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High-Dose Epirubicin and r-met-hu G-CSF (Filgrastim) in the Treatment of Patients With Advanced Breast Cancer: A Hellenic Cooperative Oncology Group Study

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The delivery of high-dose epirubicin in patients with advanced breast cancer usually entails serious myelotoxicity and frequent treatment delays. Concurrent administration of G-CSF probably allows the administration of epirubicin on schedule with minimal morbidity. From August 1990 to February 1992, 42 women with advanced breast cancer were treated with six cycles of epirubicin 110 mg/m^2 every 4 weeks. Filgrastim 5 μg/kg per day for 14 days was administered subcutaneously starting 24 hours after chemotherapy. All patients had multiple metastatic sites, and 39 had visceral metastases. All cases were evaluable for response, toxicity, and survival. Treatment was delayed in only two cases. The actually administered average dose per unit time per patient amounted to 99.6% of the dose prescribed by the protocol. Two (4.5%; 95% confidence interval [C.I.] 0–16%) patients demonstrated a complete response and 14 (33%; 95% C.I. 19–49%) a partial response. Median time to progression was 31 weeks and median survival was 60 weeks. Severe granulocytopenia was seen in six patients; stomatitis and diarrhea in one patient each. Myoskeletal pain was noticed in 23 (55%) patients, while cardiac problems were reported in 3 cases. The present study shows that the prophylactic use of r-met-hu G-CSF allows the administration of high-dose epirubicin every 4 weeks with minimal morbidity and an improved quality of life.
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Key words: breast cancer, epirubicin, growth factor

INTRODUCTION

4′-Epiadriamycin (EPI) is one of the most active drugs in the treatment of breast cancer and is probably less toxic than its parent compound. Preclinical [1–4] as well as clinical [5,6] data demonstrated that anthracyclines have a steep dose-response curve, and thus small increases of the drug dose may be critical in order to obtain the maximal antitumor effect. Our group [7] as well as others [8,9] have tested the efficacy of high-dose (90–120 mg/m^2) EPI in phase II studies in patients with advanced breast cancer. Unfortunately, intensification of the dose was accompanied by a high incidence of grade 3 leukopenia and frequent treatment delays, which limited its use. With this background information in mind, we initiated a phase II study using the same dose of EPI (110 mg/m^2) as in our previous study concurrent with Filgrastim, in an attempt to increase the dose intensity of chemotherapy while decreasing the degree of leukopenia to acceptable levels, and thus improving patient compliance with the protocol.

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PATIENTS AND METHODS

From August 1990 to February 1992, 42 women with advanced breast cancer entered this multicenter study. Eligibility criteria included the presence of measurable or evaluable disease; a life expectancy of longer than 2 months; absence of active heart disease, infection, and prior exposure to anthracyclines or mitoxantrone; evidence of adequate bone marrow, renal, and hepatic function; and informed consent according to our institutional

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policies. Patients with osseous metastases as the only indicator lesions were included in the study, provided that the lesion was osteolytic or mixed, assessed by X-ray, and had progressed after receiving hormonal treatment if the tumor was hormone receptor positive. All patients were required to have a normal left ventricular ejection fraction as measured by nuclear angiography or echocardiography, and to have stopped any previous hormonotherapy, radiotherapy, or chemotherapy for the 4 weeks preceding their entry in the study.

Pretreatment evaluation included a complete medical history, clinical examination, EKG, CBC, complete biochemistry, chest-X-ray, bone scan, and CT scan as indicated. Tumor response was assessed at each treatment cycle starting with the third cycle. EPI was to be given at the clinic at a dose of 110 mg/m^2 as a rapid (15–30 min) infusion. Filgrastim was supplied free of charge by Amgen-Roche (Basel, Switzerland) in 2 ml vials (300 μg/ml) and administered subcutaneously at a dose of 5 μg/kg per day. The treatment was started 24 hours after chemotherapy and was continued for 14 days. Each cycle was repeated every 28 days. In cases of WBC <4,000/mm^3 or platelet count <100,000/mm^3, treatment was delayed for 1 week or longer until recovery. In cases of grade 3 toxicity, the dose of EPI was reduced by 50% in all subsequent cycles. Anti-emetic therapy included either ondansetron or metoclopramide. Scalp hypothermia was routinely used in all participating centers. Complete blood counts, including differential cell counts, were repeated weekly. Biochemical analysis was carried out before each course of chemotherapy. Patients were asked to record their axillary temperature twice daily and to report any specific complaints.

