	Total ($n=142$) *n* (%)
CR	0	10 (11)	10 (7)	4 (9)	6 (6)	10 (7)
PR	6 (13)	30 (33) (95% CI: 18.7–46.5)	36 (26)	11 (24)	28 (29)	39 (27)
CR + PR	6 (13)	40 (43)	46 (33)	15 (33)	34 (35) (95% CI: 25.7–45.1)	49 (35)
SD	28 (61)	37 (40)	65 (47)	19 (41)	33 (34)	52 (37)
PD	10 (22)	12 (13)	22 (16)	6 (13)	24 (25)	30 (21)
ND	2 (4)	3 (3)	5 (4)	6 (13)	5 (5)	11 (8)

FAC, 5-fluorouracil, doxorubicin, cyclophosphamide; FEC, 5-fluorouracil, epirubicin, cyclophosphamide; MV, mitoxantrone–vinorelbine; CR, complete response; PR, partial response; ORR, objective response rate; SD, stable disease; PD, progressive disease; ND, unable to determine.

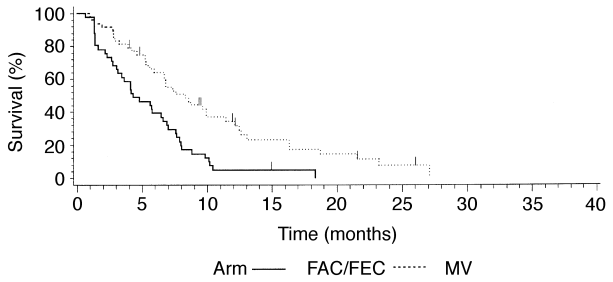

Fig. 2. Progression-free survival for patients receiving adjuvant or neoadjuvant chemotherapy. FAC, 5-fluorouracil, doxorubicin, cyclophosphamide; FEC, 5-fluorouracil, epirubicin, cyclophosphamide; MV, mitoxantrone–vinorelbine.

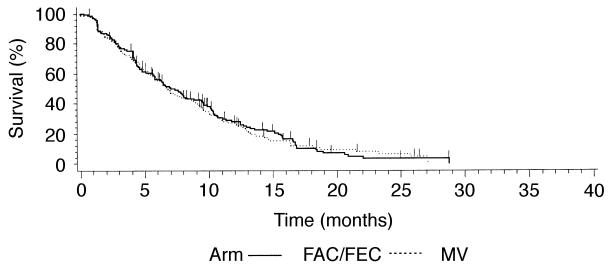

Fig. 4. Progression-free survival for patients receiving the two regimens. FAC, 5-fluorouracil, doxorubicin, cyclophosphamide; FEC, 5-fluorouracil, epirubicin, cyclophosphamide; MV, mitoxantrone–vinorelbine.

Cardiotoxicity was evaluated by clinical assessment, measurement of LVEF, and ECF and was documented in 10 patients (7%) in the FAC/FEC arm and 9 patients (6%) in the MV arm; among these patients, 2 in FAC/FEC and 7 in MV had previously received an anthracycline-based regimen. Other grade 3 or 4 toxicities were rare; the number of cases among all cycles are given for FAC/FEC and MV, respectively, as follows: mucositis, 2 versus 8 (5 patients); constipation and abdominal pain, 0 versus 6; diarrhoea 1 versus 0; fatigue 1 versus 4; local toxicity, 0 versus 2; hepatic dysfunction: 0 versus 1. 13 patients were withdrawn from the FAC/FEC arm and 37 from the MV arm with the major differences relating to febrile neutropenia/delayed haematological recovery (3 versus 25).

The dossiers of the patients have been recently checked to assess late haematological toxicities possibly related to chemotherapy and two events have been registered: one acute myelomonocytic leukaemia in the FEC arm and one refractory anaemia with an excess of blasts in the MV arm.

4. Discussion

The comparison between the tested MV regimen to the conventional FAC/FEC regimen in first-line chemotherapy for patients with MBC showed similar efficacy for both treatments in terms of response rate, confirmed by the equivalence test, and comparison of time to progression ($P=0.79$) and overall survival ($P=0.27$) were also not different. Nevertheless this study has shown that the MV regimen is superior to FAC/FEC in patients presenting with distant metastasis who had previously received FAC/FEC as adjuvant systemic therapy in terms of response rate ($P=0.025$) and time to progression $P=0.0007$). The opposite is true for the non-pretreated patients where FAC/FEC was better than the MV regimen. The low response rate observed in both arms needs to be interpreted in light of the study population which had a profile of high risk with regard to classical prognostic factors. More than 80% of patients presented with visceral metastases, mainly in the liver (49%) and 50% of patients had at least two sites of tumour involvement. In addition, 32% of patients were pretreated by adjuvant chemotherapy and 85% of these had previously received an anthracycline/anthracenedione regimen. The ORR obtained in the FAC/FEC arm seems to be low with respect to the expected response rate observed in the literature. However, in the chemotherapy-naïve group patients who received FAC/FEC the response rate is 43% (95% CI 33–53) which is closer to the 55% expected response rate.

