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## Original Paper

# Dose Intensification of Epidoxorubicin and Cyclophosphamide in Metastatic Breast Cancer: a Randomised Study with Two Schedules of Granulocyte-macrophage Colony Stimulating Factor

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**A randomised phase II/III study was conducted in patients with advanced breast cancer to determine the dose intensity achievable through an acceleration of administration of chemotherapy with epidoxorubicin and cyclophosphamide (EC) alone, as compared with the combination of this regimen with two different schedules of granulocyte-macrophage colony stimulating factor (GM-CSF). 73 patients received EC intravenous (i.v.) (epidoxorubicin 100 mg/m$^2$, cyclophosphamide 600 mg/m$^2$) on day 1 (group A), or the same chemotherapy plus sub-cutaneous (s.c.) GM-CSF (5 μg/kg/day) either from days 3 to 12 (group B) or from days −6 to −3 (group C). The primary objective of the study was the investigation of dose intensity delivered in the three treatment arms, whereas the secondary objective was response rate. A significant increase ($P = 0.006$) in dose intensity of 21% was observed for treatment group B, whereas the increase in dose intensity achieved in group C (7%) was not significant ($P = 0.086$). Response rates (complete response (CR) + partial response (PR)) of 56% were observed in group A, 65% in group B, and 57% in group C, respectively. This difference in response rates did not reach statistical significance ($P = 0.271$). We thus conclude that an acceleration of the EC regimen over the standard schedule could be accomplished with postchemotherapeutic GM-CSF support, leading to an increase in dose intensity, whereas pretherapeutic short-term GM-CSF administration did not reach this goal.** © **1998 Elsevier Science Ltd. All rights reserved.**

**Key words: breast cancer, dose intensification, colony stimulating factor, chemotherapy, GM-CSF**
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## INTRODUCTION

ONLY A very small percentage of patients with advanced breast cancer respond to conventional cytostatic treatment in conventional dosages, thus continuing to make advanced breast cancer an incurable disease in the vast majority of cases [1]. Based upon the model forwarded by Skipper and associates [2] and Hryniuk and colleagues' hypothesis on the importance of dose intensity in the treatment of malignant disease [3, 4], several investigations have thus examined the effectiveness of augmenting doses of cytostatic chemotherapy in patients with advanced breast cancer (reviewed in [5]). Randomised studies on dose–response relationships using combinations of cytostatic drugs have shown some benefit in terms of induction of remissions in metastatic disease in such instances in which higher dosages of cytostatic drugs were

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used [6–8]. These observations were further corroborated by studies in which autologous stem cell support was used in addition to high doses of cytostatic drugs [9–11].

Currently, the intensification of cytostatic treatment is made possible by the use of colony stimulating factors (CSF) which lead not only to the administration of higher doses of cytostatic drugs than used to date but also to the possibility of reducing the time intervals between chemotherapy cycles [12–15]. However, very sparse data exist as to the optimal schedule of delivery of CSFs versus the schedule of administration of cytostatic drugs, and few studies have analysed the question of dose intensity achieved by the inclusion of CSFs into treatment regimens (reviewed in [15]).

Based upon these considerations, this phase II/III study was initiated to determine the dose intensity achievable with the use of granulocyte-macrophage CSF (GM-CSF) in patients with advanced breast cancer who were treated with chemotherapy consisting of an augmented dose of epirubicin in combination with cyclophosphamide (EC). Within this three arm study, patients were randomised to receive either EC alone; EC+GM-CSF for 10 days following the application of chemotherapy; or GM-CSF administered on days −6 to −3 before EC. This study design served to analyse the optimal schedule of GM-CSF used either following chemotherapy or as a 'loading dose' before the administration of chemotherapy to achieve a reduction of the time interval between cycles of chemotherapy leading to dose intensification. This being the primary objective, the secondary objectives were to compare the three treatment arms for haematological toxicity, side-effects of GM-CSF and, finally, antitumour activity.

