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Phase II Trial of High-dose Epirubicin and Cyclophosphamide in Advanced Breast Cancer

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Between February 1990 and December 1991 high-dose epirubicin (Epi)(120 mg/m²) plus cyclophosphamide (CTX)(600 mg/m²) were given every 3 weeks to 52 patients with locally advanced and metastatic breast cancer. 26 patients with locally advanced disease received four courses of this regimen before and after local treatments. 26 patients had metastatic disease: they received eight courses unless progression or unacceptable toxicity occurred. Responses were seen in 37/48 (77%) evaluable patients including 14 complete responses (CR), 23 partial responses (PR), nine stable disease, two progressive disease. Among the 25 evaluable patients with locally advanced disease, 9 had a CR and 11 a > 80% decrease in tumour volume. 6 patients (24%) had a pathologically confirmed complete response. 18 patients (72%) had a tumour reduction to 0–2 cm. The 3-year disease-free survival was 60%. Of the 23 evaluable patients with metastatic disease, 5 obtained a CR and 10 a PR, yielding an overall response rate of 65%. Myelosuppression was substantial with a grade 3–4 leucopenia in 76% of the patients even if neutropenic fever occurred in only 7% of the courses. A clinical congestive heart failure occurred in 1 patient following a total Epi dose of 960 mg/m² and a bilateral quadrantectomy and radiotherapy. We conclude that (1) high-dose Epi + CTX is a very active regimen, in particular for the patients with locally advanced breast cancer; (2) breast conservation after this regimen in some of these patients may be considered; (3) neutropenia is the dose-limiting toxicity. Currently, a phase II study using the same combination given every 2 weeks together with r-methuG-CSF is ongoing.

Key words: high-dose, epirubicin, cyclophosphamide, breast cancer
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INTRODUCTION

TREATMENT WITH standard chemotherapy doses has, as yet, no curative impact on advanced breast cancer [1].

Recently, two randomised studies on the dose–response effects with chemotherapy combinations have shown some survival benefit in metastatic disease employing the higher drug doses [2, 3]. In another study, higher response rates were observed in the higher dose arm, when the actually delivered dose was evaluated [4].

Many years after its introduction, doxorubicin is still the most effective cytotoxic agent for the treatment of advanced breast cancer. Epirubicin, the 4-epimer of doxorubicin, has been clinically employed for approximately 10 years. Its antitumour activity appears to be almost identical to that of the parent drug against breast cancer [5–7], but it produces less cardiac and haematological toxicity at equimolar doses [5, 6].

Although preclinical data have shown an exponential dose–response relationship for antracyclines [8, 9], the results obtained in the few clinical studies conducted thus far on anthracycline dose–response are still controversial. There is some evidence of a dose–response relationship for doxurubicin at the lower dose range, although this does not seem to apply at higher doses [10]. In fact, a high-dose doxorubicin-containing regimen showed no response or survival advantage over the same regimen used at standard doses [11].

In contrast, another prospective randomised study demonstrated a dose–response effect when standard versus intensified doxorubicin-containing regimens were compared [12].

In a randomised study, a 50% higher dose of epirubicin, used as a single agent, provided no advantages over the lower doxorubicin dose in advanced breast cancer [13]. Conversely, Habenshow and colleagues obtained better response rates and longer response durations with the higher (100 mg/m²) than with the lower (50 mg/m²) epirubicin dose [14].

Clinical studies have recently been conducted using higher epirubicin doses (> 110 mg/m²) given alone in non-small cell lung cancer [15, 16] and in breast [17, 18] and bladder cancer [19]. Treatment activity was promising and the toxicity was acceptable.

In the present study, the feasibility and efficacy of a combination of high-dose epirubicin (120 mg/m²) plus standard dose cyclophosphamide (600 mg/m²) was studied, both in patients with locally advanced disease and in those with metastatic breast cancer.

