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Original article

Identification of the highest dose of docetaxel associable with active doses of epirubicin. Results from a dose-finding study in advanced breast cancer patients

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Summary

Purpose: To determine the maximum tolerated dose (MTD) and the dose limiting toxicity (DLT) of docetaxel in combination with fixed doses of epirubicin.

Patients and methods: Women with locally advanced or metastatic breast cancer were given docetaxel, 60 mg/m^2 in escalated doses by steps of 10 mg/m^2, in association with two fixed doses of epirubicin (90 mg/m^2, and 75 mg/m^2). Since neutropenia was foreseen to be the most likely DLT, a third group with prophylactic G-CSF support was planned to define the MTD of docetaxel with 90 mg/m^2 of epirubicin. Selected patients underwent pharmacokinetic evaluation of docetaxel.

Results: Fifty-eight patients entered the study. At the first step (90 mg/m^2 of epirubicin) the MTD was obtained at 60 mg/m^2 of docetaxel. At the second step (75 mg/m^2 of epirubicin) the MTD of docetaxel was 80 mg/m^2. At the third step (epirubicin 90 mg/m^2) G-CSF allowed a safe escalation of docetaxel up to 90 mg/m^2. Neutropenia was the most common hematological adverse event. Without G-CSF, grade 4 neutropenia occurred in 69% of cycles, of which 11% was complicated by fever. In G-CSF group, grade 4 neutropenia and neutropenic fever occurred in 31% and 3%, respectively. Most frequent non-hematological adverse effects were asthenia (45%), nausea (39%) and mucositis (36%). No patient developed congestive heart failure. Two toxic deaths occurred. Overall response rate was 73% in 42 out of 58 patients, with no apparent epirubicin dose-related effect. No statistically significant effect of the two doses of epirubicin was observed in docetaxel pharmacokinetics.

Conclusions: On the basis of the toxicity profile, the docetaxel pharmacokinetics and the response rate observed, epirubicin 75 mg/m^2 combined with docetaxel 80 mg/m^2 can be recommended for further studies.

Key words: breast cancer, docetaxel, epirubicin, phase I

Introduction

Thirty years after their introduction into clinical practice [1], anthracyclines (doxorubicin and epirubicin) remain among the most active single agents in the treatment of metastatic breast cancer patients. Anthracycline-containing regimens have been shown to be more effective than CMF-like regimens, and have replaced them for the treatment of the majority of these patients [2]. However, since the overall survival was not substantially modified by the use of anthracyclines, the search for new drugs and new strategies has continued to be pursued. The taxanes (docetaxel and paclitaxel) are registered for the use in breast cancer patients relapsing after or refractory to anthracyclines, and are under extensive investigation in combination with anthracyclines as first-line chemotherapy for metastatic disease. Recently, two randomized studies using docetaxel reported stimulating results. One study, carried out in patients who had undergone prior treatment with alkylators, indicated docetaxel to be more active than doxorubicin [3]. The other study compared the association of docetaxel and doxorubicin (AT) to the standard regimen AC (doxorubicin and cyclophosphamide). The AT regimen has been proven to be better than AC in terms of both response rate and time to progression [4]. On these premises, the association of doxorubicin and docetaxel is now under investigation as an adjuvant treatment in early breast cancer patients. In Europe, doxorubicin has for the most part been replaced by epirubicin due to its similar activity and efficacy and associated lower cardiotoxicity [5].

The objective of our study was to verify the highest dose of docetaxel which can be safely associated with active doses of epirubicin. Moreover, we also wanted to explore the usefulness of a hematopoietic growth factor (G-CSF) to further increase the doses of docetaxel whenever neutropenia was the dose-limiting toxicity of this combination. To reach these objectives we needed to make some assumptions before defining the study

design. Because docetaxel is more active than doxorubicin we chose the dose escalation of this drug. Doses of epirubicin of 60 mg/m^2 or lower were less active than doses above 90 mg/m^2 [6]. A clear dose-response relationship for doses of epirubicin above 90 mg/m^2 was not supported by clinical data. Furthermore, no data indicated that 90 mg/m^2 of epirubicin might be better than 75 mg/m^2. Finally, active doses of doxorubicin in polichemotherapy regimens ranged from 50–60 mg/m^2. The activity of epirubicin is equivalent to that of doxorubicin and it has been reported that approximate equitoxic dose ratios of doxorubicin/epirubicin are the following: hematological toxicity 1/1.2, non-hematological toxicity 1/1.5, cardiac toxicity 1/1.8 [7]. On these premises we designed a dose escalation study of docetaxel with two different fixed doses of epirubicin (90 mg/m^2, and 75 mg/m^2, respectively), which we considered the best doses of epirubicin to be used in polichemotherapy regimens in advanced breast cancer on the basis of available clinical data.