## PATIENTS AND METHODS

*Patients*

A total of 73 eligible patients were entered into the study between January 1992 and June 1994. The patients' characteristics are shown in Table 1. Eligible patients were women aged 18–70 years with histologically confirmed high-risk metastatic breast cancer. Patients who had received prior chemotherapy for advanced disease or patients who had finished adjuvant chemotherapy less than 6 months before randomisation were not eligible for the study. Prior hormonal therapy and prior limited radiotherapy (involving not more than 30% of the functioning bone marrow) were permitted. Eligibility requirements included the presence of progressive measurable and/or evaluable disease, a Karnofsky performance score > 60%, a white blood cell count (WBC) of > 3000/mm$^3$, a platelet count of > 130 000/mm$^3$, serum creatinine and serum bilirubin < 1.5 mg/dl and levels of serum transaminases < 4× the normal value. A left ventricular ejection fraction of > 75%, as measured by echocardiography, was required.

Patients with clinical or radiological evidence of brain metastases or other serious medical problems, as well as patients with evidence of active infection, were excluded from the trial.

The study was conducted according to the ethical standards described in the Helsinki declaration. Ethical approval for the study had to be given by the ethical committees of the participating institutions and all patients gave informed consent prior to participation in the study.

Randomisation was performed prospectively according to blinded randomisation lists provided to each centre. The study was carried out at the Divisions of Oncology of the University Hospitals of Graz and Vienna in collaboration with six other institutions.

*Monitoring*

At the start of therapy, patients underwent a physical examination, including measurement of tumour size, complete blood count and serum chemistry, the examination of serum levels of tumour markers CEA and CA 15.3, chest radiographs, liver ultrasound, ECG, echocardiography and bone scintigraphy in case of clinical indication. During treatment, patients were required to have complete blood counts and checks of vital signs once a week, whereas ECG and serum chemistries were repeated before each treatment cycle. Assessment of tumour response either by X-ray, sonography or computed tomography, whichever was appropriate, was repeated after three cycles of therapy. Vital signs were checked before and 2 h after the first GM-CSF dose. After the termination of chemotherapy, follow-up examinations were performed each month and included physical examination, performance scale assessment, complete blood count, the assessment of serum levels of tumour markers CEA and CA 15.3 and serum chemistry, as well as the assessment of the size of the target lesion.

*Treatment schedule*

Chemotherapy consisted of epidoxorubicin 100 mg/m$^2$ and cyclophosphamide 600 mg/m$^2$ (EC) given by i.v. short-term infusion on day 1. Patients were randomised to receive this

*Table* 1. *Patients' characteristics*

| | Treatment group | | |
|---|---|---|---|
| | A | B | C |
| Patients entered (no.) | 24 | 24 | 25 |
| Median age (range in years) | 62 (44–70) | 54 (37–70) | 56 (37–70) |
| Karnofsky index % (range) | 90 (80–100) | 90 (70–100) | 90 (70–100) |
| Previous adjuvant chemotherapy | 5 (21%) | 13 (54%) | 8 (32%) |
| Dominant site of metastases | | | |
| visceral | 20 (83%) | 17 (71%) | 19 (76%) |
| bone | 3 (13%) | 4 (17%) | 4 (16%) |
| soft tissue | 1 (4%) | 3 (13%) | 2 (8%) |
| Number of metastatic sites | | | |
| 1 | 15 (63%) | 15 (63%) | 17 (68%) |
| 2 | 7 (29%) | 5 (21%) | 4 (16%) |
| 3 | 2 (8%) | 4 (17%) | 4 (16%) |

therapy either without growth factor support (group A), or with *Escherichia coli*-derived rHu GM-CSF (CSF 39-300, Sandoz/Schering-Plough, Basel, Switzerland) administered s.c. at a dose of 5 μg/kg/day on days 3–12 following cytostatic therapy (group B) or on days −6 to −3 preceding chemotherapy (group C).

