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High-dose epirubicin as primary chemotherapy in advanced breast carcinoma: a phase II study

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Summary. A total of 40 patients with metastatic breast cancer were treated with 120 mg/m^2 i.v. epirubicin every 3 weeks for a maximum of 10 cycles. Nine achieved a complete response and 17 showed a partial response, for an objective response rate of 65% (95% confidence interval, 47%–83%); the median duration of response was 7 months (range, 1–15 months) and median survival amounted to 13 months (range, 2–20 months). Leucopenia (grade 2 or 3) was seen in 14 patients on day 21 of the cycle. A subset of nine patients underwent blood counts on day 10, when all had marked neutropenia ($<1 \times 10^9$/l). Other toxicity was frequent and included nausea/vomiting (80%), alopecia (95%) and stomatitis (35%). Five patients showed a significant fall in cardiac output, but this reverted to normal after treatment. Epirubicin should have a role in the development of high-dose regimens for the treatment of advanced breast cancer.

Introduction

Cytotoxic chemotherapy can be useful in the palliative management of advanced breast carcinoma. A number of active agents can be used alone or in combination and response rates of up to 80% have been reported [4]. Doxorubicin is considered to be the most effective single agent. In randomised studies the response rates for combinations are usually 40%–60%, similar to that obtained using high-dose doxorubicin alone [2, 6, 7]. In an attempt to increase the antitumour activity of doxorubicin and diminish its toxicity, an anthracycline analogue, epirubicin, has been developed. A prospective randomised clinical trial conducted by the EORTC indicated that the activity of epirubicin given at a dose of 90 mg/m^2 was equivalent to that of doxorubicin at 75 mg/m^2, but that epirubicin was associated with less toxicity [8].

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We conducted a phase II trial of 120 mg/m^2 epirubicin given i.v. every 3 weeks to patients with advanced breast carcinoma so as to evaluate whether a higher dose of epirubicin could achieve a superior response rate with acceptable toxicity.

Patients and methods

A total of 40 patients with metastatic breast carcinoma who had not previously received cytotoxic chemotherapy (except post-operative adjuvant treatment that did not include an anthracycline) were entered in this clinical trial lasting from March 1, 1988, until May 31, 1989. Other eligibility criteria included the presence of measurable or evaluable disease, an age of ≤ 65 years, a WHO performance status of 0–2, total WBC/count of $>3.5 \times 10^9$, a platelet count of $>100 \times 10^9$/l and normal renal function. Patients with liver dysfunction as demonstrated by serum bilirubin values of >25 μmol/l and/or aspartate transaminase levels of >2 times the upper limits of normal were excluded. Patients were also excluded if they showed involvement of the central nervous system; active infection; a history of congestive heart failure; significant arrhythmias; uncontrolled hypertension; ischaemic heart disease; any medical social or psychological condition preventing adequate follow-up; or prior radiotherapy to all sites of evaluable disease. Patients presenting osteoblastic bone lesions or pleural effusions as the sole manifestations of disease were not considered to be evaluable.

Epirubicin (120 mg/m^2) was given either diluted in 250 ml 5% dextrose in water as an i.v. infusion over 30 min (30 patients) or as a slow i.v. injection over 2 or 3 min (10 subjects). Cytotoxic chemotherapy was planned for a total of ten cycles given at 3-week intervals, after which patients with responding or static disease were followed up without treatment until progression of disease was noted. Before each course a full physical examination was carried out, including a complete blood count, biochemical screening, measurements of lesions in two perpendicular axes and photographs of all visible lesions. Skeletal and visceral disease was evaluated every 3 months by relevant imaging tests. Cardiac function was assessed by radionuclide (MUGA) scanning before treatment and, subsequently, at 3-month intervals. Treatment was stopped if patients developed clinical signs of cardiac failure or if the left ventricular ejection fraction decreased by >15%.

Dose modifications were adopted when bone marrow suppression occurred. If the WBC count on day 21 was $<3 \times 10^9$/l or the platelet count was $<100 \times 10^9$/l, treatment was delayed for a minimum of 1 week. If a delay of >2 weeks was required to achieve these levels, treatment was discontinued. In patients showing a WBC count of $<2 \times 10^9$/l on day 21 whose values recovered within 2 weeks, the dose was reduced by

20% in subsequent cycles. In a subset of nine patients, nadir counts were measured on day 10 and dose adjustments were made as follows: for a nadir of $>1 \times 10^9$/l, the dose was increased by 15 mg/m^2; for a value of $0.3-1 \times 10^9$/l it remained unchanged; and for a nadir of $<0.3 \times 10^9$/l, it was decreased by 15 mg/m^2.

Response rate, duration of response, survival and toxicity were assessed. Criteria for response were those defined by the UICC (International Union Against Cancer) [3]. A complete response (CR) was defined as the total disappearance of all evidence of tumour, with no new lesions being detected. A partial response (PR) required a reduction of $\geq 50\%$ in the sum of the products of the longest perpendicular axes of all measurable lesions and the absence of new lesions. No change (NC) indicated a decrease of <50% or an increase of <25% in the sum of the products of the longest perpendicular diameters of measurable lesions. Progressive disease (PD) was defined as an increase of $\geq 25\%$ in the product of the longest perpendicular axes of any existing lesion or the appearance of new ones. When the regression of some lesions was accompanied by the progression of others or the appearance of new lesions, this mixed response was considered to represent PD.

The duration of response was calculated from the beginning of cytotoxic chemotherapy until the date of objective evidence of PD. Survival was dated from the first treatment until death or was censored on the date of the last follow-up. Response duration and survival were analysed by the life-table method and toxicity was evaluated according to WHO criteria.