Patients and methods

Patient selection

Eligible patients were women aged 18–75 years with documented locally advanced (stage III) or metastatic breast cancer (stage IV), and performance status (PS) ≤ 2 They were required to have adequate bone marrow, renal, hepatic, and cardiac function, defined respectively as: Absolute Neutrophyle Count (ANC) $\geq 2000/\mu l$, Platelet count (PLT) $\geq 100{,}000/\mu l$, and Hemoglobin (Hb) ≥ 10 g/dl, creatinine < 1.6 mg/dl; total bilirubin ≤ 1.5 time the upper-normal limits (UNL) of the Institutional normal values. SGPT and SGOT ≤ 2.5 UNL, and alkaline phosphatase ≤ 5 UNL (unless bone metastases were present in the absence of any liver disorders), left ventricular ejection fraction (LVEF) ≥ 50 as measured by radionuclide angiocardiography (MUGA) or by echocardiography. Prior adjuvant or neoadjuvant chemotherapy was allowed, provided that a cumulative dose of no more than 360 mg/m^2 of epirubicin or 200 mg/m^2 of doxorubicin had been given, and that there had been a therapy-free interval of at least 12 months Criteria for exclusion were any prior therapy with docetaxel or paclitaxel or any prior chemotherapy for metastatic disease. The study was approved by the Protocol Review Committee and Ethical Committee of each participating center. Written informed consent was obtained from all patients before study entry.

Study design and treatment

The study was conducted as a dose escalation study in which the main objective was to determine the DLT and the MTD of docetaxel in combination with two fixed doses of epirubicin, with and without G-CSF. The dose escalation design was planned with three consecutive steps (Table 1).

Docetaxel was always escalated by 10 mg/m^2. During the first step, the starting doses were: epirubicin 90 mg/m^2 i.v. bolus on day 1, followed by docetaxel 60 mg/m^2 i.v., infused over one hour, every three weeks. After the determination of the DLT the study proceeded to the second step to determine the MTD of docetaxel in association with 75 mg/m^2 of epirubicin. The starting dose of docetaxel in the second step was the DLT observed at the first step Since neutropenia and related complications were expected to be the main DLTs, a third step was planned to define the MTD of docetaxel associated with 90 mg/m^2 of epirubicin, with the support of G-CSF. Lenograstim was administered at the dose of 150 μg/day starting 48 hours after completion of chemotherapy, until there was evidence of hematological recovery, i.e., ANC $> 2000/\mu l$ after the nadir. Docetaxel and lenograstim were supplied by Rhone-Poulenc Rorer, Milan, Italy. Patients received a prophylactic medication regimen consisting of oral prednisone 50 mg (or oral methylprednisolone 40 mg) 12, 3 and 1 hour before the administration of docetaxel, and then at 12, 24, 36, and 48 hours post administration.

Table 1. Dose escalation design.

Dose level	Epirubicin (mg/m^2)	Docetaxel (mg/m^2)
First step		
1	90	60
2	90	70
3	90	80
Second step		
3bis	75	80
4bis	75	90
Third step + G-CSF		
5	90	70
6	90	80
7	90	90
8	90	100

At least three patients had to be treated at each dose level. If one patient experienced a DLT at least three additional patients were treated at the same dose level. If an additional patient experienced a DLT, no further dose escalation was allowed and the previous dose level was declared the MTD. At least six patients were treated at dose levels defined as MTD. No intrapatient dose escalation was allowed. At the first cycle of chemotherapy, patients treated in the first two steps were not allowed to receive prophylactic administration of antibiotic or G-CSF. In metastatic patients treatment with docetaxel and epirubicin was planned for a maximum of six cycles, unless there was evidence of progression of disease, unacceptable toxicity, patient refusal or a cumulative dose of epirubicin ≤ 1000 mg/m^2. Patients with stable disease or in response after six cycles continued the treatment at the investigator's discretion.

Toxicity was graded according to the NCI Common Toxicity Criteria. Hematological toxicity was recorded at nadir. DLT was defined as the occurrence of one of the following toxicities during the first cycle of chemotherapy. Hematological toxicity. ANC $< 500/\mu l$ for > 7 days or $< 100/\mu l$ for > 3 days; febrile neutropenia (ANC $< 500/\mu l$ and fever ≥ 38.5 °C (single evaluation) or fever > 38 °C in two evaluations lasting 12 hours each); PLT $< 25{,}000/\mu l$ for > 7 days or with bleeding requiring PLT transfusion; infection of grade ≥ 3. Non-hematological toxicity: any grade 3–4, excluding alopecia, grade 4 vomiting, neurologic (grade 2 or more). Any other toxicity persisting on day 28 that did not allow the administration of chemotherapy was considered a DLT

