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Epirubicin or epirubicin and cisplatin as first-line therapy in advanced breast cancer. A phase III study

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Abstract *Purpose*: To compare the efficacy and toxicity of epirubicin to that of the combination of epirubicin and cisplatin in patients with advanced breast cancer. *Patients and methods*: A total of 155 patients were randomized to receive either epirubicin (70 mg/m^2) days 1 and 8 every 4 weeks or epirubicin (60 mg/m^2) days 1 and 8 plus cisplatin (100 mg/m^2) day 1 every 4 weeks. Epirubicin was continued until disease progression or to a cumulative dose of 1000 mg/m^2. Cisplatin was discontinued after six cycles. In 45 premenopausal women an oophorectomy was performed. None of the evaluable patients had received chemotherapy for metastatic disease. *Results*: Among evaluable patients (74 in the epirubicin group and 65 in the epirubicin plus cisplatin group) there were 19% vs 29% complete responses, and 42% vs 37% partial responses, with no significant difference. In the epirubicin plus cisplatin group the response rate was significantly higher in previously untreated patients as compared with patients who had received adjuvant chemotherapy (74% vs 55%, $P = 0.002$). Median times to disease progression were 8.4 months in the epirubicin group and 15.3 months in the epirubicin plus cisplatin group ($P = 0.045$). Median survival times were 15.1 and 21.5 months, respectively ($P = 0.41$). In the epirubicin plus cisplatin group leukopenia and thrombocytopenia were significantly more frequent, 29% of the patients developed mild to moderate peripheral neurotoxicity, 34% reported tinnitus and hearing changes, 6 patients developed nephrotoxicity (one died due to nephrotic syndrome), and 3 patients developed leukaemia (two died of this cause). Congestive heart failure occurred in six patients in the epirubicin group and three patients in the epirubicin plus cisplatin group. *Conclusion*: Cisplatin plus epirubicin is an active, although highly toxic regimen when used as first-line therapy in advanced breast cancer. The time to disease progression was significantly longer in the cisplatin plus epirubicin group (increased by 82%). Due to toxicity, the combination regimen cannot be recommended. However, the study indicated a very high activity of cisplatin in advanced breast cancer. Studies of first-line therapy in advanced breast cancer including cisplatin or other platin derivatives in combination with, for example, the taxanes are suggested.

Key words Breast cancer · Cisplatin · Chemotherapy · Epirubicin

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Introduction

Cytotoxic chemotherapy is an established modality in the treatment of advanced breast cancer. However, the 5-year survival rate in stage IV breast cancer is still less than 5% [10] and despite intensive efforts, advanced breast cancer remains an incurable disease. Thus, new active drugs and drug combinations must be explored. The anthracyclines, doxorubicin and epirubicin are considered to be two of the most active agents in the treatment of breast cancer [2, 11, 18, 20]. No significant differences in antitumour activity have been found between epirubicin and doxorubicin [2, 18]. A major problem in the clinical use of doxorubicin is the cumulative cardiotoxicity [18]. Of great clinical interest are observations indicating that epirubicin has a lower potential for cardiotoxicity [2, 12, 18, 21].

Despite its wide spectrum of clinical activity, cisplatin initially made little impact in the treatment of advanced breast cancer. There were two main reasons for this. First, early studies usually in heavily pretreated patients suggested little activity (for review, see references 30, 31 and 33). Second, its toxicity spectrum including severe

emesis and the need for hydration to minimize nephrotoxicity, made it unsuitable compared with established less-complicated regimens (e.g. cyclophosphamide, methotrexate, 5-fluorouracil). However, during recent years data have emerged suggesting that cisplatin used as first-line chemotherapy may be much more active than first thought against breast cancer (for review, see references 30, 31 and 33). Thus, the overall response rate among patients with advanced breast cancer given high-dose cisplatin without prior chemotherapy is 42–54% [13, 15, 19, 32] indicating that cisplatin is among the most active agents in this disease. Cisplatin and anthracyclines appear to have different mechanisms of action and their toxicities only partly overlap. The two compounds might therefore have a synergistic effect, and their use in combination chemotherapy could be of potential clinical benefit.

The primary objective of this phase III study was to compare response rate, time to progression and toxicity of epirubicin as a single agent with those of the combination of epirubicin and cisplatin using maximally tolerable and haematological equitoxic doses in patients with advanced breast cancer. The second objective was to compare survival duration with the two regimens.

