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Intensive Chemotherapy with High-dose Epirubicin Every 2 Weeks and Prophylactic Administration of Filgrastim in Advanced Breast Cancer

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50 women with advanced breast cancer were treated with an intensified regimen which consisted of high-dose epirubicin (110 mg/m^2) every 2 weeks and filgrastim (5 μg/kg) subcutaneously for 13 days, starting 24 h after chemotherapy. 44 patients completed all six cycles. The median interval between cycles of treatment was 14.3 days. The actually administered median dose per unit time per patient was 53 mg/m^2/week, amounting to 97.2% of the dose prescribed by the protocol. 7 [14%, 95% confidence interval (C.I.) 4–24%] patients achieved a complete and 25 (50%, 95% C.I. 36–64%) a partial response. Median time to progression was 32 weeks and median survival 64 weeks. Stomatitis and fever each occurred in 7 (14%) patients. Grade 3 haematological toxicity was observed in 6 (12%) patients. 1 (2%) patient developed grade 4 cardiac toxicity. This intensified regimen appears to be a well tolerated and effective treatment in advanced breast cancer.

Key words: intensive chemotherapy, epirubicin, growth factor, breast cancer
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INTRODUCTION

ADVANCED BREAST cancer represents a frustrating clinical challenge to medical oncology since it remains incurable against systematic chemotherapy despite intensive efforts. During the last decade it has been suggested in several clinical reports that intensive chemotherapy may play an important role in the outcome of patients with advanced breast cancer [1, 2]. Nevertheless, this important issue has not been addressed properly through prospective comparative studies [3].

Anthracyclines, such as doxorubicin and 4′-epidoxorubicin (EPI), are considered to be the most active drugs in the treatment of advanced breast cancer. Furthermore, EPI appears to be equally effective and probably less toxic than its parent compound [4–7]. Preclinical studies have shown that both agents have a steep dose–response curve which means that small increments of dose may be crucial for maximal lethal effect on cancer cells [8, 9]. There are several reports suggesting that this may also be true in patients with advanced breast cancer or other chemoresponsive tumours such as germ cell tumours or small cell lung cancer (SCLC) [10–13]. Hryniuk and Bush [1], who introduced the concept of dose intensity, retrospectively analysed the results of several published studies in which the combination of cyclophosphamide, doxorubicin and fluorouracil (CAF) was tested in patients with advanced breast cancer. When the responses observed in these studies were plotted against the relative dose intensities, calculated from doses actually delivered, a steep linear relationship was apparent. In another study, Bezwoda and colleagues [14] treated 18 patients with advanced breast cancer previously exposed to doxorubicin with high doses of epirubicin (110–150 mg/m^2), and they showed that responses were more often seen with the higher doses. In a phase I–II study of intensified treatment with doxorubicin in advanced breast cancer, Jones and colleagues [15] treated 26 patients with escalated doses to maximal tolerance. They reported an overall response rate of 85% and a complete response (CR) rate of 38%. The authors claim that these data suggest a steep dose responsiveness to doxorubicin in advanced breast cancer.

These, as well as other similar studies, support the hypothesis that anthracyclines probably have a steep dose–response curve in advanced breast cancer.

We previously reported our results with the use of high-dose (110 mg/m^2) EPI monotherapy every 4 weeks with prophylactic use of rec-met-hu granulocyte colony-stimulating factor (G-CSF, filgrastim) in patients with advanced breast cancer [16]. Since the response rate in that study seemed to be inferior to that achieved with intensive doxorubicin treatment [12], we explored the efficacy of the same EPI dose given every 2 instead of every 4 weeks. We report here our experience with this intensified treatment.

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PATIENTS AND METHODS

From December 1991 until December 1992, 50 women with advanced breast cancer entered this study. Eligibility criteria included the presence of measurable or evaluable lesions, a life expectancy of more than 2 months, absence of active heart disease or infection, evidence of adequate bone marrow, renal and hepatic function and an informed consent according to our institutional policies. Patients who were previously treated with mitoxantrone in an adjuvant setting were considered eligible, provided that the relapse-free interval after the completion of adjuvant chemotherapy was more than 12 months. Patients who were previously treated with chemotherapy for advanced disease were not eligible for this study. All patients were required to have a normal left ventricular ejection fraction as measured by nuclear angiography or echocardiography, and to be free of any previous anticancer treatment for the 4 weeks preceding their entry in the study.

Pretreatment evaluation included a complete medical history, clinical examination, electrocardiogram, complete blood counts (CBC), complete biochemistry, chest X-ray, bone scan and computed tomography (CT) scan as indicated.