Study parameters

Before starting therapy, all patients underwent history, physical examination with weight and height measurement, evaluation of performance status, complete blood cell count (CBC) with white blood cells (WBC) differential, biochemical tests including alkaline phosphatase, LDH, SGOT, SGPT, bilirubin, serum creatinine, and creatinine clearance, electrolytes, calcium, total protein, albumin, glucose, uric acid, urea, urinalysis ECG, chest X-rays, LVEF measured by MUGA scan or by echocardiography, abdominal ultrasound or CT scan, bone scan with bone X-rays of the hot spots were also required. Other examinations were performed if clinically indicated. Prior to each cycle, biochemistry, CBC, evaluation of toxicity, and tumor evaluation by physical examination were done. At each cycle CBC was performed twice a week, every day in the case of ANC $< 500/\mu l$. Every other cycle, instrumental tumor measurement and evaluation of response were performed. Although response was not the primary objective in this study, standard criteria were used for determination of response [8].

Pharmacokinetic design and calculation

The elimination from plasma of docetaxel was investigated in patients receiving docetaxel 80 mg/m^2 as one-hour infusion together with epirubicin given as an i.v bolus, either at the dose of 90 mg/m^2 or at the dose of 75 mg/m^2, during the first cycle of chemotherapy. Some patients underwent another evaluation at the second cycle of chemotherapy. Heparinized venous blood samples were obtained before docetaxel administration, at 15, 45 and 60 minutes during the one-hour infusion, and at 15, 30, 60 minutes, 2, 3, 5 and 23 hours thereafter. Blood samples were immediately centrifuged at room temperature and the plasma was separated and stored in aliquots at −20 °C until analysis. Docetaxel was measured by high-performance liquid chromatography using a method previously described for paclitaxel assay [9]. The method was validated in our laboratory for docetaxel plasma analysis. Three calibration curves, each constructed daily by triplicate chromatographic analyses of eight docetaxel standard points ranging from 2000 ng/ml to 8 ng/ml, were executed on different days. The recovery of docetaxel ranged from 85% to 90% and linear regression analysis between docetaxel standard concentrations and chromatographic responses provided a good linearity ($r^2 > 0.999$). Within- and between-day accuracy and precision evaluated as Relative Mean Error (RME%) and Coefficient of Variation (CV%), respectively, were always lower than 10%. The lower limit of quantification, evaluated according to Shah et al. [10] was 15 ng/ml. Chromatographic analyses of six different plasma samples obtained from healthy subjects showed no interfering substance near the elution zone of docetaxel. Pharmacokinetic data of docetaxel were obtained by noncompartmental analysis (statistical moment theory) [11]. Maximum peak plasma concentration (C_{max}) was put on par with the mean concentration in the plasma samples after drug administration. Area under the concentration-time curves (AUC_{0-24h}) were calculated by trapezoidal rule using data to 24 hours. Apparent clearances (CL) were calculated by dividing the dose administered by AUC_{0-24h}. The terminal half-lives were calculated by dividing ln(2) by the slope of the terminal exponential phase Data were expressed as mean ± standard deviation. Statistical analysis of pharmacokinetic data between the two groups of patients was performed by using Student's *t*-test Statistical significance was determined to be $P < 0.05$.

Results

A total of 58 women entered the study. Their main characteristics are shown in Table 2. All but two patients had a performance status of 0. Twenty-one (36%) patients were premenopausal. Thirty-five patients had a stage III disease, and received ET chemotherapy as a neoadjuvant therapy. Thereafter, they all underwent radical surgery, adjuvant chemotherapy, and finally loco-regional radiotherapy.

Overall 299 cycles of chemotherapy were given with a median of five cycles (range 1–8) per patient. Fifty-three patients received at least four cycles of chemotherapy. Twenty-eight patients received at least six cycles of chemotherapy. Eighteen patients with locally advanced disease completed at least four or five cycles of chemotherapy, and then underwent breast surgery. In the remaining 12 patients, reasons for the interruption of chemotherapy before the sixth cycle were, respectively: two patients (level 3bis, and 4bis, respectively) decided to shift to high-dose chemotherapy after a partial response obtained after the third cycle of chemotherapy; five patients due to toxicity (two asymptomatic cardiotoxicity after 4 cycles, one grade 3 fluid retention at the fifth cycle, one grade 3 sensorial neuropathy at the fourth cycle, and one allergic reaction to docetaxel at cycle 2); two toxic deaths (at the first cycle of chemotherapy at the level 2; and at the second cycle at the level 5); one progression of the disease at the fourth cycle; one refusal to continue after the fifth cycle; one patient because of difficulties with venous access after five cycles of chemotherapy.

Table 2 Patient characteristics.