In this trial, either FAC or FEC were permitted as the standard regimen because these two regimens are equivalent in terms of all efficacy parameters [27,33]. The stratification on the basis of prior neoadjuvant/

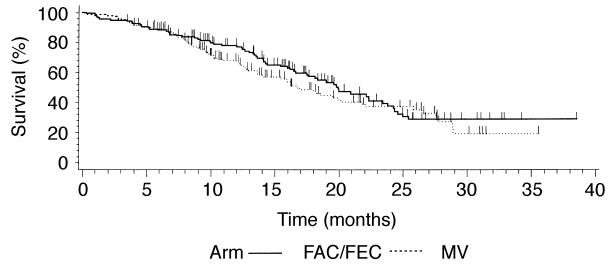

Fig. 3. overall survival for the two regimens: FAC/FEC or MV. FAC, 5-fluorouracil, doxorubicin, cyclophosphamide; FEC, 5-fluorouracil, epirubicin, cyclophosphamide; MV, mitoxantrone–vinorelbine.

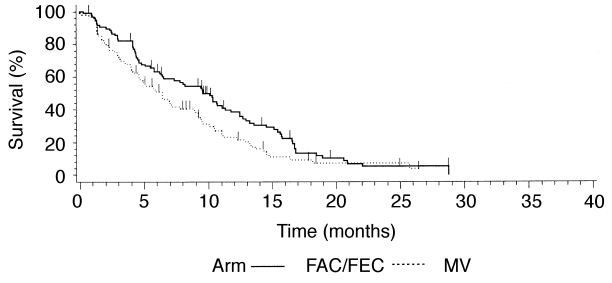

Fig. 5. Progression-free survival for those not receiving adjuvant/neoadjuvant chemotherapy. FAC, 5-fluorouracil, doxorubicin, cyclophosphamide; FEC, 5-fluorouracil, epirubicin, cyclophosphamide; MV, mitoxantrone–vinorelbine.

Table 5
Nausea/vomiting and alopecia: worst grade of toxicity observed among the first six cycles

	FAC or FEC No. of patients (%)	MV No. of patients (%)
Nausea/vomiting WHO grade	$n=136$	$n=141$
0	29 (21)	62 (44)
1	41 (30)	39 (28)
2	44 (32)	29 (21)
3	20 (15)	8 (6)
4	2 (1)	3 (2)
Grade 3–4 FAC/FEC versus MV; $P=0.031$		
Alopecia WHO grade	$n=135$	$n=141$
0	26 (19)	56 (40)
1	36 (27)	48 (34)
2	32 (24)	27 (19)
3	41 (30)	10 (7)
Grade 3 FAC/FEC versus MV; $P=0.0001$		

FAC, 5-fluorouracil, doxorubicin, cyclophosphamide; FEC, 5-fluorouracil, epirubicin, cyclophosphamide; MV, mitoxantrone–vinorelbine; WHO, World Health Organization.

adjuvant therapy or none suggests that this reduces the chances of achieving a subsequent response and restricts the range and intensity of treatment for metastatic disease [34–36]. In a trial which is similar to the current study, Blajman and colleagues [37] compared the classical FAC regimen to a combination of doxorubicin and vinorelbine as first-line chemotherapy for MBC; however this is currently the only available published randomised study and their population had less severe prognostic ratings (only 50% of patients presenting with visceral metastasis and only 7.5% having received previous anthracycline-containing regimens as adjuvant therapy) which could explain the higher response rate they obtained. Nevertheless, the two studies give results which are comparable in terms of response duration, time to progression and overall survival for the whole population included.

The MV regimen produced more cases of neutropenia resulting in delayed haematological recovery and hospitalised febrile neutropenia ($P=0.001$) compared with the FAC/FEC regimen in this population, while, by contrast, the FAC/FEC regimen was significantly more toxic in relation to the non-haematological adverse effects which cause concern to patients: alopecia ($P=0.0001$) and nausea/vomiting ($P=0.031$). The two regimens are not different with regard to the number of toxic deaths (one in each arm) and the number of late haematological toxicities (one in each arm).

Since MV is able to produce a higher response rate and a longer time to progression, we can conclude that this combination is superior to FAC/FEC for patients pretreated in the adjuvant setting. Clinicians must, however, be prepared to weigh up the consequences of treatment and consider whether potentially manageable toxicities related to neutropenia and the risk of infection requiring antibiotic therapy should affect the decision to use treatment which is associated with a greater acceptability to their patients because of a reduced incidence of alopecia and nausea/vomiting.

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