Material and methods

Eligibility criteria

Patients with histologically proven, locally advanced or metastatic breast cancer and bidimensionally measurable disease were eligible, as were those who had received one prior adjuvant chemotherapy (cyclophosphamide, methotrexate, 5-fluorouracil). Also included were patients with prior endocrine therapy or radiotherapy, either adjuvant or for metastatic disease, up to 4 weeks prior to their inclusion. Further eligibility criteria were: age $\leq$70 years, Eastern Cooperative Oncology Group (ECOG) performance status $\leq$3, life expectancy $>$3 months, WBC count $\geq$3000/μl and platelet count $\geq$100,000/μl, unless due to metastatic bone marrow involvement. Criteria of ineligibility were: evidence of renal disease (serum creatinine $>$1.2 mg/dl and/or ^{51}Cr-EDTA clearance $<$60 ml/min) or hepatic disease (serum bilirubin $>$1.5 mg/dl), brain involvement or leptomeningeal disease, other concomitant cancer, or clinical evidence of cardiac disease defined as congestive heart failure, arrhythmia or a history of myocardial infarction.

Pretreatment evaluation and follow-up

Pretreatment evaluation included a complete history and physical examination, blood cell counts (haemoglobin, WBC, and platelets), serum chemistry profiles (creatinine, calcium, alkaline phosphatase, transaminase, and bilirubin), chest radiography, electrocardiography, ^{51}Cr-EDTA clearance, and bone scans. Areas of increased uptake on bone scans were further evaluated with roentgenograms to determine the nature of the abnormalities. Ultrasound scan of the liver was performed if the serum alkaline phosphatase or transaminases were elevated. Blood cell counts were monitored weekly for the first 8 weeks and thereafter before each treatment and 1 week after treatment. Biochemical profiles were repeated every 4 weeks. In patients receiving cisplatin, ^{51}Cr-EDTA clearance was done every 8 weeks. Evaluable or measurable parameters except bone lesions were reevaluated every second month. Bone lesions were evaluated every third month.

Study design

Informed consent was obtained from all patients, and the study was approved by the regional ethical committee. Consecutive patients were centrally registered and, after stratification for performance status (ECOG 0–1 or 2–3), randomized to either group A (epirubicin 70 mg/m^2 days 1 and 8 every 4 weeks, regimen A) or group B (epirubicin 60 mg/m^2 days 1 and 8 plus cisplatin 100 mg/m^2 day 1 every 4 weeks, regimen B). Epirubicin treatment was continued until disease progression or to a cumulative dose of 1000 mg/m^2. Cisplatin was discontinued after six cycles. The doses of epirubicin was adjusted according to the WBC and platelet counts on the day of treatment as follows: 100% for WBC counts ($\times 10^3$/μl) $\geq$3.0 and platelet counts ($\times 10^3$/μl) $\geq$100; 50% for WBC counts 2.0–2.9 and/or platelet counts 50–99; 0% for WBC counts $<$2.0 and/or platelet counts $<$50. The cisplatin dose was adjusted according to nephrotoxicity as follows: 100% for ^{51}Cr-EDTA clearance $>$60 ml/min; 50% for ^{51}Cr-EDTA clearance 40–60 ml/min, and 0% for ^{51}Cr-EDTA clearance $<$40 ml/min.

The nadir counts were derived from weekly blood counts. In case of fever due to leukopenia (nadir WBC $< 1.5 \times 10^3$/μl) and/or bleeding due to thrombocytopenia (nadir platelets $< 30 \times 10^3$/μl) in the previous course, the treatment was reinstituted at a dose of 67% of the previous dose.

Epirubicin was supplied by Pharmacia & Upjohn in a powdered form and reconstituted in sterile water (5 mg/ml). The drug was administered by a 5-min infusion through an established intravenous line. Cisplatin was supplied by Bristol-Myers Squibb as a sterile aqueous solution containing 1 mg cisplatin/ml and 9 mg sodium chloride/ml. Treatment consisted of 1000 ml 0.9 *N* saline isotonic glucose solution over 1.5 h, 500 ml mannitol 20% over 0.5 h followed by cisplatin in 500 ml 0.9 *N* saline over 0.5 h. As posthydration, 2000 ml 0.9 *N* saline isotonic glucose was given. All patients receiving cisplatin were hospitalized. The antiemetic regimen consisted of metoclopramide from 60 to 150 mg/day depending on the grade of the emesis.