	No. of patients (%)
Total number of patients	58 (100)
Median age (years)	55
Range	26–71
Stage	
III	35 (60)
IV	23 (40)
Dominant mestatatic site (23 patients)	
Visceral	13 (57)
Bone	3 (13)
Soft tissue	7 (30)
Prior adjuvant therapy (23 patients)	
None	6 (26)
Chemotherapy	11 (48)
Hormonal therapy	2 (9)
both	4 (17)
Prior endocrine therapy for metastatic disease	7 (30)

Evaluation of dose limiting toxicity

As planned three different MTDs of docetaxel in combination with 90 and 75 mg/m^2 of epirubicin without G-CSF, and in combination with 90 mg/m^2 of epirubicin with the support of G-CSF were defined (Table 3).

The first step. No patient had a DLT at the first dose level. The first three patients treated at the second dose level had no DLT. At the third dose level, all the four treated patients had a DLT: two febrile neutropenia, one grade 3 cutaneous reaction, and one ANC < 100 lasting for five days. Therefore, four additional patients were treated at the previous dose level (the second). However, all these four patients experienced a DLT (one toxic death, two febrile neutropenia, and one long lasting neutropenia). Overall, at the second dose level four out of seven patients suffered from a DLT. As a consequence, this dose level could not be declared the MTD, according to the protocol definition. The MTD was thus the first dose level: epirubicin 90 mg/m^2 and docetaxel 60 mg/m^2.

The second step. The starting dose level was epirubicin 75 mg/m^2, and docetaxel 80 mg/m^2. Three patients were treated at the dose level 3bis without any remarkable toxicity. Two of three patients treated at the upper dose level (4bis) had febrile neutropenia as a DLT. Ten additional patients were enrolled at the dose level 3bis. Only 2 out of 13 patients had a DLT: a grade 3 mucositis, and a neutropenia < 100 lasting for four days. Therefore, this dose level (epirubicin 75 mg/m^2, and docetaxel 80 mg/m^2) was declared MTD. Overall, 69 cycles were

Table 3. Dose-limiting toxicities and ANC nadir.

Dose level	No of patients	DLTs (other than hematologic)	Febrile neutropenia	ANC < 100 lasting > 3 days	Mean (± SD) ANC nadir	Day of ANC nadir (mode)
No G-CSF						
1 (E_{90} T_{60})	6	–	–	–	224 (± 248)	11
2 (E_{90} T_{70})	7	1 Toxic death	2	1	114 (± 117)	9
3 (E_{90} T_{80})	4	1 (G3 skin)	2	1	90 (± 51)	8
3bis (E_{75} T_{80})	13	1 (G3 mucositis)	–	1	200 (± 184)	10
4bis (E_{75} T_{90})	3	–	2	–	108 (± 78)	10
With G-CSF						
5 (E_{90} T_{70})	7		–		647 (± 921)	7
6 (E_{90} T_{80})	6		1		553 (± 262)	8
7 (E_{90} T_{90})	6		-		775 (± 917)	7
8 (E_{90} T_{100})	6	1 (G3 myalgia)	1		679 (± 323)	7

Table 4. Hematological toxicity by cycles.

Dose level	Total no of cycles	Febrile neutro-penia (%)	WBC (%)			ANC (%)			Platelets (%)			Hemoglobin (%)		
			2	3	4	2	3	4	2	3	4	2	3	4
No G-CSF														
1 (E_{90} T_{60})	37	5	14	54	24	3	19	73	–	–	–	11	–	–
2 (E_{90} T_{70})	35	14	14	51	26	6	14	54	–	3	–	34	11	–
3 (E_{90} T_{80})	21	19	10	33	57	–	19	62	5	24	–	62	14	–
3bis (E_{75} T_{80})	69	1	22	61	7	6	12	77	3	1	–	26	1	–
4bis (E_{75} T_{90})	14	14	7	43	50	–	7	79	–	–	7	14	–	–
With G-CSF														
5 (E_{90} T_{70})	35	3	26	17	20	11	20	29	11	–	–	40	–	–
6 (E_{90} T_{80})	29	7	28	38	3	14	38	21	–	–	–	10	–	–
7 (E_{90} T_{90})	32	–	44	41	–	16	22	34	–	–	-	38	–	–
8 (E_{90} T_{100})	27	4	22	44	4	–	22	41	4	11	7	26	–	–

given to these 13 patients, with a median of five cycles (range 3–8) per patient. All but one patient received the planned full doses of chemotherapy. Only one patient stopped therapy due to toxicity after five cycles (fluid retention, with a weight gain > 20%). Because of grade 3 mucositis at the 1st cycle, one patient reduced the doses of both drugs by 15%. The majority of cycles, 64 of 69 (93%) were given without any delay. Among the five delayed cycles only two recognized toxicity as the main cause, one delayed ANC recovery (11 days) and an episode of a transient fall in LVEF. Only 3% of cycles (2 of 69) were given with the support of G-CSF.

