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Original Paper

Randomised Phase II Study of Epirubicin–Vindesine Versus Mitoxantrone–Vindesine in Metastatic Breast Cancer

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The purpose of this study was to compare the activity and toxicity of epirubicin–vindesine (EV) with mitoxantrone–vindesine (MV) in patients with metastatic breast cancer. A total of 295 patients was randomly allocated to treatment with vindesine 3 mg/m^2 combined with either epirubicin 40 mg/m^2 or mitoxantrone 10 mg/m^2. All drugs were given by intravenous push, treatment cycles were repeated at 3–4 week intervals. 255 patients were available for response, and 283 for toxicity. EV and MV yielded similar objective response rates (34 and 26%, respectively), response durations, times to progression and survival. Median time to remission was 1.8 and 3.1 months ($P = 0.006$) with EV and MV, respectively. In patients with visceral metastases, response rate was higher with EV than MV (40 versus 23%; $P = 0.03$). Patients receiving MV had less nausea/vomiting ($P = 0.007$) and alopecia ($P = < 0.001$) of WHO grade ≥ 2. Bone marrow, cardiac and other toxicities were mild with both treatments. The observed differences in activity and toxicity between the two regimens appear to have clinical relevance. EV proved to be more active in visceral disease and to be able to induce remissions more rapidly. Accordingly, patients with visceral metastases or severe tumour-related symptoms may benefit from epirubicin-based treatment. Subjective toxicities, i.e. nausea/vomiting and alopecia, were less frequent and severe with MV. Thus, MV may prove useful in patients with more indolent disease and appears to warrant phase III evaluation in such patients.

Key words: metastatic breast cancer, epirubicin, mitoxantrone, vindesine
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INTRODUCTION

LITTLE PROGRESS has been achieved in recent years by standard-dose chemotherapy in metastatic breast cancer. Objective tumour responses can be achieved in 40–70% of patients with 10–20% complete remission. However, responses are usually temporary and standard-dose chemotherapy has shown little effect on survival [1–3]. Hence, palliation has remained the major objective of such treatment in patients with metastatic breast cancer.

Generally, doxorubicin has been considered to be the single most active agent in metastatic breast cancer. Doxorubicin-based regimens have usually been found to yield higher response rates but have failed to translate into prolonged survival [4, 5]. Because toxicity associated with doxorubicin can be significant,

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agents have been searched for which have similar activity but lower toxicity. Two such drugs which have received much attention are epirubicin and mitoxantrone [6–8]. When used at equi-myelotoxic doses, the therapeutic activity of these two agents has been similar to doxorubicin or only modestly lower. However, the new agents, particularly mitoxantrone, have usually been better tolerated by the patients. Moreover, both agents have been found to be less cardiotoxic than doxorubicin [6, 9].

Another agent that has shown significant preliminary activity in metastatic breast cancer is the *vinca* alkaloid, vindesine [10, 11]. The major toxicity of vindesine has been myelosuppression. Other adverse effects have been reported to be mild and, in particular, subjective tolerance of the drug has usually been good. Hence, combining either epirubicin or mitoxantrone with vindesine may yield a high therapeutic index, i.e., good antitumour activity at low toxicity. The purpose of this randomised phase II study was to compare prospectively the activity and toxicity of epirubicin–vindesine (EV) versus mitoxantrone–vindesine (MV) in patients with metastatic breast cancer.

PATIENTS AND METHODS

A total of 295 women with histologically proven breast cancer was entered into this trial. Eligibility criteria included measurable or evaluable metastatic disease; objective evidence of tumour progression; Karnofsky performance status of ≥ 50; expected survival of > 3 months; age of ≤ 75 years; adequate bone marrow, hepatic and renal functions; no prior treatment with anthracyclines, mitoxantrone or vindesine; no central nervous system (CNS) metastasis; and informed consent according to institutional guidelines. Patients with myocardial infarction within the last 6 months, symptomatic coronary heart disease, congestive heart failure or uncontrolled hypertension were excluded from the study.