The response rate to ovarian ablation in premenopausal women with metastatic breast cancer is about 35%. Oophorectomy and ovarian radiation are regarded as equally effective (although rigorous comparative trials have not been completed) [7]. Thus, in premenopausal women an oophorectomy was also performed by irradiation before the start of chemotherapy.

Evaluation of response

Evaluation of response (including response in bone lesions) was done according to WHO criteria [34]. Patients with early death (before 4 weeks) were recorded as having progressive disease. Time to progression was calculated as the time from the first drug administration to progression for both responders and nonresponders. The response duration of complete responders was calculated as time from the date of complete response (CR) to the date of progression, and response duration of partial responders from the time of the start of treatment to progression.

Furthermore, analysis of the results was performed on an "intent to treat" basis and thus all randomized patients were considered evaluable for response, toxicity and survival analysis. None of the patients was lost to follow-up.

Statistical methods

Patient characteristics and responses were compared using Fisher's exact test or the chi-squared test for categorical variables and *t*-tests for continuous variables. Confidence limits for differences between response rates were calculated according to the method of Wulff [35]. Survival time and time to disease progression were analysed by Kaplan-Meier estimates [14]. Data from each treatment group were compared by the log-rank test.

Results

From July 1987 to November 1990 a total of 155 consecutive patients were randomized for entry into the study. Patient characteristics are given in Table 1. Seven of the patients in group A were ineligible, one due to elevated creatinine values, one due to cardiac disease, three due to nonevaluable disease, and two due to prior chemotherapy for metastatic disease. Among patients randomized to group B, three were ineligible, one due to cardiac disease, one due to elevated serum bilirubin, and one due to prior chemotherapy for metastatic disease. Six patients in group B refused further treatment with cisplatin after one cycle (two patients) and two cycles (four patients) due to severe emesis, leaving 139 patients evaluable for response. There were no significant differences between the two groups with regard to age, performance status, prior adjuvant therapy, menopausal status, sites and number of metastatic sites, disease-free interval to first recurrence, and lead time from prior adjuvant chemotherapy. Six patients in group A and seven in group B had locally advanced disease. In group A, 36 patients were estrogen or progesterone receptor-positive, 17 negative, and 28 had unknown receptor status. Also in group A, 14 patients had received endocrine therapy for metastatic disease. In group B, 31 patients were estrogen or progesterone receptor-positive, 20 negative, and 23 had unknown status, and 11 patients had received endocrine therapy for metastatic disease.

Table 1 Patient characteristics

	Epirubicin	Epirubicin + cisplatin
Patients registered	81	74
Patients evaluable	74	65
Age (years)		
Median	52	55
Range	34–68	27–69
Performance status		
0–1	68	61
2–3	13	13
Menopausal status		
Pre	32	22
Post	49	52
Adjuvant chemotherapy	36	27
Sites of metastases		
Lung	30	26
Liver	15	17
Bone	40	32
Soft tissue	68	62
Number of metastatic sites		
1	34	26
2	30	31
≥3	19	18
Disease-free interval (months)		
Median	20	30
Range	0–164	0–286
Interval from prior adjuvant chemotherapy (months)		
Median	18	17
Range	0–151	0–122
Cumulative dose of epirubicin (mg/m^2)		
Median	915	885
Range	68–1194	59–1121
No. of cycles		
Median	7	9
Range	0.5–14	0.5–22
Duration of treatment (months)		
Median	6	9
Range	1–10	1–24

The median cumulative dose of epirubicin was 915 mg/m^2 (range 68–1194 mg/m^2) in group A and 885 mg/m^2 (range 59–1121 mg/m^2) in group B, and these values were not significantly different. In group A, the median dose intensity of epirubicin was 132 mg/m^2 (range 75–212 mg/m^2) per 4 weeks. In group B, the median dose intensity of epirubicin was 88 mg/m^2 (range 33–140 mg/m^2) per 4 weeks. In both groups, all dose reductions were performed due to haematological toxicity. The median cumulative dose of cisplatin was 518 mg/m^2 (range 97–619 mg/m^2). Dose reductions were performed in 29 patients due to haematological toxicity and in 16 patients due to nonhaematological toxicity (paraesthesias 10 patients, motor weakness 1 patient, nephrotoxicity 5 patients). The median duration of treatment was 6 months (range 1–10 months) in group A and 9 months (range 1–24 months) in group B ($P < 0.001$).