Complete response (CR) was defined as 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 tumor lesions. An objective response not satisfying the criteria for a PR, or an increase by 25% or less in the tumor measurements in the absence of any new or progressive lesion, was deemed stable disease (SD). Progressive disease (PD) was an increase by more than 25% in the above measurements, or any new lesion. Toxicity criteria were those adapted from the World Health Organisation [10].

Time to progression was calculated from the start of treatment to the day renewed progression or recurrence of the disease was documented, and survival from the day of first treatment to the date of death. Patients who had no recurrent tumor or were alive on the day of last update were censored. The sample size of 42 patients was deemed satisfactory since it allows the estimation of an expected response rate of 60% with a standard error of 7.6%. No interim analyses were planned or performed because of the small sample size. Time to progression and survival rate were calculated by the Kaplan–Meier method [11].

TABLE I. Patient Characteristics

Patient entered	42
Median age (range)	55 (34–69)
Performance status (WHO)	p %
0	15 (35%)
1	19 (45%)
2	8 (20%)
Previous treatment	
No treatment	10 (24%)
Chemotherapy only	7 (17%)
Radiotherapy only	5 (12%)
Hormonotherapy only	4 (10%)
Chemotherapy	4 (10%)
Chemohormonotherapy	3 (7%)
Hormono- and radio-therapy	4 (10%)
All three treatments	5 (12%)
Number of metastatic sites	
1	5 (12%)
2	23 (55%)
3	14 (33%)
Site of metastases	
Bone only	1 (2%)
Soft tissue only	1 (2%)
Viscera only	8 (19%)
Bone and soft tissue	1 (2%)
Bone and viscera	16 (38%)
Soft tissue and viscera	10 (24%)
Bone, viscera, and soft tissue	5 (12%)

p = number of patients.

RESULTS

The characteristics of the 42 patients entered into the study are shown in Table I. All patients had multiple metastatic sites, and in 39 visceral metastases were present. The estrogen receptor (ER) status was unknown in half of the patients. This was due mainly to the fact that several patients were referred to us by rural hospitals, where laboratories are not equipped for ER measurements. All cases were evaluable for response, toxicity, and survival.

Treatment

Treatment was delayed in two patients only, for 8 days in one case and repeatedly for a total of 47 days in another, due to repeated episodes of leukopenia. A total of 182 treatment cycles were administered. Twenty-nine patients completed the 6 cycles of treatment, whereas 13 patients interrupted treatment after 2–5 courses due to progression or renewed progression. The actually administered average dose per unit time per patient was 27.4

TABLE II. Relationship Between Site of Metastases and Response to Chemotherapy

Site	Response			
	CR	PR	SD	PD
Tissue only	0	0	0	1
Viscera only	1	3	2	2
Bone only	0	0	1	0
Bone and viscera	1	4	3	8
Bone and soft tissue	0	1	0	0
Viscera and soft tissue	0	3	2	5
Bone, viscera, and soft tissue	0	3	1	1

CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease.

TABLE III. Relationship Between Pretreatment Performance Status Level and Response to Chemotherapy

Performance status	Response			
	CR	PR	SD	PD
0	1	3	3	8
1	1	9	4	5
2	0	2	2	4

See Table II for abbreviations.

mg/m^2/week, amounting to 99.6% of the dose prescribed by the protocol.

Response

Two (4.5%; 95% confidence interval [C.I.] 0–16%) patients demonstrated a CR, 14 (33%; 95% C.I. 19–49%) a PR, while 9 (21%; 95% C.I. 10–37%) showed stabilization of the disease. Seventeen patients had disease progression. The two CRs lasted for 44 and 67 weeks, respectively. The relationships between type of response to chemotherapy and site of metastases or pretreatment performance status level are shown in Tables II and III.Ten of the patients who had a response or stable disease have had a recurrence or renewed progression.