Pretreatment evaluation included history, physical examination, determination of performance status, complete peripheral blood cell count including platelets, blood chemistry, electrocardiogram, chest X-ray and ultrasound of the liver. Bone scan, bone X-ray and computed axial tomography (CAT) scans of liver and abdomen were obtained if clinically indicated or if needed for bidimensional tumour measurement. Baseline measurements of left ventricular ejection fraction (LVEF) were made by using echocardiography or radionuclide cardioangiography. Tumour responses were evaluated after the first two cycles of chemotherapy and then every three cycles. In each cycle, blood cell counts and blood chemistry were performed. Controls of LVEF were obtained if clinically indicated, using the same technique as used for baseline determination.

Patients were registered via telephone at the statistical study centre, the Department of Biostatistics at the University of Innsbruck, Austria, and randomly assigned to treatment with either epirubicin or mitoxantrone. Patients were stratified according to participating institution, dominant site of disease (visceral, bone or soft tissue) and prior chemotherapy.

Patients received vindesine 3 mg/m^2 combined with either mitoxantrone 10 mg/m^2 or epirubicin 40 mg/m^2, given by intravenous (i.v.) push. The initial three cycles were repeated at 3 week intervals, with further courses every 4 weeks. Study treatment was discontinued in the event of tumour progression, severe toxicity, refusal by patient or cumulative epirubicin and mitoxantrone doses of ≥ 1000 and ≥ 160 mg/m^2, respectively.

Toxicities were graded according to World Health Organization (WHO) criteria [12]. If white blood cell (WBC) and platelet counts, respectively, were < 4000 and $< 100\,000/\mu$l at the time of the next cycle, or the respective nadir values were < 1500 and $< 75\,000$ µl, doses of each drug were reduced by 25%. If WBC and platelet counts, respectively, were < 1500 and $75\,000/\mu$l at the time of the next cycle, treatment was delayed until full recovery. The dose of vindesine was reduced by 50% in case of neurotoxicity of $\geq$ grade 1. In the event of higher grade neurotoxicity, vindesine was replaced by vinblastine 5 mg/m^2 i.v. after full recovery of neurotoxicity. Patients were removed from study if they developed clinical symptoms of congestive heart failure, significant arrhythmias or a reduction in LVEF to ≤ 0.45.

Tumour responses were assessed according to International Union Against Cancer criteria [13]. Briefly, complete response was defined as disappearance of all known disease for a minimum of 4 weeks, partial response as a reduction of $\geq 50\%$ in the sum of the areas of all measured lesions for a minimum of 4 weeks without growth of any lesion or appearance of new lesions. Progressive disease was defined as a $\geq 25\%$ increase in total tumour load or any appearance of a new lesion. Patients with $< 50\%$ decrease in tumour load or tumour progression of $< 25\%$ were classified as having stable disease. Patients had to have a minimum of two treatment cycles to be evaluable for response. However, all patients were included in the analyses of time to progression and survival according to intent to treat. Time to progression and survival time were measured from start of therapy to the time of first documentation of tumour progression and death, respectively. Durations of partial and complete remissions were measured from the start of treatment and first documentation of complete response, respectively, to the first documentation of tumour progression.

Assuming a response rate of 25–40% for either treatment, 150 patients were planned to be treated in each study arm in order to detect a 15% difference in response rates between the two treatments with a statistical power of 80% and a two-sided type 1 error of 5%. To test for baseline comparability of treatment groups, adjustments for co-variables were made using Cox's proportional hazard model [14]. Response rates between the two groups were compared by using the χ^2 test. Confidence intervals for response rates were calculated by using the normal approximation of the binomial distribution [15]. Response durations, time to progression and survival time were estimated using the Kaplan–Meier method [16]. To estimate the effects of treatment and of various prognostic factors on various response parameters, the log-rank test was used [17]. Toxicity scores were recorded as the worst episode by each patient. χ^2 tests were used to compare toxicities in the two groups.