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PATIENTS AND METHODS

Between February 1990 and August 1991, 52 consecutive patients with histologically proven locally advanced and metastatic breast cancer were entered into the study. Eligibility criteria included age under 70 years, locally advanced (stages II B, only T3 N0, IIIA and IIIB) or metastatic disease with at least one measurable or evaluable lesion, ECOG performance status (PS) of 0–2. A white blood cell (WBC) count of 3000/mm^3 and a platelet count of 100 000/mm^3 were required for study entry. In addition, patients were required to have adequate liver function (serum bilirubin level $\leq$ 35 μmol/l) and adequate renal function (serum creatinine level $\leq$ 220 μmol/l). Prior adjuvant chemotherapy with regimens not containing anthracyclines or hormonal therapy, either as adjuvant or for metastatic disease, were permitted, but must have been discontinued at least 4 weeks before starting the protocol therapy. Because of the potential cardiotoxicity of epirubicin, patients with a baseline left ventricular ejection fraction (LVEF) lower than 50% (measured by cardiac ultrasonography) were ineligible. Patients with active angina or myocardial infarction within the last 6 months or with a significant arrythmia requiring ongoing medication were excluded, as were patients with cerebral metastases or with a history of prior malignancies, other than carcinoma *in situ* of the cervix and non-melanoma skin cancer.

The patients were required to give oral informed consent, according to the institution's requirement. The study was approved by the Clinical Research Review Board of the Regina Elena Cancer Institute.

All patients had a complete medical history and a physical examination including documentation of all measurable disease, performance status, signs and symptoms of disease. Laboratory studies at presentation included determination of complete blood cell counts, differential, platelet count, BUN (blood urea nitrogen), creatinine, serum bilirubin, SGOT (serum glutamic oxalacetic transaminase), SGPT (serum glutamic pytoxic transaminase), alkaline phosphatase, albumin, total protein, calcium, phosphate, and serum electrolyte levels, as well as a chest X-ray, bone scan and liver and cardiac ultrasonography.

All the patients had interim counts with complete blood count (CBC), differential and platelet counts performed between days 8 and 14, as well as on the day of treatment. Blood chemistries were taken before every treatment course. A chest X-ray and a cardiac ultrasonography were performed at the end of the neoadjuvant and the adjuvant chemotherapy in patients with locally advanced disease; the patients with metastatic disease were submitted to cardiac ultrasonography every four courses. All the patients were submitted to a bone scan and liver ultrasonography and then once a year during follow-up.

Treatment

The chemotherapy regimen used consisted of epirubicin 120 mg/m^2 and cyclophosphamide 600 mg/m^2 given intravenously (i.v.) on day 1. The courses were repeated every 3 weeks if there was a recovery from myelotoxicity (WBC $\geq$ 3000/mm^3, platelets $\geq$ 100 000/mm^3). In the event of grade 4 myelotoxicity, the subsequent doses were reduced by 25%. No initial dose escalations were planned.

A combination of dexamethasone and metoclopramide was most frequently used to prevent chemotherapy-induced nausea and vomiting. Four courses of high-dose epirubicin plus cyclophosphamide were given to patients with locally advanced disease as neoadjuvant chemotherapy. Patients with a complete response or a > 80% partial response received four additional courses of the same chemotherapy after surgery. Patients with a < 80% partial response or with no response to the neoadjuvant chemotherapy were given four courses of a potentially non-cross-resistant regimen in the adjuvant setting. Patients who had been submitted to conservative surgery (i.e. quadrantectomy + axillary dissection) were treated with radiotherapy (QU.A.RT.) at the end of the adjuvant chemotherapy. Patients with positive oestrogen and/or progesterone receptors were given adjuvant tamoxifen at a daily dose of 20 mg for 5 years.

Patients with metastatic disease received eight courses of this regimen unless progression of the disease or unacceptable toxicity occurred. Complete response (CR) was defined as the disappearance of all clinically evident disease for at least 1 month; partial response (PR) was defined as a > 50% decrease in the sum of the products of the largest perpendicular diameters of all measurable lesions, in the absence of any new lesion and with no progression of any other measurable disease. No change (NC) was considered an objective response, without satisfying the PR criteria, an increase of less than 25% or a no change in disease status. Progressive disease (PD) was a more than 25% increase of these measurements or the appearance of new lesions. To define an objective response, a minimum of two courses of chemotherapy were required unless a clear disease progression occurred during treatment. The PS and toxicity criteria were those adopted by the WHO.

Duration of the response in patients with metastatic disease was calculated from the first day of treatment to the occurrence of disease progression. Disease-free and overall survival in the patients with locally advanced disease were dated from surgery or the on-study day to the date of tumour progression or death, respectively.

RESULTS

Between February 1990 and August 1991, 52 consecutive patients entered the study, which included patients with both locally advanced (26 patients) and recurrent or metastatic disease (26 patients). The patients' characteristics are shown in Table 1.

48 patients were evaluable for response to chemotherapy. 4 were not evaluable: 1 because of a cytologically positive pleural effusion and 3 because they were lost to follow-up. 50 patients were evaluable for toxicity, 2 were lost to follow-up.