Survival

Up to January 1, 1994, after a median follow-up of 130 weeks for the survivors, 12 patients were alive. The cause of death was disease progression (28 patients), treatment (1), and acute ileus (1). In the latter patient a second tumor (colon cancer) was diagnosed during exploratory laparotomy. The median time to progression was 31 weeks and median survival was 60 (range, 8–158) weeks (Fig. 1).

Toxicity and Morbidity

Table IV indicates the lowest hematologic values observed during treatment and the number of patients with different toxicity grades. The median cycle number where WBC and neutrophil counts were at their lowest was the second, and, for platelets and hemoglobin, the third. Severe granulocytopenia was seen in six patients only. In one patient, who had a complete tumor response, protracted episodes of leukopenia (with a neutrophil nadir of 0.8 × 10^9) necessitated treatment interruptions in four courses (with supplementary delays reaching 28 days).

Nonhematologic toxicity is summarized in Table V. In two cases, infections were seen with low granulocyte counts. One other patient had a circumscribed pseudomonas infection of an exulcerated tumor. Stomatitis was observed in one patient only. Three cases of cardiac problems are reported: in two cases a supraventricular tachycardia appearing in later cycles, which the patients had not reported in their past history; in one patient, a diminution of >10% (from 45% to 40%) of the echocardiographic ejection fraction was observed.

Myoskeletal pain was noted in 23 patients. Filgrastim treatment was not interrupted or reduced in any patients. No hyperergic reactions were seen. All the treatments were administered on an outpatient basis, except for two patients, who were hospitalized for a total of 24 days.

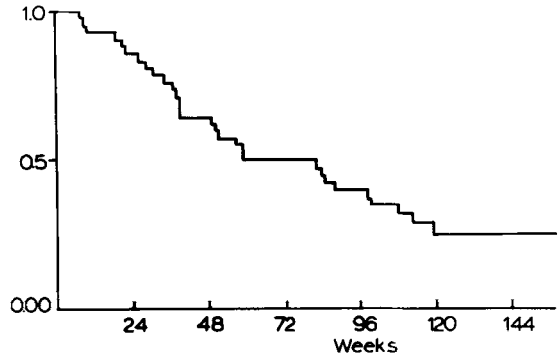

Fig. 1. Actuarial survival of all patients.

TABLE IV. Hematologic Toxicity

	Nadir	Number of patients	Counts	
			Median	Range
WBC	<1	2	2.9	0.7–6.8
(×10^9/l)	1–2	7		
	2–3	13		
	3–4	14		
	>4	6		
Neutrophils	<0.5	6	1.3	0.1–4.5
(×10^9/l)	0.5–1	10		
	1–1.5	8		
	1.5–2	13		
	>2	5		
Platelets	25–50	1	129	28–210
(×10^9/l)	50–75	3		
	75–100	9		
	>100	29		
Hemoglobin	<8	2	10.4	7–13
(g/dl)	8–12	35		
	12–13	5		

TABLE V. Nonhematologic Toxicity

	Grade	Number of patients
Nausea/vomiting	0	21
	1	13
	2	8
Alopecia	0	2
	1	8
	2	32
Stomatitis	0	41
	1	1
Cardiotoxicity	0	39
	1	3
Myoskeletal pain	None	19
	Present	23
Infection	0	38
	1	3
	2	1
Fatigue	None	35
	Present	7
Diarrhea	0	38
	1	4
Neurological	0	39
	1	2

DISCUSSION

The dose-response effect in conventional chemotherapy of breast cancer still remains controversial. Most studies that have attempted to provide an answer to this important question were retrospective analyses and showed serious methodological weaknesses [12,13]. The lack of a proper methodology probably explains why there are contradictory results from retrospective analyses of the dose-response effect, especially in cases of advanced breast cancer [14,15].