The treatment results for evaluable patients are shown in Table 2. The CR rate was 19% in group A and 29% in group B ($P = 0.22$), and the median duration of CR was 36.0 and 16.8 months, respectively ($P = 0.21$). The partial response (PR) rate was 42% in group A and 37% in group B ($P = 0.67$). The median duration of PR was 9.9 and 16.8 months, respectively ($P = 0.32$). Among evaluable patients without prior chemotherapy, 19% in group A showed a CR, whereas 37% in group B showed a CR ($P = 0.11$). In group A, 70% of the patients without previous chemotherapy showed a response, whereas 48% with previous chemotherapy showed a response ($P = 0.11$). In group B, the corresponding figures were 74% and 55% ($P = 0.002$).

No change was found in 30% (95% confidence limits 20–41%) in group A and in 29% (95% confidence limits 19–42%) in group B (not significantly different), with a median duration of 6.8 months (range 2.2–33.7 months) and 12.6 months (range 2.8–50.3 months), respectively ($P = 0.004$). For evaluable patients the median overall time to progression was 8.4 months (range 0.1–66.3 months) and 15.3 months (range 0.1–77.7 months) for groups A and B, respectively ($P = 0.045$; Fig. 1), and the overall survival was 15.1 months (range 0.1–66.3 months) and 21.5 months (range 0.1–77.7 months) ($P = 0.41$; Fig. 2).

The treatment results for all patients are shown in Table 3. The CR rate was 17% in group A and 28% in group B ($P = 0.15$). The PR rate was 40% in group A

Table 2 Response rate and duration for evaluable patients according to prior adjuvant chemotherapy and treatment (*E* epirubicin, *P* cisplatin)

	Treatment	No. of patients	Complete response					Partial response				
			No.	%	95% confidence limits (%)	Duration (months)		No.	%	95% confidence limits (%)	Duration (months)	
						Median	Range				Median	Range
No prior chemotherapy	E	43	8	19	8–33	36.0	5.4–61.5	22	51	35–67	11.2	4.7–45.1
	E + P	41	15	37	22–53	16.8	2.0–75.9	15	37	22–53	16.8	3.1–54.2
Adjuvant therapy	E	31	6	19	7–37	32.9	6.0–56.5	9	29	14–48	9.2	6.2–19.9
	E + P	24	4	17	5–37	16.0	4.4–33.3	9	38	19–59	11.4	6.3–27.5
All patients	E	74	14	19	11–30	36.0	5.4–61.5	31	42	31–54	9.9	4.7–45.1
	E + P	65	19	29	19–42	16.8	2.0–75.9	24	37	25–50	16.8	3.1–54.2

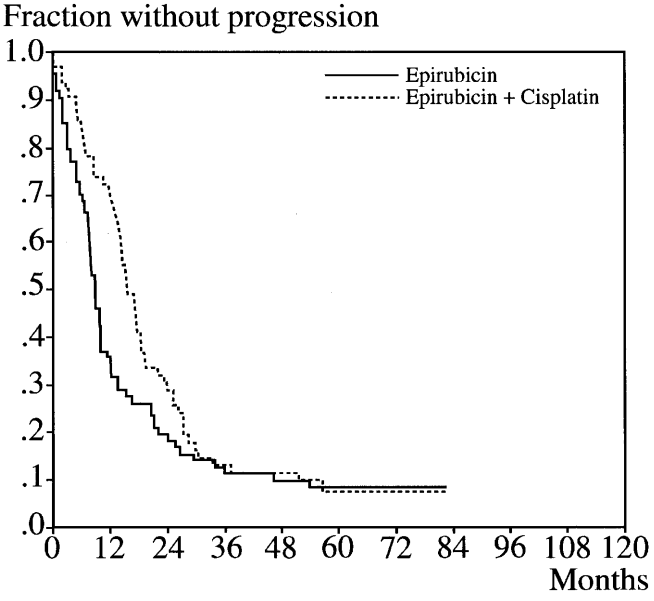

Fig. 1 Time to disease progression by initial treatment randomization in 74 patients with advanced breast cancer treated with epirubicin and 65 patients treated with epirubicin plus cisplatin ($P = 0.045$)