Overall, among the first 33 patients treated without the use of a G-CSF we observed 12 DLTs. Two non-hematological toxicities (skin reaction, mucositis), one toxic death, and nine hematological toxicities (three long-lasting neutropenia, and six febrile neutropenia). Since mielotoxicity was the most common cause of DLT, the study went on to the third step.

The third step. Patients were treated with the support of the prophylactic use of a hematopoietic growth factor. At level 5 (epirubicin 90 mg/m^2 and docetaxel 70 mg/m^2) no DLT was observed in seven treated patients. At level 6, one out of six patients had febrile neutropenia. At level 8, six patients were treated and two had a DLT: one febrile neutropenia, and one grade 3 myalgia. Therefore, level 7 (epirubicin 90 mg/m^{2}and docetaxel 90 mg/m^2, day 1, plus G-CSF 5 μg/kg starting on the day 2), at which no DLT was observed in six treated patients, was the recommended dose with the use of the G-CSF. At the latter dose level, four patients received at least six cycles of chemotherapy, and the other two patients underwent breast surgery after four cycles. Over 32 given cycles, no dose reduction occurred, and only one patient had a five day delay of one course of chemotherapy, because of further laboratory investigations.

Regardless of dose levels, 123 cycles were given with G-CSF support with a median of five cycles (range 2–6) per patient. Full doses of chemotherapy were given in more than 90% of cycles (114 of 123), and treatment delay for more than three days occurred in 7% of cycles (9 of 123).

As planned three different recommended doses were identified:

- epirubicin 90 mg/m^{2}and docetaxel 60 mg/m^2
- epirubicin 90 mg/m^{2}and docetaxel 90 mg/m^2 plus G-CSF
- epirubicin 75 mg/m^{2}and docetaxel 80 mg/m^2

Hematological toxicity

Hematological toxicity was evaluated at nadir (Table 4). Thrombocytopenia was rarely reported, and no significant correlation with any dose level was observed. Only

three episodes of grade 4 thrombocytopenia were observed through 229 cycles. Grade 4 anemia was never detected, and only four patients had grade 3 anemia. Grade 2 anemia (Hb < 10 g/l) was recorded in 13 of 33 (39%) patients in no G-CSF group, and in 13 of 25 (52%) patients in G-CSF group. On the contrary, neutropenia was the most prominent type of toxicity.

Among the group of patients who did not receive G-CSF, at the first cycle all but two patients suffered from grade 4 neutropenia, regardless of the dose level. A direct relationship between dose level and depth of ANC nadir was observed (Table 3). As a consequence, febrile neutropenia was most encountered at higher dose levels. Levels 2, 3, and 4bis were affected by febrile neutropenia in 14% and 19%, and 14% of cycles, respectively. On the other hand, among 13 patients and 69 cycles of chemotherapy given at the third bis dose level only one (1.4%) episode of febrile neutropenia was recorded.

As expected neutropenia was clearly ameliorated by the use of the G-CSF. The mean ANC nadir was constantly above 500, and febrile neutropenia ranged from 3% to 7% (Tables 3 and 4).

Non-hematological toxicity

The majority of non-hematological adverse events were mild to moderate. Severe adverse events were rare and there were no grade 4 toxicities. Most frequent adverse events, occurring in at least 5% of cycles, were reported in Figure 1 for dose levels without G-CSF and in Figure 2 for dose levels 5 to 8 (with G-CSF). All patients had grade 3 alopecia. The most relevant non-hematological toxicity, regardless of the grade, was asthenia. It was observed in more than 40% of cycles. However, only one patient suffered from asthenia as a severe toxicity (Figure 2). Nausea, and mucositis were also common toxicities. A slight increase in mucositis was observed in patients treated without G-CSF, compared to patients who received it. Allergic reactions during the infusion of docetaxel were observed in four (1.7%) cycles.

Clinical cardiac toxicity (congestive heart failure – CHF) was never observed. Overall, 176 evaluations of LVEF were done. Only six (3.4%) reported a drop of LVEF to less than 50% The mean value of LVEF remained virtually unaltered along the course of chemotherapy treatment (Figure 3). Two patients (dose levels 1 and 2) stopped therapy after four cycles of chemotherapy because of a transient decrease of LVEF to less than 50%. Four episodes of asymptomatic supraventricular arrhythmia were observed.