The characteristics of the 50 patients who entered into this study are shown in Table 1. 35 (70%) patients presented with multiple metastatic sites and 21 (42%) has visceral metastases.

EPI was administered at a dose of 110 mg/m^2 as a rapid (15–30 min) infusion. Filgrastim was administered subcutaneously at a dose of 5 μg/kg per day. The treatment was started 24 h after chemotherapy and continued for 13 days. Each cycle was repeated every 14 days. In case of leucopenia or thrombocytopenia, treatment was delayed until recovery to 3.5 × 10^9/l and 100 × 10^9/l, respectively. In case of grade 3 toxicity, the dose of EPI was to be reduced by 50% in all subsequent cycles. Anti-emetic therapy included ondansetron ± dexamethasone. Clinical examination, CBC and biochemical analysis were repeated prior to each course of chemotherapy. Examinations with imaging techniques were repeated 3–4 weeks after the completion of chemotherapy.

Table 1. *Patients' characteristics*

	No. of patients
Total number of patients	50
Age (years)	
Median	60
Range	30–73
Performance status (ECOG)	
0	21
1	22
2–3	7
Oestrogen receptors	
Positive	21
Negative	8
Unknown	21
RFI (years)	
Median	2
Range	0–13
Prior treatment	
Adjuvant chemotherapy	
CMF	15
CNF	6
Hormonotherapy	22
Radiation	19
Metastatic sites	
Local	13
Lymph nodes	25
Bone	28
Liver	19
Lung	17
Skin	4
Other	16
Multiple metastases	35
Visceral metastases	21

RFI, relapse-free interval; CMF, cyclophosphamide methotrexate, 5-fluorouracil; CNF, cyclophosphamide, mitoxantrone (novantrone), 5-fluorouracil.

CR was defined as a complete disappearance of all clinical symptoms and signs of disease for a minimum of 4 weeks. Partial response (PR) was defined as a reduction by 50% or more in the sum of the products of the largest perpendicular diameters of the measurable lesions and of the measurable parameter of the evaluable lesions, in the absence of any new or progressive tumour lesions. Stable disease (SD) was defined as an objective response not satisfying the criteria of a PR or an increase of 25% or less in the tumour measurements in the absence of any new lesion. Progressive disease was an increase by more than 25% in the above measurements, or the appearance of a new lesion. Toxicity criteria were those adopted by the WHO [17].

Time to progression was calculated from initiation of chemotherapy to the day when progression or recurrence of the disease was documented clinically and/or radiologically, and survival from the initiation of chemotherapy to the date of death. Patients who had no recurrent tumour or were alive on the day of last update were censored. Survival was evaluated using the Kaplan–Meier method [18].

RESULTS

Compliance to treatment

A total of 281 cycles of chemotherapy were administered. 44 (88%) patients completed all six cycles, while in 6 (12%) the treatment was interrupted after one to five courses due to disease progression (2 patients), patient's voluntary withdrawal (3) and toxicity (1). Treatment was delayed in 22 cycles.

The median interval between cycles of treatment was 14.3 days (range 13.8–28.3). The actually administered median dose per unit time per patient was 53 mg/m^2/week amounting to 97.2% of the dose prescribed by the protocol (Tables 2 and 3).

Response and survival

All patients were considered evaluable for response, toxicity and survival. After the completion of chemotherapy, 7 (14%, 95% C.I. 4–24%) patients achieved a CR and 25 (50%, 95% C.I. 36–64%) a PR. CRs were observed in patients with metastases in the lung pleura, nodes, liver and ovary.

On 1 September 1993, after a median follow-up of 11 months (range 8–21), 27 patients were alive. Among those who achieved a CR, 5 relapsed. Median time to progression was 32 weeks and median survival 64 weeks for the entire group (Figure 1).

Toxicity

The different forms of toxicity from chemotherapy are shown in Table 4. Stomatitis occurred in 7 (14%) and fever in 7 (14%) patients only. Grade 3 haematological toxicity was observed in 6 (12%) patients. Nausea/vomiting was easily manageable with ondansetron. Bone pain, probably related to filgrastim, occurred in 20% of the patients. 1 patient with extensive liver metastases, pretreated with tamoxifen only, exhibited supraventricular

Table 2. Treatment characteristics

Number of cycles per patient		*c*	*n*
		1	2
		2	1
		3	1
		4	0
		5	2
		6	44
% of protocol dose per cycle	*c*	Median	Mean
	1	100	98.9
	2	100	94.9
	3	99.7	92.8
	4	99.7	91.2
	5	99.7	91.2
	6	99.6	86.9
Interval between cycles (days)			
Mean		15.6	
Median		14.3	
Range		13.8–28.3	
Dose intensity (mg/m²/week)			
Mean		50	
Median		53	
Mean % of protocol dose		97.2	
Median % of protocol dose		99.9	

c, number of treatment cycles; *n*, number of treated patients. Total no. of cycles = 128.