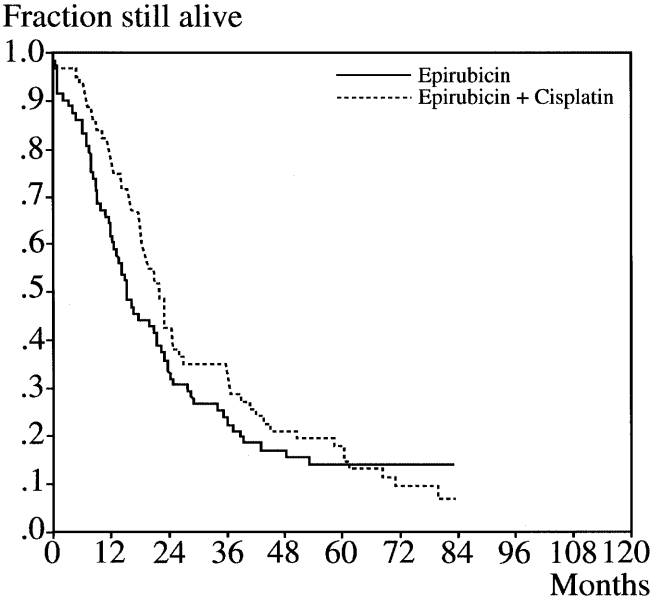

Fig. 2 Survival from initial treatment randomization in 74 patients with advanced breast cancer treated with epirubicin and 65 patients treated with epirubicin plus cisplatin ($P = 0.41$)

and 34% in group B ($P = 0.57$). For all patients the median overall time to progression was 8.6 months (0.1–66.3 months) and 14.4 months (range 0.1–77.7 months) in groups A and B, respectively ($P = 0.07$) and the overall survival 15.2 months (range 0.1–66.3 months) and 20.6 months (range 0.1–77.7 months), respectively ($P = 0.45$; data not shown).

Table 3 Response rate and duration for all patients according to prior adjuvant chemotherapy and treatment (*E* epirubicin, *P* cisplatin)

	Treatment	No. of patients	Complete response					Partial response				
			No.	%	95% confidence limits (%)	Duration (months)		No.	%	95% confidence limits (%)	Duration (months)	
						Median	Range				Median	Range
No prior chemotherapy	E	43	8	19	8–33	36.0	5.4–61.5	22	57	35–67	11.2	4.7–45.1
	E + P	46	17	37	23–52	16.8	2.0–75.9	15	33	20–48	16.8	3.1–54.2
Adjuvant therapy	E	36	6	17	6–33	32.9	6.0–56.5	9	28	14–45	9.5	6.2–19.9
	E + P	27	4	15	4–34	16.0	4.4–33.3	9	37	19–58	11.4	6.3–27.5
All patients	E	81[a]	14	17	10–27	36.0	5.4–61.5	31	40	29–51	9.9	4.7–45.1
	E + P	74[a]	19	28	19–40	16.8	2.2–75.9	24	34	23–46	15.2	3.1–54.2

[a] Including two patients in the epirubicin group and one patient in the epirubicin plus cisplatin group who had previously received themotherapy for metastatic disease

The responses in relation to dominant site of disease are shown in Table 4. CRs occurred mainly, as expected, in soft tissue disease, although the complete disappearance of hepatic, lung, and osseous lesions was also seen. Nevertheless, no significant difference between the two treatment regimens was found.

Oophorectomy was performed in 22 patients in group A and in 23 in group B. Among these patients, five and seven in group A and two and ten in group B showed a CR and PR, respectively.

Toxicity

The median WBC nadirs ($\times 10^3/\mu l$) were 1.4 (range 0.1–3.9) and 0.8 (range 0.1–3.5) in groups A and B, respectively ($P < 0.001$; Table 5). WBC counts ($\times 10^3/\mu l$) above 3.0, from 2.0 to 3.0, from 1.0 to 1.9, and below 1.0 were found in 5.1%, 15.4%, 42.3% and 37.2% of the patients in group A and in 1.4%, 5.7%, 31.4%, and 61.4% of the patients in group B. The median platelet nadirs ($\times 10^3/\mu l$) were 141 (range 3–524) and 64 (range 6–192) in groups A and B, respectively ($P < 0.001$; Table 5). Platelet counts ($\times 10^3/\mu l$) above 100, from 50 to 100, from 25 to 49, and below 25 were found in 67.9%, 21.8%, 5.1%, and 5.1% of the patients in group A and in 49.0%, 24.5%, 10.2%, and 16.3% of the patients in group B.