Activity

Almost all patients had measurable disease and they all were evaluated based on an intention to treat analysis. Overall, 42 patients (73%) responded to chemotherapy. LABC patients obtained 6% of complete responses (2 of 35) and 74% (26 of 35) of partial responses, with an overall objective response rate of 80% (95% confidence interval (CI): 63%–91%). Among 23 metastatic patients, 9% complete responses (2 of 23) and 52% partial responses (12 of 23) were observed. The overall response rate in metastatic patients was 61% (95% CI: 39%–80%). Detailed results separated by dose levels are reported in Table 5.

Pharmacokinetics

The pharmacokinetics of docetaxel 80 mg/m^2 associated with epirubicin 90 mg/m^2 were evaluated at the first cycle of chemotherapy in one patient and at the first and second cycle of chemotherapy in two patients. The pharmacokinetics of docetaxel 80 mg/m^2 associated with epirubicin 75 mg/m^2 were evaluated at the first and second cycle of chemotherapy in five patients. Overall, five and ten pharmacokinetics of docetaxel were then analysed. Mean plasma concentration-time curves and pharmacokinetic parameters of docetaxel are shown in Figure 4. No statistically significant effect of the two doses of epirubicin (90 mg/m^2 and 75 mg/m^2, respectively) in docetaxel pharmacokinetic was observed (upper panel in Figure 4). Mean docetaxel Cmax was 2.7 ± 1.5 μg/ml in patients who received epirubicin 90 mg/m^2 and 2.1 ± 0.8 μg/ml in patients who received epirubicin 75 mg/m^2 ($P = 0.431$). AUC_{0-24h} of docetaxel were 2.7 ± 1.0 (μg/ml)*h in patients who received epirubicin 90 mg/m^2 and 2.7 ± 0.7 (μg/ml)*h in patients who received epirubicin 75 mg/m^2 ($P = 0.981$).

Discussion

The present study indicates that docetaxel can be safely and effectively combined with active doses of epirubicin as first line chemotherapy in patients with locally advanced or metastatic breast cancer.

As expected, neutropenia was the most common adverse event in patients who did not receive prophylactic administration of G-CSF. Grade 4 neutropenia occurred in the majority of the cycles (69%), with no significant difference in the incidence among the five dose-levels. However, by analyzing results in terms of depth of neutropenia, instead of grade of toxicity, a remarkable difference among the five dose levels (from 1 to 4 bis) was observed (Table 4): the higher the dose of epirubicin and docetaxel the higher the depth of neutropenia. Indeed, this directly affected the incidence of febrile neutropenia. Only 5% and 1% of febrile neutropenia was recorded at the dose levels 1 and 3bis, respectively. On the contrary, at the other dose levels (2, 3, 4bis) more than 14% episodes of neutropenic fever were observed. At the first MTD identified (epirubicin 90 mg/m^2 and docetaxel 60 mg/m^2) no DLT occurred. However, increase of the doses of Docetaxel led to an unacceptable toxicity. At 70 mg/m^2 four DLTs (one toxic death, one long-lasting neutropenia, and two febrile neutropenias), were observed. Similarly, at 80 mg/m^2 all