All chemotherapy cycles were administered on an outpatient basis, whereas GM-CSF was administered by the patients themselves or by their family physicians.

To detect a potentially inadequate haematological recovery without concomitant GM-CSF application at baseline, the interval between cycles 1 and 2 was chosen to be 3 weeks for all three treatment groups. Subsequently, the interval between chemotherapy applications was reduced to 14 days in all treatment groups in order to increase dose intensity in all treatment groups. Dose modifications were made on the basis of toxicity encountered during the preceding course. Thus, epidoxorubicin and cyclophosphamide were reduced by 25% for an absolute neutrophil count (ANC) of < 2000/μl to > 1500/μl and/or a platelet count of < 100 000/μl to > 75 000/μl. For an ANC of < 1500/μl and/or a platelet count of < 75 000/μl, courses were postponed for 8 days, and the patients' blood cell count checked on a weekly basis. In the case of postponement of chemotherapy in group C, 3-day pretreatment with GM-CSF had to be reintroduced weekly. Dose adaptation of GM-CSF was not part of this study.

Treatment was planned to be discontinued in case of severe toxicity (WHO grade III–IV, except for alopecia) or a patient's refusal to receive further therapy. In the absence of progressive disease (PD), a total of six courses was scheduled to be delivered to each patient.

*Dose intensity*

The main objective of the study was to compare dose intensity achieved in the three treatment groups. Dose intensity, expressed in mg/m$^2$/day, was calculated as the total amount of drug (E + C) given in milligrams, divided by body surface area and time in days elapsed between the start of treatment and the day of the last chemotherapy course. Reference standard dose intensity was that of an equivalent regimen (same drugs, same doses) delivered at 3-weekly intervals. An arbitrary plan foresaw calculations of dose intensity at the fourth and the sixth cycle which was chosen according to previous experience gained in a similar setting [13]. The sample size was chosen according to the primary objective and analysis performed by intention-to-treat.

*Response*

Tumour responses were included as a secondary objective of the study and patients evaluated after three and six cycles of therapy according to WHO criteria. Patients were included in a final descriptive evaluation of tumour response if at least one response assessment was performed (i.e. at least three courses of chemotherapy administered). Thus, 9 of 73 patients (12%) could not be evaluated because of premature discontinuation before completion of the third treatment course.

Time to progression and overall survival were calculated from the first day of treatment as secondary endpoints of the study. All eligible patients were included in the survival analysis.

*Toxicity*

WHO criteria were used to evaluate toxicity in all patients who received chemotherapy [16].

*Statistical analyses*

Analyses of dose intensity as the primary objective were performed by intention-to-treat. Response rates as the secondary objective were reported in a descriptive manner.

## RESULTS

*Patients' characteristics and treatment history*

As shown in Table 1, patients from all treatment groups were comparable for age, performance status, pretreatment, as well as dominant sites and number of metastases. Of the 73 eligible patients entered into the study, 36 (49%, 12 patients from each treatment group) completed six treatment cycles, as scheduled.

*Withdrawal from therapy*

In 37 (51%) patients, treatment was discontinued prematurely before the sixth course of chemotherapy due to chemotherapy-related complications in 10 patients, consisting of myelotoxicity in 6 patients, a septic tooth abscess in 1 (group A), local tissue necrosis after paravasation of cytostatics in 1 (group C) and emesis and diarrhoea in 2 patients (Table 2). Major protocol violations of the treatment schedule resulted in withdrawal from the study of 6 patients. 4 patients were withdrawn because of hypersensitivity reactions to GM-CSF. 2 patients withdrew their consent and treatment was stopped in 15 patients due to progressive disease (6, 6 and 3 patients from groups A, B and C, respectively).

*Number of courses of chemotherapy*

The median number of courses applied did not differ significantly between the treatment groups (103 (group A), 108 (group B) and 119 (group C) courses). Apart from hypersensitivity reactions to GM-CSF, the number of events leading to premature discontinuation of treatment was comparable.