Three patients in group A and 18 in group B developed neutropenic fever (WBC count $< 1.0 \times 10^3/\mu l$). All patients in group A, but only eight in group B, experienced bacteraemia. All patients with neutropenic fever received prophylactic antibiotics. Administration of growth factors was not allowed. No patients died due to infection. Bleeding due to thrombocytopenia (platelet counts $< 50 \times 10^3/\mu l$) was observed in one patient in group A and in ten patients in group B, and one patient in group A died due to bleeding. Cumulative anaemia was modest, and 53% experienced grade I and 4% grade II toxicity in group A. The corresponding figures in group B were 64% and 19%.

Nausea and vomiting grade II and III occurred in 8 and 12 patients in group A and in 35 and 39 in group B, respectively ($P < 0.00005$). Mucositis grade II and III occurred in 23 and 12 patients in group A and in 18 and 13 patients in group B, respectively (not significantly different). In both groups, all patients who received more than two cycles experienced grade III alopecia. Six patients in group A and three in group B developed congestive heart failure. The cardiotoxicity was seen after cumulative doses of 874, 914, 947, 1000, 1000, and 1040 mg/m^2 in group A and after 471, 830, and 976 mg/m^2 in group B. One patient in group A died due to cardiotoxicity after a cumulative dose of 874 mg/m^2.

In group B, 29% of the patients developed peripheral neurotoxicity. In 13 patients this consisted of slight, in nine moderate and in one severe paraesthesias. Motor weakness occurred in one patient. Tinnitus and symptomatic hearing changes occurred in 34%, but in none of the patients did the hearing loss interfere with function.

Table 4 Sites of response in evaluable patients

Site	Epirubicin				Epirubicin + cisplatin			
	Complete response		Partial response		Complete response		Partial response	
	No. of patients	%	No. of patients	%	No. of patients	%	No. of patients	%
Soft tissue	29	46	11	18	31	60	7	14
Bone	1	3	14	44	0	0	6	26
Lung	5	17	8	28	8	33	7	29
Liver	1	8	4	31	2	22	3	33

Table 5 Haematological toxicity

Nadir		Epirubicin	Epirubicin + cisplatin	*P*-value
WBC ($\times 10^3/\mu l$)	Median	1.4	0.8	< 0.001
	Range	0.1–3.9	0.1–3.5	
Platelets ($\times 10^3/\mu l$)	Median	141	64	< 0.001
	Range	3–524	6–192	
Hemoglobin (mmol/l)	Median	6.5	5.9	< 0.001
	Range	5.3–7.7	4.5–7.3	

Five patients developed nephrotoxicity grade II and one patients died due to nephrotic syndrome. Finally, three patients in this group developed leukaemia. Two presented with acute monocytic leukaemia of FAB subtype M5 and one showed an M4 myelomonocytic subtype. The patients were in complete remission at the time the leukaemia developed. Two of the patients died 1 month after development of leukaemia, and in one of these intensive antileukaemic chemotherapy was attempted. One patient showed a CR after intensive chemotherapy and received an allogenic marrow transplantation. The patient died 52 months after development of leukaemia due to progression of the breast cancer. The cumulative risk of leukaemia was 16.0 ± 9.9% (mean ± SE), and 33 months after the start of therapy, the relative risk was 668 (95% confidence interval 138 to 1953). The patients and the cytogenetic findings have been described in detail by Pedersen-Bjergaard et al. [24].

Discussion

The purpose of the present study was to determine whether the activity of epirubicin plus cisplatin was superior to those of epirubicin alone in patients with advanced breast cancer when used in a haematological equitoxic dose schedule.