Response to treatment

Of the patients with locally advanced disease (25 evaluable), 9 achieved a complete clinical response (36%), 11 showed a > 80% partial response (44%) and 2 patients a < 80% partial response (8%), yielding an overall response rate of 88%. Stable disease was observed in 3 patients only.

Table 2 shows the downstaging obtained at the end of the four courses of primary chemotherapy. The degree of downstaging was inversely correlated with the size of the primary tumour at the start of chemotherapy. 5 of the 11 patients (45%) with a 3–5-cm primary tumour presented a CR at surgery, the CR being confirmed pathologically in 4 of these patients. Two CRs were observed at surgery (14%) in the remaining 14 patients with a > 5 cm primary tumour. Of the 25 evaluable patients, 6 pathological CRs (24%) were observed; 2 further patients had only microscopic disease left after chemotherapy.

Although a reduction of the primary tumour to 0–2 cm was obtained in 18 of the 25 patients (72%), a QU.A.RT was performed only in 7 (28%); the remaining 18, including 8 patients with a primary tumour greater than 2 cm at the end of

Table 1. Patients' characteristics

		No. of patients
Age (years)		
Median		54
Range		34–69
Performance status (WHO)		
0		41
1		11
Menopausal status		
Premenopausal		18
Postmenopausal		34
Disease extent		
Locally advanced		26
II B (T3 N0)		5
III A		13
III B		8
Metastatic		26
Dominant site:	Bone	10
	Soft tissues	6
	Liver	6
	Lung	3
	Pleural effusion	1
Prior adjuvant treatments		12
Chemotherapy (CMF)		3
Tamoxifen		7
CMF + tamoxifen		2
Disease-free survival (months)		
Median		18.5
Range		4–72

the neoadjuvant chemotherapy, were submitted to a radical mastectomy.

Conservative surgery could not be performed if the breast was too small to perform acceptable cosmesis, if the tumour location was not adequate (i.e. subareolar), if multifocal lesions were present or if the patient opted for radical surgery.

Sites of recurrences were as follows: soft tissues (3 patients), liver (2 patients), bone (2 patients) and brain (1 patient). There were no local recurrences observed in the patients submitted to the QU.A.RT. The disease-free survival was 60% at 3 years (Figure 1).

Of the 23 evaluable patients with metastatic disease, 5 obtained a CR and 10 a PR, yielding an overall response rate of 65%; 6 patients (26%) had SD and 2 (9%) PD. The median duration of the responses were 11 months (range 7–21) for the PRs and 11 months (range 9–42+) for the CRs. 1 patient has still maintained the CR 42 months after the end of treatment.

The median time to progression was 10 months (range 2–27).

Table 2. Downstaging of the primary tumour in locally advanced disease

T before CT		T at surgery			
Size	No. of patients	> 3 cm	< 3 cm	0 cm	pCR
3–5 cm	11	—	6	5	4
5.1–6 cm	5	—	4	1	—
6.1–7 cm	3	—	3	—	1
> 7 cm	6	3	2	1	1

T, tumour; CT, chemotherapy; pCR, pathological complete response.

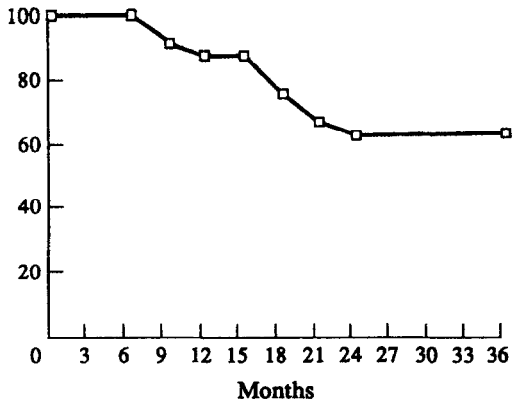

Figure 1. Disease-free survival in patients with locally advanced breast cancer.

Toxicity

Table 3 summarises the toxicity observed in the 50 evaluable patients. Alopecia was ubiquitous. Leucopenia was also very frequent (94%); in particular, a grade 3 and 4 neutropenia occurred in 117 of the 250 evaluable chemotherapy courses (47%). There were 17 episodes of febrile neutropenia out of 250 courses administered (7%). Anaemia was also frequent but severe in only 4 patients. Thrombocytopenia was infrequent (28%) and never severe. Most patients suffered nausea and vomiting. Mucositis (56%) became a serious problem in only 3 patients.