Anthracyclines (doxorubicin, epirubicin, and theprubicin) are considered the most active agents in the management of breast cancer. Thus far, no clinically significant differences in activity between these agents have been established. There are several published randomized studies that address the question of whether higher than conventional doses of anthracyclines have a significant impact on prolongation of survival of patients with advanced breast cancer [16–20]. In three of these studies a significant increase of response rate was observed with higher doses [16,19,20], which was translated in two studies to a survival benefit [16,20]. However, dose intensification of anthracyclines is usually accompanied by serious side effects, mainly myelotoxicity and mucositis. These side effects often contribute to dose reductions and treatment delays, thus compromising dose intensity. In a previous study our group treated 52 women with advanced breast cancer with high-dose epirubicin (110 mg/m^2) monotherapy every 21 days. The median treatment interval per patient was 26 days, and the median drug dose actually received per patient was 79% of the protocol dose [7]. The drug dose per unit time was slightly higher than in the present study; about one quarter of the patients had a single metastatic site and one quarter had no visceral disease. The median survival in the previous study was 31 weeks, whereas the median survival has not been reached in the present study. Even though the results of the two studies might seem quite different, they have been conducted with different criteria and thus cannot be compared.

Until recently there were no solutions to overcome these serious consequences caused by high-dose chemotherapy other than reducing the dose or delaying treatment. The introduction of growth factors (G-CSF, GM-CSF) in the management of patients with advanced malignancies allows high-dose chemotherapy with minimal morbidity [21–24].

Growth factors have been incorporated in the treatment of patients with advanced breast cancer by several groups in an attempt not only to raise the dose of the chemotherapeutic agents but also to increase the frequency of administration. Bronchud et al. [25] treated 15 patients with advanced breast cancer with escalating doses of doxorubicin followed by continuous infusion of G-CSF at a dose of 10 μg/kg/day from day 1 to day 8 and 5 μg/kg/day through days 8–11. As a consequence of the administration of G-CSF, the investigators were able to give a high dose of doxorubicin every 2 weeks. All seven patients treated either with three cycles of doxorubicin (125 mg/m^2) or two cycles of even higher doses (150 mg/m^2) responded, with four of them achieving a CR [25].

In another study 18 patients with advanced breast cancer were treated with multiple cycles of doxorubicin (75 or 90 mg/m^2) plus cyclophosphamide (750 or 1,000 mg/m^2) every 21 days with GM-CSF support. The increase in dose intensity produced a high response rate (89% objective responses with 28% complete), which was comparable with those observed in other dose-intensity studies. However, the stimulatory effect of GM-CSF on hemopoiesis observed after the first cycle was substantially diminished in subsequent cycles. As a result of this phenomenon, all patients treated with the highest dose of chemotherapy suffered grade 3 or 4 neutropenia and thrombocytopenia. Also the administration of GM-CSF was accompanied by several side effects, including pyrexia, malaise, and mild hypotension [26]. These reactions were not observed in our study, where the only complaint attributed to Filgrastim administration was myoskeletal pain, which fortunately was easily controlled by analgesics. As for bone pain, the respective role of the growth factor and of bone metastases (the latter present in over half of our patients) cannot be differentiated, bone pain being mostly by these patients. This uneventful use of Filgrastim allowed us to deliver almost 100% of the dose prescribed by the protocol in all cycles.

Treatment was given on schedule in all but two patients. The prophylactic use of Filgrastim resulted in a reduction of infection rate to 9% from the 19% that was noticed in the previous study, in which high-dose epirubicin was delivered without the growth factor [7]. However, this difference was not significant at the 5% level.

Randomized, double-blind, placebo-controlled trials have shown that the use of G-CSF reduces the incidence of febrile neutropenia and the duration of neutropenia [27,28]. This beneficial effect was associated with a reduction of hospitalization time for infection and a decreased requirement for intravenous antibiotics.

In conclusion, in the present study we were able to show that the prophylactic use of Filgrastim enabled the administration of high-dose epirubicin on schedule with minimal morbidity, and thus improved the patient's quality of life. The excellent compliance of patients to the treatment urged us to further investigate, in a study that has been just completed, the role of dose intensity in the management of patients with advanced breast cancer by reducing the interval between epirubicin administration from 4 to 2 weeks. Whether this doubling of dose intensity will result in prolongation of life remains to be determined in a phase III study.

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