*Dose intensity analysis*

In order to gain an overview over a representative period and according to previous experience of other investigators in a similar context [13], dose intensity analysis (by intention-to-treat) was performed in 52 (71%) patients who had received four treatment courses (16 in groups A and B, 20 in group C) and in 36 (49%) patients who had completed all six treatment cycles (12 patients in groups A, B, and C, respectively). Overall, 330 cycles were given: 103 cycles of EC, 108 cycles of EC + GM-CSF for 10 days following chemotherapy and 119 cycles of EC + GM-CSF on days −6 to −3 prechemotherapy, respectively.

A statistically significant increase in dose intensity of administered chemotherapy was found for treatment group B only. In this group, dose intensity was 18% ($P = 0.0002$) and 21% ($P = 0.006$) higher after four and six treatment courses, respectively, as compared to group A.

Figure 1 shows that patients from group B had significantly shorter treatment intervals ($P < 0.001$) and received significantly higher cumulative doses of cytostatics throughout cycles 2–6, as compared with patients from group A, who received treatment without GM-CSF and in whom a dose intensity of 94% of the reference standard regimen was obtained (see above).

The increase in dose intensity achieved in treatment group C did not reach the level of statistical significance, but was still 6 and 7% higher than in group A after four and six treatment cycles, respectively.

*Table 2. Reasons and time points for withdrawal from therapy due to side-effects*

| Reason | Total no. of patients | Treatment groups A | B | C |
|---|---|---|---|---|
| Myelotoxicity | 6 | 1(4th cycle)* | 2(2nd cycle) | 3 (4th or 5th cycle) |
| Major infection | 1 | 1 (1st cycle) | — | — |
| GM-CSF hypersensitivity | 4 | — | 2 (2nd or 3rd cycle) | 2 (2nd or 3rd cycle) |
| Extravasation of cytostatics | 1 | — | — | 1 (3rd cycle) |
| Emesis/vomiting | 2 | 1 (3rd cycle) | — | 1 (4th cycle) |
| Withdrawal of consent | 2 | 1 (2nd cycle) | 1 (4th cycle) | — |
| Major protocol violations | 6 | 3 (1st cycle) | 1 (1st cycle) | 2 (1st or 4th cycle) |

*The last cycle of chemotherapy administered is shown in parentheses.

*Treatment intervals and postponement of treatment*

Figure 1 also shows the intervals between treatment with cytostatics in all three groups of patients. Postponement of treatment was due to myelotoxicity in all instances in accordance with the protocol. The efficacy of GM-CSF in sustaining leucocyte recovery in patients from group B was constant throughout treatment and the addition of GM-CSF given for 10 days after chemotherapy allowed patients to receive EC every 15.5 days, resulting in an increase in dose intensity of 21% versus patients who received chemotherapy without GM-CSF.

*Myelotoxicity*

Within this outpatient trial, haematological evaluation was carried out in weekly intervals. Figure 2 shows that the mean values of leucocyte counts recorded throughout scheduled treatment cycles 2–6 were higher in treatment group B, as compared to groups A and C. However, the difference was not statistically significant ($H$-test, $P = 0.856$), when values recorded on day 1 of each chemotherapy cycle were compared. Nevertheless, it is important to note that patients from group B received statistically higher dose intensity than patients from groups A or C. Figure 2(a) also shows that patients from the other groups (A and C) showed comparable leucocyte values on day 1 until cycle 4. From then on patients from group C presented with persistently higher values than patients from group A. Moreover, when mean leucocyte counts of subsequent cycles were compared with the baseline of each group, a constant decline of values was registered in group A, while no such sign of bone marrow depletion was observed in groups B or C. For treatment courses 4 and 5, the difference was statistically significant (Wilcoxon-test versus course 4: $P = 0.025$; versus course 5: $P = 0.001$; Figure 2a).