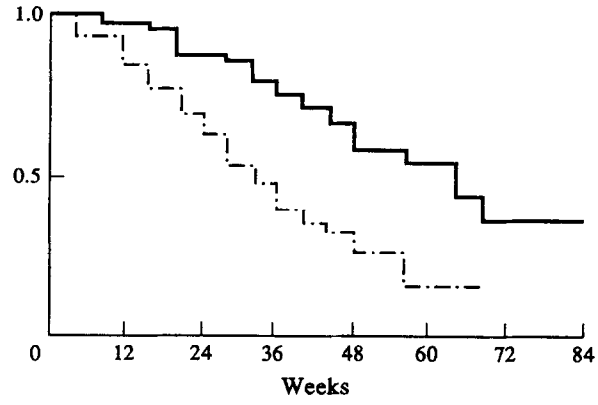

Figure 1. Time to progression (—·—·—) and survival (——) of all patients.

tachycardia with gallop, hypotention requiring continuous dopamine drip infusion, and peripheral oedema after the second cycle of treatment. Ultrasound, electrocardiogram and cardiac enzyme measurements did not indicate myocardial damage or ischaemia. The condition did not respond to treatment with digitalis and diuretics. Finally, the patient died 6 weeks later. Even though the cause of death was unclear, it was attributed to cardiac toxicity from the treatment.

Table 3. Selective data from the three consecutive HeCOG phase II *studies, with high-dose epirubicin in advanced breast cancer*

	Study		
	HE1088	HE1090	HE1091
Number of patients	52	42	50
Median age (years)	53	55	60
Median performance status (ECOG)	1	1	1
Patient characteristics*			
Years	11(21)	14(33)	8(16)
Years	41(79)	28(66)	42(84)
Multiple metastases	40(77)	42(100)	35(35)
Visceral metastases	38(73)	40(95)	21(42)
Prior chemotherapy	37(71)	23(55)	21(42)
Response*			
CR	3(6)	2(4.5)	7(14)
PR	14(29)	14(33)	25(50)
Toxicity*			
Grade 3–4 leucopenia	14(27)	9(21)	3(6)
Stomatitis	7(14)	0(0)	2(4)
Infection	10(19)	4(10)	3(6)
Treatment characteristics			
Received six cycles*	27(52)	29(69)	44(88)
Median interval between cycles (days)	26	28	14.3
Mean % of protocol dose	NM	99.6	97.2
Median % of protocol dose	76	100	99.9
Median dose intensity (mg/m²/week)	29	27	53

NM, not mentioned; HE 1088, epirubicin (110 mg/m²) every 3 weeks; HE 1090, epirubicin (110 mg/m²) and filgrastim every 4 weeks; HE 1091, epirubicin (110 mg/m²) and filgrastim every 2 weeks (present study). CR, complete response; PR; partial response. *Values are no. of patients (%).

Table 4. Incidence (%) of various toxicities from chemotherapy

	Grade				
	None	1	2	3	4
Anaemia	48	16	28	8	0
Leucopenia	88	2	4	2	4
Thrombocytopenia	88	4	6	2	0
Nausea/vomiting	46	30	18	6	0
Stomatitis	86	10	4	0	0
Alopecia	34	2	18	46	0
Bone pain	80	10	10	0	0
Fatigue	84	12	4	0	0
Fever	86	6	8	0	0
Infection	96	0	4	0	0
Neurological	96	4	0	0	0
Cardiac	98	0	0	0	2

DISCUSSION

In conventional chemotherapy of breast cancer the dose effect still remains a controversial issue. There are several published randomised trials which addressed the question of whether higher than conventional doses of anthracyclines have a significant impact on prolongation of survival of patients with advanced breast cancer [19–24]. Survival benefit was reported in only two of them [19, 23]. However, the administration of high doses of anthracyclines is usually accompanied by serious side-effects such as mucositis and myelotoxicity. In our first study using high-dose (110 mg/m^2) EPI every 3 weeks in advanced breast cancer, grade 3–4 leucopenia and grade 2–3 stomatitis were observed in 27 and 14% of the patients, respectively. In addition, the median treatment interval was 26 days and the median drug dose actually received per patient amounted only to 76% of the initial planned dose. The CR rate was only 6% [25]. This unacceptable toxicity and poor compliance to the treatment led us to conduct a sequential study in which the same dose of EPI was administered every 4 weeks, but in this case prophylactic use of filgrastim on days 2–14 of each cycle was added, which enabled us to administer 99.6% of the dose prescribed by the protocol with lesser morbidity. The incidence of stomatitis and infection was lower than in the previous study where growth factor was not used. This beneficial effect was associated with a reduction of hospitalisation time for infection and a decreased requirement for intravenous antibiotics, improving the patient's quality of life. Nevertheless, the CR rate in this study as in the previous one remained disappointingly low (4.5%).