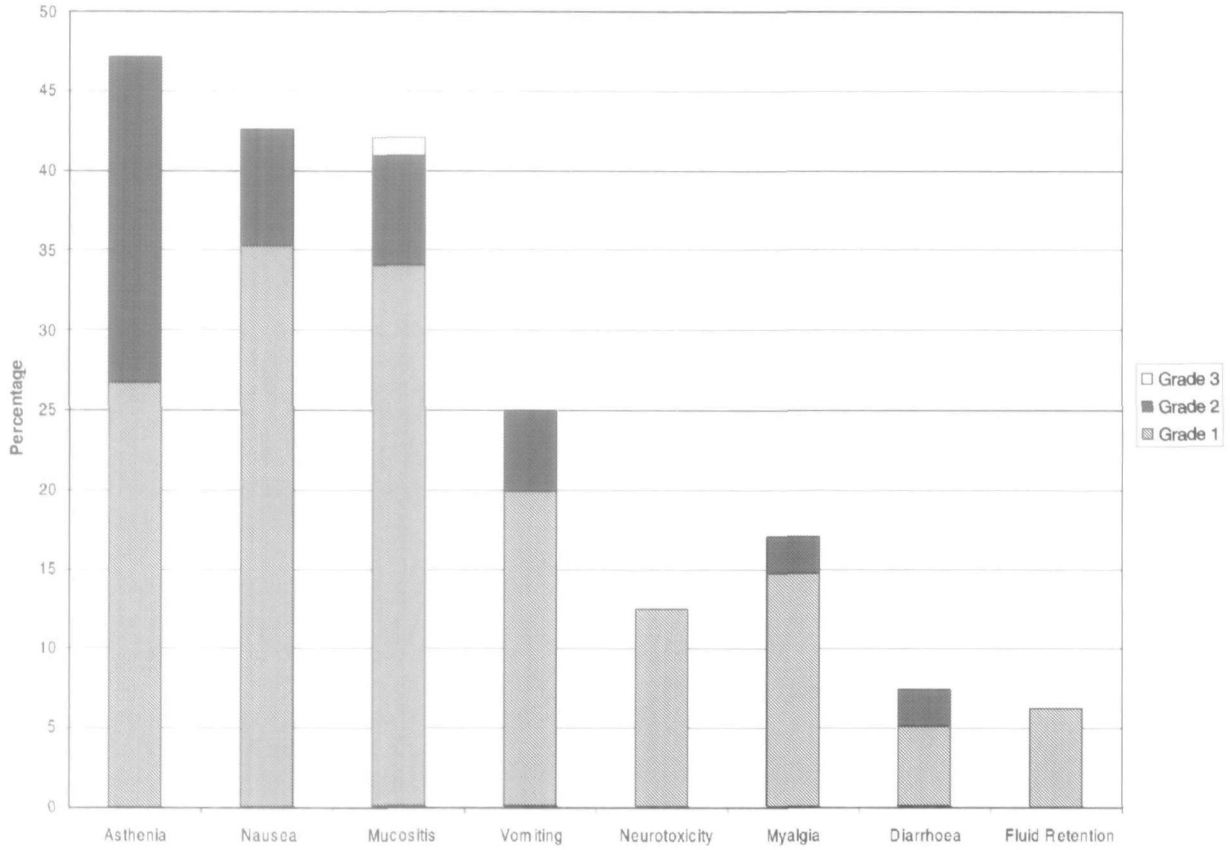

Figure 1. Most frequent (>5%) non-hematologic adverse events. Steps without G-CSF.

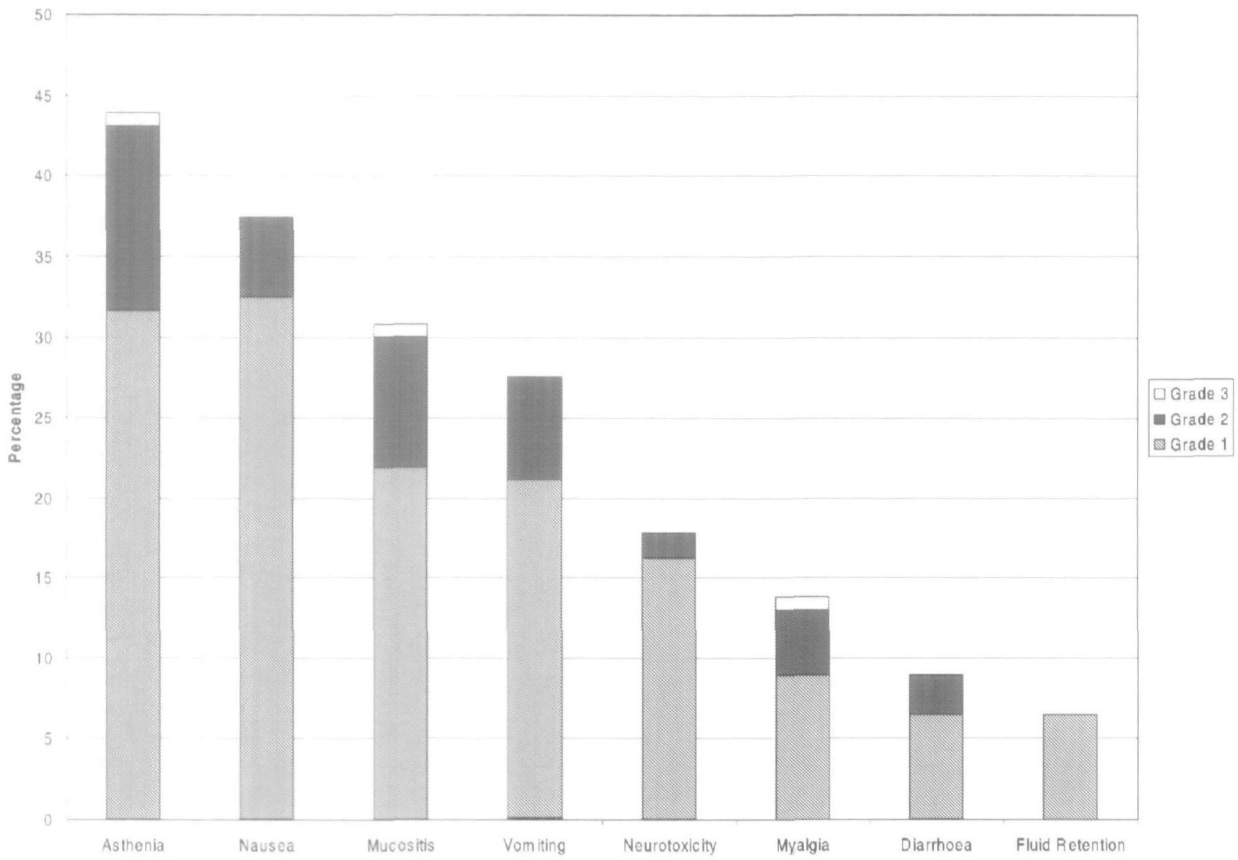

Figure 2. Most frequent (>5%) non-hematologic adverse events. Steps with G-CSF.