Cardiac toxicity was assessed by cardiac ultrasonography. 36 patients had at least three satisfactory LVEF assessments. 3 sustained a 10% fall in LVEF and 3 a fall of 20% or more. 1 patient developed congestive heart failure (CHF) at a cumulative dose of 960 mg/m^2. She had also been treated with radiotherapy as adjuvant for a bilateral quadrantectomy. At the present time the patient is satisfactorily controlled with medication.

58 of the 271 totally administered chemotherapy courses were delayed (21%). The main reasons of delay were: neutropenia (41), refusal (4), mucositis (2), fever (1) and others (10). Twenty-five per cent dose reductions of both drugs were applied in 23 of the 323 totally administered courses (7%). The reasons for these reductions were leucopenia (22) and mucositis (1). The median dose intensity was 36.8 (range 25–40) for epirubicin and 182.9 (range 134–200) for cyclophosphamide. The median relative dose intensity (actual/projected) was very high for both drugs: 0.92 and 0.91, respectively.

Table 3. Toxicity in 50 evaluable patients

	Grade			
Side-effects (WHO)	1	2	3	4
Anaemia	22	13	4	—
Leucopenia	1	8	24	14
Platelets	6	8	—	—
Nausea/vomiting	4	24	18	—
Alopecia	1	—	49	—
Mucositis	7	18	3	—
Diarrhoea	9	2	1	—
Cardiac	—	—	1	—

DISCUSSION

In combination cytotoxic regimens, epirubicin has usually been given at the same dosage as doxorubicin. For single-agent use, epirubicin has commonly been administered at 75–90 mg/m^2 every 3 weeks. However, recent studies suggest that doses as high as 135–150 mg/m^2 can be administered to advanced breast cancer patients with acceptable toxicity [20, 21].

Evidence from an overview conducted by Hryniuk [22] suggests that there is a linear dose–response relationship for doxorubicin used in the treatment of advanced breast cancer in the approximate dose–intensity range of 10–30 mg/m^2 per week. The importance of dose intensity has also been demonstrated in a study where breast cancer patients, treated with higher doxorubicin doses, showed a higher response rate and a longer median survival than those receiving lower doses [2].

The intensity of treatment achievable with doxorubicin is limited by myelosuppression, and the total cumulative dose that can be given safely is limited by cardiotoxicity. Evidence suggests that epirubicin may show antitumour activity similar to that of its parent compound, while producing less cardiotoxicity.

In the present study, the combination of high-dose epirubicin (120 mg/m^2) plus cyclophosphamide was highly active against advanced breast cancer patients: 14 CRS and 23 PRs out of 48 evaluable patients were obtained, yielding an overall response rate of 77%.

The efficacy of this regimen was particularly evident in the patients with locally advanced disease with an 80% rate of clinical CR or a greater than 80% PR, and a 24% rate of pathological CRs. The results in patients with metastatic disease (PR 43%, CR 22%, MDR 9–10 months) were not much better than that obtainable with standard chemotherapy.

Breast conservation is possible after this regimen in the majority of the patients; in fact, of 25 patients with a primary tumour greater than 3 cm and 9 with a tumour of 6 cm or more, 72% obtained a tumour reduction to 2 cm or less, thus potentially rendering conservative surgery possible. However, major tumour shrinkage was obtained in patients with smaller initial lesions (Table 2). At 3 years, 60% of these patients are alive and disease-free.

Despite the high doses of epirubicin used, cardiac toxicity was similar to that reported with lower doses [13]. A retrospective analysis of seven phase I–II studies with high-dose epirubicin showed a relatively high incidence of the LVEF decline but a low incidence of clinical CHF [23]. In the present study, the incidence of a LVEF decrease was 19% and only 1 patient developed CHF; she had previously received bilateral radiotherapy. Our data, therefore, confirm that the use of high-dose epirubicin is more favorable than doxorubicin in terms of cardiotoxicity.

Severe stomatitis was infrequent and was not a major problem. On the contrary, neutropenia was the dose-limiting side-effect although serious infective complications occurred in only 7% of the courses.

The use of colony-stimulating factors to enhance bone marrow recovery after chemotherapy may enable cytoxic drugs to be given safely at higher doses and/or at shorter intervals than is currently feasible. A phase II study using the same combination given every 2 weeks together with r-methuG-CSF is currently ongoing.

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