RESULTS

Between January 1986 and June 1989, 295 patients were entered into the study, 149 and 146 into the EV and MV groups, respectively. 255 patients were evaluable for tumour response, 283 for toxicity. 5 patients were excluded for not meeting the eligibility criteria. 35 patients were not considered evaluable for tumour response because of early death due to cancer in 16; protocol violation in 9; refusal of therapy in 7 (also excluded from assessment of toxicity); and toxicity in 3 patients. However, these patients were included in analyses of time to progression and survival according to intent to treat. Patient and tumour characteristics were reasonably well balanced between the two groups (Table 1).

Approximately 60% of the patients in both groups had visceral metastases, more than 50% had two or more sites of disease. At

Table 1. Pretreatment characteristics of patients evaluable for tumour response

	EV (n = 129) No. (%)	MV (n = 126) No. (%)	
Age, years			
Median	57	56	
Range	29–75	27–75	
Premenopausal	34 (26)	29 (23)	
Postmenopausal	95 (74)	97 (77)	
Karnofsky performance status			
90–100	66 (51)	65 (52)	
60–80	52 (40)	52 (41)	
< 60	11 (9)	9 (7)	
Dominant site of disease			
Visceral	78 (60)	81 (64)	
Bone	39 (30)	35 (28)	
Soft tissue	12 (9)	10 (8)	
Prior chemotherapy	46 (36)	32 (25)	P = 0.10
Adjuvant	19 (15)	12 (10)	
Palliative	27 (21)	20 (16)	
Disease free interval			
< 2 years	75 (58)	69 (55)	
≥ 2 years	54 (42)	57 (45)	
Median (months)	19	24	

EV, epirubicin–vindesine; MV, mitoxantrone–vindesine.

the time of this analysis, all patients were off study and median time of follow-up was 31.5 months.

Objective tumour responses were recorded in 34 and 26% of the patients receiving EV and MV, respectively (Table 2). The corresponding 95% confidence intervals were 26–43% and 18–34%, respectively (P = 0.15). Complete remissions were rare in both groups. Progressive disease was observed in 27 and 38% of the patients treated with EV and MV, respectively (P = 0.08). Table 3 shows tumour responses according to dominant site of disease and prior chemotherapy, two criteria used for stratification. Patients with visceral metastases were more likely to respond to EV than MV (40 versus 23%, P = 0.03), as were patients without prior chemotherapy (37 versus 22%, P = 0.03).

Time to progression and survival curves for the two treatment groups were superimposable (data not shown). Median time to progression in patients randomised to receive EV and MV, respectively, was 5.4 and 5.1 months, and corresponding median survival was 14.7 and 13.3 months (non-significant; n.s.). Median survival of patients with visceral and non-visceral metastases was 12 and 20 months, respectively (P = 0.001), with no difference between the treatment groups. At 2 years, 23 and 32% of patients randomised to EV and MV, respectively, were still alive (n.s.). Median survival in patients with objective tumour response and stable disease was 19 and 17 months, respectively (P = 0.617), and was 7 months in patients with progressive disease (P = 0.002). Median response duration was 7.5 and 8.8 months for EV and MV, respectively. Median time to remission was significantly shorter with EV (1.8 versus 3.1 months, P = 0.006).

Table 2. Tumour response

	EV (n = 129) No. (%)	MV (n = 126) No. (%)	
Complete response	5 (4)	7 (6)	
Partial response	39 (30)	26 (21)	
Complete and partial response	44 (34)*	33 (26)	P = 0.15
Stable disease	50 (39)	45 (36)	
Progressive disease	35 (27)	48 (38)	P = 0.08

* 95% confidence intervals for EV and MV, respectively, 26–43% and 18–34%.
For abbreviations see legend to Table 1.