The mean neutrophils counts showed similar courses favouring group B (Figure 2b). In 6 patients in whom treatment had to be prematurely discontinued because of haematological toxicity, protracted neutropenia was the major cause. 1 patient in group A, 1 in group B and 3 patients in group C were withdrawn from therapy for this reason.

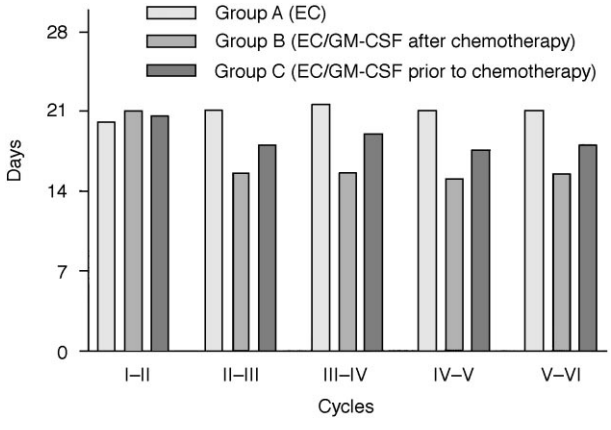


**Figure 1. Mean treatment intervals between cycles I–VI.**

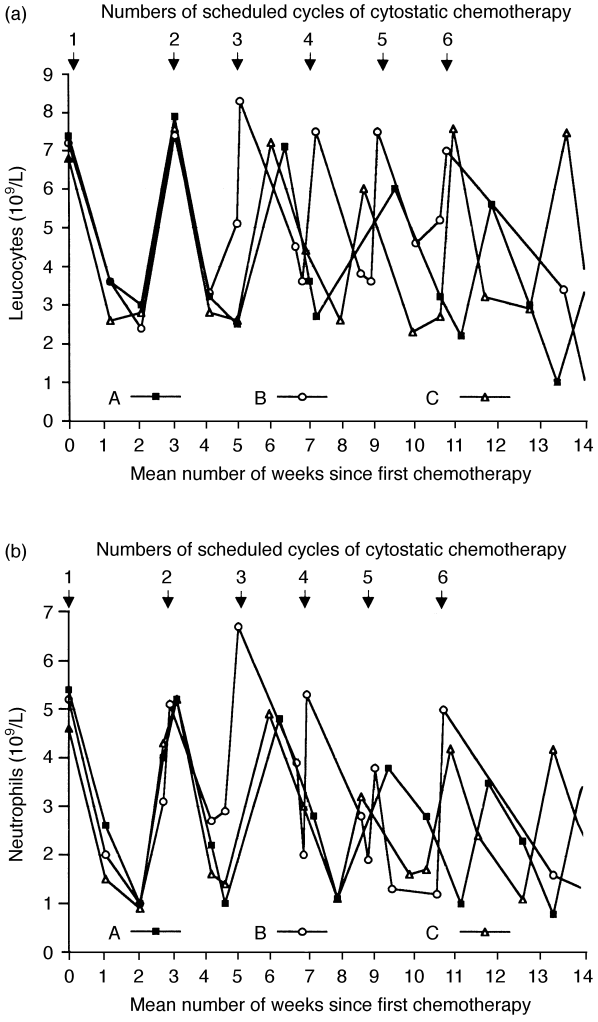


**Figure 2. Mean (a) leucocyte values and (b) number of neutrophils in treatment groups A, B and C.**

The mean thrombocyte count recorded in patients from groups B and C throughout cycles 2–6 was significantly lower, as compared with patients from group A. The mean values deteriorated within each group with prolonged duration of treatment, but remained above 150 000/μl. Clinically relevant thrombopenia of WHO grade IV toxicity was recorded in 3 patients after the third course of chemotherapy (group B: 2 patients, group C: 1 patient) which required platelet transfusion in all three cases.

Haemoglobin counts deteriorated in each treatment group leading to cumulative anaemia WHO grade III and IV in 20% of patients after the third cycle of chemotherapy.