The response rate with epirubicin was 70% in patients without prior chemotherapy and 48% in patients who had received adjuvant chemotherapy (not significantly different). The efficacy of epirubicin has been evaluated in several studies. Generally, the efficacy figures encountered in the present study are comparable to results obtained by others [1, 4, 9, 22, 25, 27]. In the present study, the observed response rate to epirubicin plus cisplatin was not significantly different from the response rate to epirubicin (74% in untreated patients and 55% in patients who had previously received adjuvant chemotherapy). The overall time to progression was significantly increased among evaluable patients who received the cisplatin-based regimen (82%). This finding suggests the superiority of the combination regimen. However, when the analysis was performed on an "intent to treat" basis, time to progression and survival were similar for the two regimens. There are several explanations for this. When large numbers of ineligible patients are included in an intent to treat analysis any differences in the two arms may be obscured. Six of nine nonevaluable patients did not receive more than two doses of cisplatin. Furthermore, the regimen provided a relatively low dose-intensity of epirubicin, the most active drug in advanced breast cancer. Consequently the gain obtained by the addition of cisplatin may be missed because of the necessary dose reduction of epirubicin.

The response rate corresponded to recently reported response rates of 64–83% derived from phase II studies [13, 28]. Several randomized trials comparing cisplatin combination chemotherapy with conventional regimens have been reported [5, 6, 16, 17]. The efficacy figures found in these studies are also comparable to ours. Some [16, 17] have shown an advantage for cisplatin-based regimens compared with traditional regimens in term of overall response rates and duration of response. However, no trial has demonstrated superiority in overall survival. In the present trial, patients without prior adjuvant chemotherapy had a higher response rate than those with such exposure. Similar results have been reported by Roth et al. [28].

Cisplatin is a toxic cytostatic, and inclusion of this compound in a combination regimen is bought at a price. The toxicity was considerable. Myelosuppression was manifest primarily as leukopenia and thrombocytopenia, with anaemia being less significant. Myelosuppression was the dose-limiting toxicity in most patients. The incidence of neutropenic fever and bacteraemia was

in accordance with a previous report [28]. As would be expected nausea and vomiting were universal and required intensive antiemetic therapy. Six patients refused further treatment with cisplatin due to emesis. Introduction of 5-HT_3-receptor antagonists could at least partly resolve this problem. Nephrotoxicity was the dose-limiting toxicity in five patients (7%) and one patient died due to nephrotic syndrome. Previously, renal toxicity has been noted in 28% to 36% of patients treated with a single dose of 50 mg/m^2 cisplatin [3].

An increased risk of leukaemia was encountered in patients receiving the combination regimen as each of the drugs probably has a low leukaemogenic potential [24]. More recently, the DNA-topoisomerase II-targeting agents etoposide and teniposide have been demonstrated to be leukaemogenic, at least when they are administered in combination with cisplatin [23] or alkylating agents [24]. A synergistic effect on leukaemogenesis between drugs that react directly with DNA and drugs that target DNA-topoisomerase II has been suggested [24]. The leukaemias related to epirubicin seemed to be acute monocytic or myelomonocytic with balanced chromosome translocations to band 11q23, such as in the leukaemias after therapy with the epipodophyllotoxins [23, 26].

At doses of epirubicin <1000 mg/m^2, six patients developed congestive heart failure. One patient died of this cause after a cumulative dose of 874 mg/m^2. Three patients developed cardiotoxicity after cumulative doses $\geq$1000 mg/m^2. This compares favourably with previously published data on cardiotoxicity of epirubicin [21, 29]. Cisplatin did not seem to potentiate the cardiotoxicity of epirubicin.

Taken together, the combination of cisplatin and epirubicin seems to be highly active, increasing time to progression significantly as compared with epirubicin alone. However, toxicity prohibits its use in the routine clinical setting. The study indicates a very high activity of cisplatin in advanced breast cancer. Recently, a very high efficacy (overall response rate 63%) and manageable toxicity have been reported for the combination of cisplatin and paclitaxel in previously treated patients with advanced breast cancer [8]. Thus, studies of first-line therapy including cisplatin or other platin derivatives in combination with, for example, the taxanes are suggested.

In conclusion, epirubicin plus cisplatin is definitely an active regimen when used as first-line therapy in the treatment of advanced breast cancer. In the present study, time to progression was significantly increased in patients treated with the combination regimen compared with those treated with epirubicin alone. The toxicity associated with this therapy prohibits its use in the routine clinical setting.

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