Table 3. Tumour response according to dominant site of disease and prior chemotherapy

	EV No. (%)	MV No. (%)	
Dominant site of disease			
Visceral	31/78 (40)	19/81 (23)	P = 0.03
Bone	7/39 (18)	9/35 (26)	
Soft tissue	6/12 (50)	5/10 (50)	
Prior chemotherapy			
Yes	13/46 (28)	12/32 (38)	
No	31/83 (37)	21/94 (22)	P = 0.03

For abbreviations see legend to Table 1.

The median number of EV and MV cycles received per patient was five (range 1–17) and six (range 1–21), respectively. Bone marrow toxicity was mild in both treatment groups. Transient leucopenia resulted in dose reductions or treatment delay in 20 and 33% of patients receiving EV and MV, respectively (P = 0.016). Median leucocyte nadirs were 3200 and 2320 cells/μl with EV and MV, respectively (P = 0.002). No patient developed fever or infection due to granulocytopenia, and there was no toxic death. White blood cell toxicity is shown in Table 4. In both groups, mild thrombocytopenia was recorded in 5% of the patients. Platelet substitution was not required and there were no bleeding episodes. Red cell toxicity was not observed.

Non-haematological toxicities are summarised in Table 5. Treatment with MV was associated with significantly less nausea/vomiting (P = 0.007) and alopecia (P = < 0.001) of WHO grade ≥ 2. Neurotoxicity of grade ≥ 2 was observed in 14.5 and 5.5% of patients receiving MV and EV, respectively (P = 0.02). One patient with liver and peritoneal metastases developed a reversible paralytic ileus after the first course with MV. The patient died 5 weeks later of progressive cancer. No patient experienced congestive heart failure. Moderate reductions in LVEF were recorded in 5 and 3 patients, respectively, treated with EV and MV. The corresponding cumulative doses of epirubicin and mitoxantrone were 200, 280, 320, 450 and 600 mg/m^2 and 60, 90 and 150 mg/m^2, respectively. Transient, asymptomatic alterations in heart rhythm such as atrial arrhythmia or sinus tachycardia were recorded in 9 and 12% of patients on EV and MV, respectively.

DISCUSSION

One approach pursued in recent years to improve the outcome of cytotoxic treatment in patients with advanced breast cancer, has been the development of therapies with lesser toxicity yet

Table 4. White blood cell toxicity according to worst episode per patient

Type of toxicity*	EV (% patients) 0	1	2	3	4	MV (% patients) 0	1	2	3	4
Leucocytopenia	29†	28	32	9†	2†	13	18	34	27	8
Granulocytopenia	81	10	9	0†	0†	70	8	10	8	4

* Grading according to WHO criteria. † Significant difference at P value of < 0.05 between EV and MV at corresponding toxicity grades.
For abbreviations see legend to Table 1.

Table 5. Non-haematological toxicity according to worst episode per patient

Type of toxicity*	EV (% patients) 0	1	2	3	4	MV (% patients) 0	1	2	3	4
Nausea/vomiting	10	32	41†	15	2	19	39	25	14	3
Alopecia	11‡	6	24	59‡	0	25	18	25	32	0
Neurotoxicity	82	13	3†	2	0	75	11	11	3	0
Mucositis	95	3	1	1	0	92	4	2	2	0
Diarrhoea	85	7	6	2	0	87	5	5	3	0

* Grading according to WHO criteria. † Significant difference at P value of < 0.05 between EV and MV at corresponding toxicity grades. ‡ Significant difference at P value of < 0.001 between EV and MV at corresponding toxicity grades.
For abbreviations see legend to Table 1.

similar activity as compared to standard treatments. Three agents which have been described as promising in this regard are epirubicin, mitoxantrone and vindesine [18]. The present randomised phase II trial was an effort to compare the effects of epirubicin and mitoxantrone when combined with vindesine in patients with metastatic breast cancer. The doses used of mitoxantrone and particularly of epirubicin were low. To reduce the frequency of patients' visits to the clinic, vindesine was given along with the other agent at 3–4-week intervals rather than being administered more frequently, as previously described [10, 11, 19]. All these measures were taken in an effort to enhance patients' tolerance of treatment. At the same time, it was hoped that such low-intensity treatment would still be able to yield satisfactory palliative activity.