Of all 73 patients, 13 (18%) required red blood cell transfusions during at least one cycle of therapy: 6 patients from groups B and C, and 1 patient from group A. Erythropoietin was given to 3 patients from group A.

*Episodes of febrile neutropenia*

Febrile neutropenia of $>38.5^{\circ}C$ occurred in 3, 5 and 8 patients from groups A, B and C, respectively. The episodes became longer in intensified treatment arms B and C during the subsequent course of treatment.

*GM-CSF associated toxicities*

Major toxicities consisted of low grade fever and influenza-like symptoms (mainly moderate myalgia, arthralgia and fatigue). In total, substantially more episodes of low-grade fever and influenza-like symptoms occurred in group C than in group B (44 and 12 recordings, respectively). Moreover, the prevalence of these events decreased during the course of treatment in group B, while there was no reduction of symptoms in group C. The main toxicities exclusively ascribed to GM-CSF comprised hypersensivity reactions. Persistent cutaneous infiltrates at the injection site developed in 2 patients and generalised exanthema in 2 others. In all 4 cases, GM-CSF was discontinued after two or three courses of treatment, respectively. In addition, 8 patients from group B and 10 from group C experienced transient erythema and pruritus at the injection site, but did not need to be withdrawn from treatment.

4 patients from group B and 2 from group C developed anaphylactoid reactions to GM-CSF. Moderate hypotension occurred in all of these cases accompanied by dyspnoea or oedema in two instances. There was one 'first-dose reaction' reported during the first treatment course. In this patient, transient dyspnoea developed after the first injection and reoccurred with accompanying facial oedema as the patient collapsed.

*Non-haematological chemotherapy-associated toxicities*

Of the main toxicities directly related to chemotherapy, complete alopecia and nausea of varying degrees were reported in almost all patients. 4 patients discontinued treatment because of emesis and diarrhoea (2 patients), onycholysis (1 patient) or tissue necrosis following extravasation (1 patient). The incidence and maximal grade of stomatitis were comparable between the three treatment groups.

*Tumour response and survival*

As tumour response was a secondary objective of this study the results were analysed descriptively: 64 (88%) patients were evaluable for tumour response. 9 (12%) patients had terminated treatment prematurely, i.e. before the third course of chemotherapy, and were thus not evaluable. As shown in Table 3, an objective tumour response (CR + PR) was observed in 10 out of 18 patients (56%) from group A, in 15 out of 23 patients (65%) from treatment group B and in 13 out of 23 patients (57%) from group C, 11, 30 and 22% of patients had CR in treatment groups A, B and C, respectively. Owing to the relatively small number of patients per group, which was due to the sample size chosen for the primary study objective of dose intensity, no statistically significant difference in response (CR + PR) to treatment between the three groups was obtained ($\chi^2$-test, $P = 0.271$). Thus far, of 73 eligible patients included in the study, 28 (38%) have died after a median follow-up period of 13 months (range 4–33 months). In 35 patients who achieved objective remission (CR + PR), an overall survival rate of 69% at a median follow-up time of 17 months (range 4–35 months) has been observed. The median progression-free survival exceeded 12 months (11 +, 16 + and 9 + months for groups A, B and C, respectively). For the 12 patients who achieved complete remission, the overall survival was 83% and median progression-free survival has exceeded 16 months (10 +, 19 + and 14 + months in groups A, B and C, respectively) at the time of publication.