Results

In all, 41 patients were treated in this phase II trial, 1 of whom was withdrawn because the incorrect dose of epirubicin was given. A total of 40 subjects were evaluable for response and toxicity. The clinical characteristics of the patients are shown in Table 1. The number of courses given varied from two to ten (median, eight) and the median cumulative dose was 960 mg/m^2 (range, 240–1,200 mg/m^2).

Of the 40 evaluable cases 9 (22.5%) achieved a CR and 17 (42.5%) showed a PR, for an overall response rate of 65% (95% confidence interval, 47%–83%). Either NC or PD was observed in 14 patients (35%). The median duration of response was 7 months (range, 1–15 months) and the median duration of survival amounted to 13 months (range 2–20 months). The responses observed according to the sites of disease involvement are shown in Table 2.

The haematological toxicities are shown in Table 3. 14 patients experienced grade 2 or 3 leucopenia on day 21 of the cycle, the lowest level recorded being 1.6×19^9/l, necessitating a delay in starting the next course of treatment. Only one instance of thrombocytopenia was recorded on day 21 (85×10^9 platelets/l). Persistent leucopenia and/or thrombocytopenia was not documented in any patient. All nine patients whose counts were measured on day 10 had severe neutropenia ($<1 \times 10^9$ neutrophils/l). This group received a total of 46 courses of epirubicin (median, 5/patient; range, 3–6), in 7 of which dose reductions were made. One patient developed neutropenic sepsis, which responded to antibiotic therapy. No drug-related deaths were observed.

Nausea and/or vomiting occurred in 34 patients (85%) despite the use of prophylactic antiemetics. Alopecia was

Table 1. Characteristics of patients

Number of patients		40
Median age (range)		52 (29–65) years
Median interval from diagnosis to chemotherapy (range)		26 (1–165) months
Oestrogen receptor status:		
	Positive	10
	Negative	15
	Unknown	15
Menstrual status:		
	Premenopausal	10
	Postmenopausal	30
Previous systemic treatment:		
	None	9
	Adjuvant chemotherapy	5
	Endocrine therapy	28

Table 2. Number of sites involved and responses

	Lesions (*n*)	Objective response
Breast	19	13
Lymph nodes	17	12
Skin	12	8
Bone	8	7
Pleura and/or lung	9	6
Liver	3	3

Table 3. Haematological toxicity

	WHO grade			
	I	II	III	IV
Total WBC ($\times 10^9$/l), grade range	3–3.9	2–2.9	1–1.9	<1
Day 21 ($n = 40$)	9	10	4	0
Day 10 ($n = 9$)	2	4	3	0
Neutrophils ($\times 10^9$/l grade range	1.5–1.9	1–1.4	0.5–0.9	<0.5
Day 10 ($n = 9$)	–	–	1	8
Platelets ($\times 10^9$/l), grade range	75–99	50–74	25–49	<25
Day 21 ($n = 40$)	1	–	–	–
Day 10 ($n = 9$)	1	–	1	–

observed in 38 subjects (95%). Stomatitis, oral ulceration and/or dysphagia were noted in 14/40 cases (35%). Allergic reactions in the form of a maculo-papular rash at the injection site were reported in four of the first ten patients treated; this reaction resolved promptly after i.v. administration of prednisolone. Accidental extravasation occurred in four patients. Transient dark-brown staining accompanied by infiltration of the skin that lasted for 3 months was observed, but no ulceration or necrosis ensued. In five cases the continuation of chemotherapy by peripheal i.v. injection was impracticable after eight cycles of treatment because of inadequate venous access, but in two of these patients, ten cycles could be completed using a central i.v. catheter. This problem was seen only when epirubicin was given by infusion.

Five patients showed a deterioration of $\geq 15\%$ in their left ventricular ejection fraction on radionuclide scanning; two of them had received ten cycles of epirubicin (cumulative dose, 1,200 mg/m^2) and the other three had completed eight courses (cumulative dose 960 mg/m^2) of therapy. Two of these five patients developed clinical signs of congestive heart failure; both responded rapidly to treatment following the discontinuation of epirubicin. In all five cases the ejection fraction returned to normal.

Discussion

For several years, doxorubicin has been considered to be the most active cytotoxic agent in breast cancer. When doxorubicin is given as a single agent at high doses (75 mg/m^2), it yields response rates similar to those observed when it is used at lower doses (40–50 mg/m^2) in combination with other cytotoxic drugs such as cyclophosphamide and 5-fluorouracil. Evidence from an overview conducted by Hryniuk [5] 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 our previous study, in which patients with breast cancer who were treated with eight cycles of doxorubicin at 70 mg/m^2 every 3 weeks showed a higher response rate and longer median survival than those who received 35 mg/m^2 at 3-week intervals for 16 cycles [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, an analogue of doxorubicin, may show antitumour activity similar to that of its parent compound while producing less cardiotoxicity. The current study was therefore undertaken to assess the activity and toxicity of 120 mg/m^2 epirubicin given every 3 weeks to patients with advanced breast cancer. The response rate of 65% confirms the effectiveness of this agent against breast cancer. The toxicity associated with the relatively high doses used was acceptable. Marked myelosuppression was observed in all patients whose blood count was measured on day 10, but serious infective complications did not occur. Left ventricular function fell significantly in 5 of 40 patients, 2 of whom developed clinical evidence of congestive cardiac failure; all 5 of these subjects had received high cumulative doses of epirubicin and cardiac function recovered in each case.

The use of colony-stimulating factors to enhance bone marrow recovery after chemotherapy may enable cytotoxic drugs to be given safely at higher doses and at shorter intervals than are currently feasible [1]. The activity and toxicity profile of epirubicin demonstrated in the present study suggest that it may have a role in such high-dose regimens.

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