Both regimens proved to be well tolerated by the patients. However, nausea/vomiting and alopecia were significantly less severe and frequent with MV, which seems important considering the palliative intent of treatment. The differences observed in WBC toxicity appear to have little clinical relevance. Leucocytopenia was usually mild, in most patients not accompanied by significant granulocytopenia, and not associated with fever or apparent infection.

Response rate, time to progression and survival were similar in the two treatment groups. However, EV proved capable of inducing remissions almost twice as rapidly as mitoxantrone therapy. Furthermore, in patients with visceral metastases, a significantly higher response rate was obtained by epirubicin treatment. Rapid response induction and better ability to induce remissions in visceral metastases are features which can be of relevance in the daily management of breast cancer patients. The higher response rate achieved by epirubicin therapy in visceral disease failed to translate into prolonged survival. However, such a lack of survival benefit despite higher response rates has been a common experience in standard-dose chemotherapy studies in advanced breast cancer [4, 5, 20, 21]. The stated goal of both treatments was palliation. Thus, data on quality of life as self-assessed by the patients would have been of significant interest and potential value. Generation of such data by means of appropriate questionnaires was indeed initiated in the second year of the study. Unfortunately, however, this effort soon had to be terminated for logistic reasons and the number of patients who completed the questionnaires was too small to warrant analysis.

In retrospect, it might seem unfortunate that the study protocol did not allow for dose escalation. In the epirubicin arm, only 10% of patients had a WBC nadir of $< 2000/\mu l$ and it seems conceivable that using epirubicin and mitoxantrone at equimyelotoxic doses might have resulted in more substantial differences in activity in favour of the epirubicin regimen. However, 41% of patients in the epirubicin group experienced nausea/vomiting of WHO grade 2 and 17% of grade ≥ 3, and higher epirubicin doses almost certainly would have aggravated subjective toxicities. Furthermore, although an increase in dose intensity of standard-dose chemotherapy has often resulted in higher response rates in advanced breast cancer, prospective randomised trials have usually failed to demonstrate that this is associated with prolonged survival (reviewed in [22]). In the present study, median survival was similar in patients with an objective tumour response or stable disease (19 versus 17 months) so it seems unlikely that a shift from stable disease to more partial responses would have led to prolonged survival. A prerequisite for significant prolongation of survival in patients with metastatic breast cancer appears to be achievement of high complete response rates, which only dose intensification to levels requiring haematopoietic stem cell support has been able to accomplish [22, 23].

The response rates previously reported for various mitoxantrone-based regimens in randomised co-operative trials ranged

from 29 to 35% with durations of responses and survival of around 6 and 12 months, respectively [24, 25]. These data are comparable to the results achieved by MV in the present study, a two-drug combination which was very well tolerated by the patients. Conversely, the activity produced by EV in this study seems to be lower than previously achieved by epirubicin-based regimens in controlled multi-institutional trials [26–28]. Objective response rates in those studies have been 45–54%, median response durations 10–14 months and median survival has ranged from 15 to 20 months. Apart from potential differences in patient selection, the low epirubicin dose used in the present study seems likely to be a major reason for these discrepancies in therapeutic activity.

Expected survival, tumour-related symptoms and other variables can widely differ in patients with metastatic breast cancer. Thus, the differences in toxicity and activity observed for the two regimens seem to have clinical relevance. Epirubicin-based chemotherapy appears to offer advantages in patients with visceral disease or severe tumour-related symptoms, where rapid tumour reduction can lead to rapid relief from symptoms. However, in such situations, a higher dose intensity of epirubicin than was used in the present study appears to be indicated. Alternatively, mitoxantrone-based chemotherapy may prove useful in patients with indolent disease where adverse effects of treatment, especially subjective toxicities, are of particular concern. In such patients, the combination of mitoxantrone and vindesine appears to warrant phase III evaluation with survival and quality of life as major endpoints.

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