## DISCUSSION

Dose intensity of cytostatic drugs administered to patients with malignant diseases is important as a means of ameliorating the results of cytostatic treatment delivered to patients with malignant diseases [3–14]. It has culminated in a series of clinical studies testing the efficacy of high-dose chemotherapy with autologous stem cell support [10, 11] and the use of CSF administered, in an attempt to deliver the appropriate amount of cytostatic drugs and to adhere to the planned schedule of the cytostatic regimen while reducing morbidity associated with standard chemotherapy [15, 17–21]. Growth factor administration is usually started immediately after completion of chemotherapy and continued until haemopoiesis recovers. This prolonged administration has proved particularly effective in reducing the length of granulocyte and monocyte nadirs that follow high-dose chemotherapy [15, 22–26]. It has to be kept in mind, however, that the administration of growth factors used in conjunction with chemotherapy for multiple cycles and its post-chemotherapeutic administration might become pretreatment for the next course of chemotherapy, thus constituting possibly an important component for myeloprotection [17]. Moreover, GM-CSF given prior to chemotherapy was shown to exert a significant biological effect by rapid generation of quiescent haemopoietic progenitor cells in the bone marrow

*Table 3. Response to therapy*

| | Treatment group | | |
|---|---|---|---|
| | A | B | C |
| Evaluable patients | 18 (75)* | 23 (96) | 23 (92) |
| Complete response | 2 (11) | 7 (30) | 5 (22) |
| Partial response | 8 (44) | 8 (35) | 8 (35) |
| Objective response | 10 (56) | 15 (65) | 13 (57) |
| Stable disease | 2 (11) | 2 (9) | 7 (30) |
| Progressive disease | 6 (33) | 6 (26) | 3 (13) |

*Number (percentage) of patients.

leading to a rapid increase in the proliferative activity of haematopoietic precursors.

From these preliminary considerations, it was the primary objective of the present prospective randomised study to evaluate the effects of two schedules of GM-CSF upon dose intensity of cytostatic drugs delivered to patients with advanced breast cancer and the resulting effects upon myelopoiesis. A statistically significant increase in dose intensity administered throughout all six cycles of chemotherapy was observed only in the group of patients who received GM-CSF for 10 days following chemotherapy. Moreover, treatment intervals which had been scheduled to be 14 days were adhered to in this group, but not in the control group receiving chemotherapy alone or in the group which received GM-CSF preceding cytostatic treatment. Thus, previous considerations of a loss of effectiveness of GM-CSF, following its protracted administration in patients with advanced breast cancer receiving cyclophosphamide and an anthracycline at a dose of 20–40% higher than conventional chemotherapy [26], could not be corroborated. The long-term feasibility of EC acceleration could not only be demonstrated by the number of cycles administered, but also by the adherence to the protocol which foresaw the administration of EC in 14-day intervals. Thus, half the patients received six courses of chemotherapy as scheduled in both EC + GM-CSF groups.

The effect of accelerated and dose-intensified chemotherapeutic treatment upon responses is difficult to interpret, due to the relatively low number of patients included. The 59% objective response rate (38/64) and 22% (14/64) clinical CR rates in high-risk advanced breast cancer patients treated with EC + GM-CSF are similar to those reported with other dose-intensive regimens, including combination chemotherapy [26–28]. Nevertheless, the quality of responses favoured treatment groups which received GM-CSF, in which 7 out of 23 (30%) and 5 out of 23 (22%) achieved CR, respectively, as compared to 2 out of 18 (11%) in patients who did not receive intensified chemotherapy due to the omission of GM-CSF. However, the addition of GM-CSF was associated with further, although manageable, clinical toxicity. Further trials will have to establish and study the question of whether the addition of GM-CSF to EC and its effectiveness is worth the experience of associated toxicities. Thus, the use of GM-CSF in order to escalate chemotherapy in advanced breast cancer cannot be recommended outside of further clinical trials.

In conclusion, the present study demonstrated that an acceleration of chemotherapy with increased doses of epirubicin could be accomplished by the addition of GM-CSF administered for 10 days following cytostatic treatment, which achieved an increase of dose intensity of 21% over a chemotherapy schedule which did not include GM-CSF. The prechemotherapeutic administration of GM-CSF for 3 days before the administration of cytostatic treatment did not reach this goal. Thus, future clinical studies investigating the efficacy of intensified and/or accelerated chemotherapy in advanced breast cancer should use the former protocol of GM-CSF administration.


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