This fact led us to attempt to improve the CR rate by increasing the dose intensity of EPI, and of course, one way to achieve this goal is to reduce the interval between cycles of chemotherapy. Therefore, in the present study we were able to double dose intensity from 27 to 53 mg/m^2/week, by reducing by half the interval between cycles as compared to the previous study.

It is noteworthy that, despite the intensification of treatment in the present study, the incidence of stomatitis was impressively low (4%) and only 3 (6%) patients experienced an infection. However, the CR rate was not significantly increased, even though the number of patients with visceral metastases was smaller in the present than in the previous study. The fact that both studies were not randomised does not allow us to obtain definite information on the impact of intensified treatment with high-dose epirubicin on the response rate of advanced breast cancer. There appears to be a significant difference in the percentage of patients who completed the whole treatment programme in the present than in the previous study (88 versus 69%, respectively). This discrepancy is probably due to the fact that the duration of treatment was longer in the previous study when treatment was delivered monthly, and thus one-third of the patients stopped the treatment because of disease progression.

Although still controversial, there is some evidence suggesting that intensified regimens with haematopoietic colony-stimulating factors (CSFs) support may improve the outcome of patients with advanced breast cancer. In the pioneer work of Bronchud and colleagues 7/15 patients who were treated with high doses (125–150 mg/m^2) of doxorubicin responded, 4 of them achieving a CR [26]. In the study of Hoekman and colleagues, among 13 patients with advanced breast cancer who were initially treated with an intensified regimen, consisting of cyclophosphamide (1 g/m^2), doxorubicin (90 mg/m^2) and GM-CSF, 12 patients responded, 5 of them completely [27]. Even though the above-mentioned studies are small and non-comparative, they suggest that the use of CSFs allows the administration of high-dose anthracyclines, which may result in higher response rates than with conventional chemotherapy [28]. The CSFs offer a safer and less expensive approach to achieving an increased dose intensity, as compared to methods such as autologous bone marrow transplantation or peripheral "stem" cell infusions [29].

In conclusion, the question of whether the increased dose intensity of anthracyclines is translated to prolonged survival of patients with advanced breast cancer still remains unanswered. In order to further explore this issue, our group has initiated a prospective randomised study, where the same dose of EPI (110 mg/m^2) is administered with filgrastim every 4 or every 2 weeks. Quality of life is also measured by the LASA method. This study will hopefully provide useful information on the correlation between dose intensity, time to progression and survival of patients with advanced breast cancer.

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Dual Effect of Parity on Breast Cancer Risk

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This study examined whether breast cancer risk increased for a short period after childbirth, but decreased after a longer period of time. Data from an international case–control study on breast cancer conducted in the 1960s were used to study the modifying effect of age at enrolment on the relationship between parity and breast cancer risk, comparing first uniparous with nulliparous women, and then biparous versus uniparous women. The statistical analysis was performed by modelling through multiple logistic regression, adjusting for study site, age at menarche, menopausal status and obesity index. Comparing uniparous with nulliparous women, an early age at birth seems to be protective for all periods after birth, whereas a late age at birth imparts a higher risk than nulliparity in the period immediately after birth, which declines with the passage of time. The modification effect by age was not apparent when biparous women with different age at second birth were compared with uniparous women. The results support the hypothesis that pregnancy oestrogens impart a transient increase of maternal breast cancer risk when the full-term pregnancy occurs late in a woman's life.

Key words: breast neoplasms, age at birth, parity, case–control studies
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INTRODUCTION

IT HAS been suggested that hormonal changes associated with a full-term pregnancy exert a short-term, adverse and a long-term, beneficial influence on breast cancer risk [1]. This dual effect could be due to growth-enhancing consequences of the elevated pregnancy hormones on already initiated cells, superimposed on the long-term protective effect brought about by pregnancy-induced terminal differentiation of the susceptible mammary gland cells [2, 3].

With different approaches, various studies have examined this