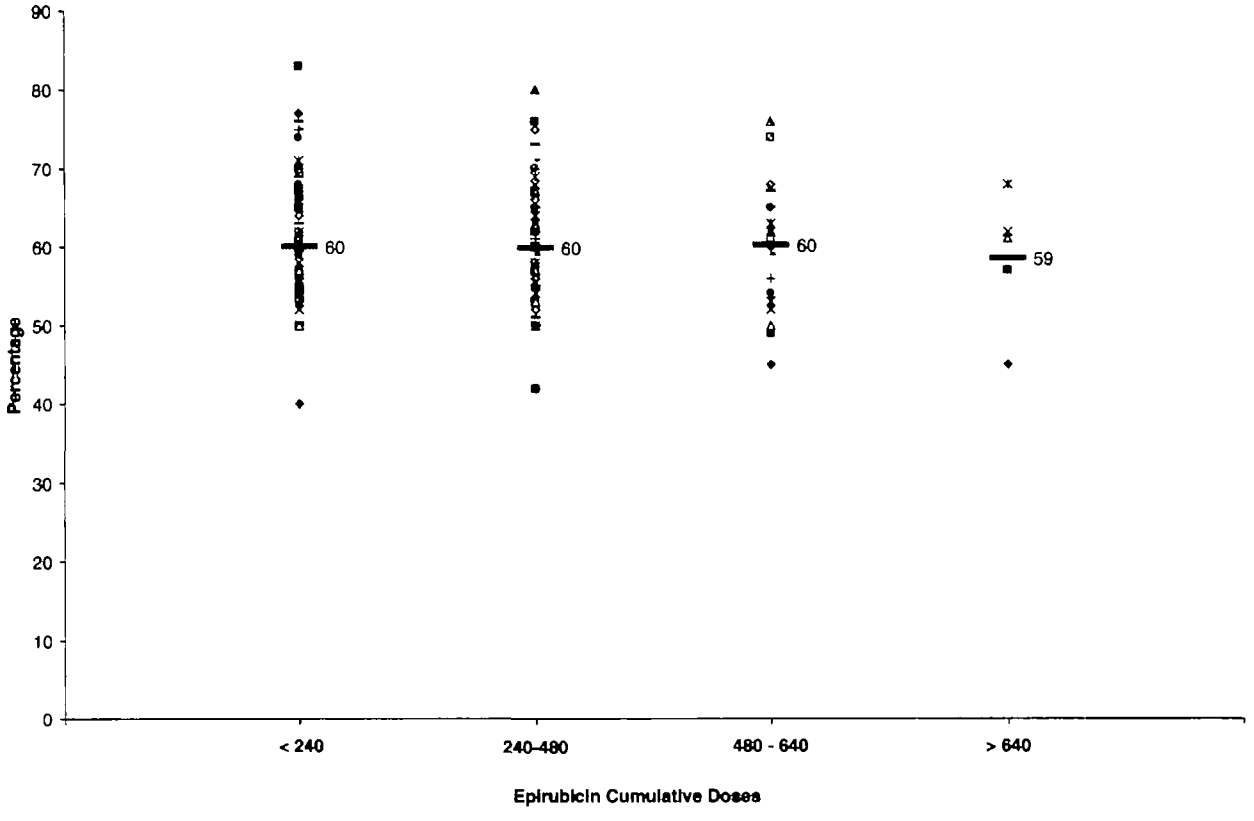

Figure 3. LVEF by MUGA throughout treatment Mean values of LVEF are reported as a line —. Doses of epirubicin are expressed in mg/m^2.

Docetaxel pharmacokinetic parameters

Pharmacokinetic parameter	Treatment: Docetaxel 80 mg/m^2 Epirubicin 90 mg/m^2	Treatment: Docetaxel 80 mg/m^2 Epirubicin 75 mg/m^2	P
C_{max}, µg/mL	2.7±1.5*	2.1±0.8	.431
Terminal half-life, hours	12.3±3.3	13.1±4.4	.691
$AUC_{0\text{-}24h}$, (µg/mL)•h	2.7±1.0	2.7±0.7	.981
CL, L/h/m2	33.8±14.7	31.1±7.3	.718

*Values expressed as mean±SD

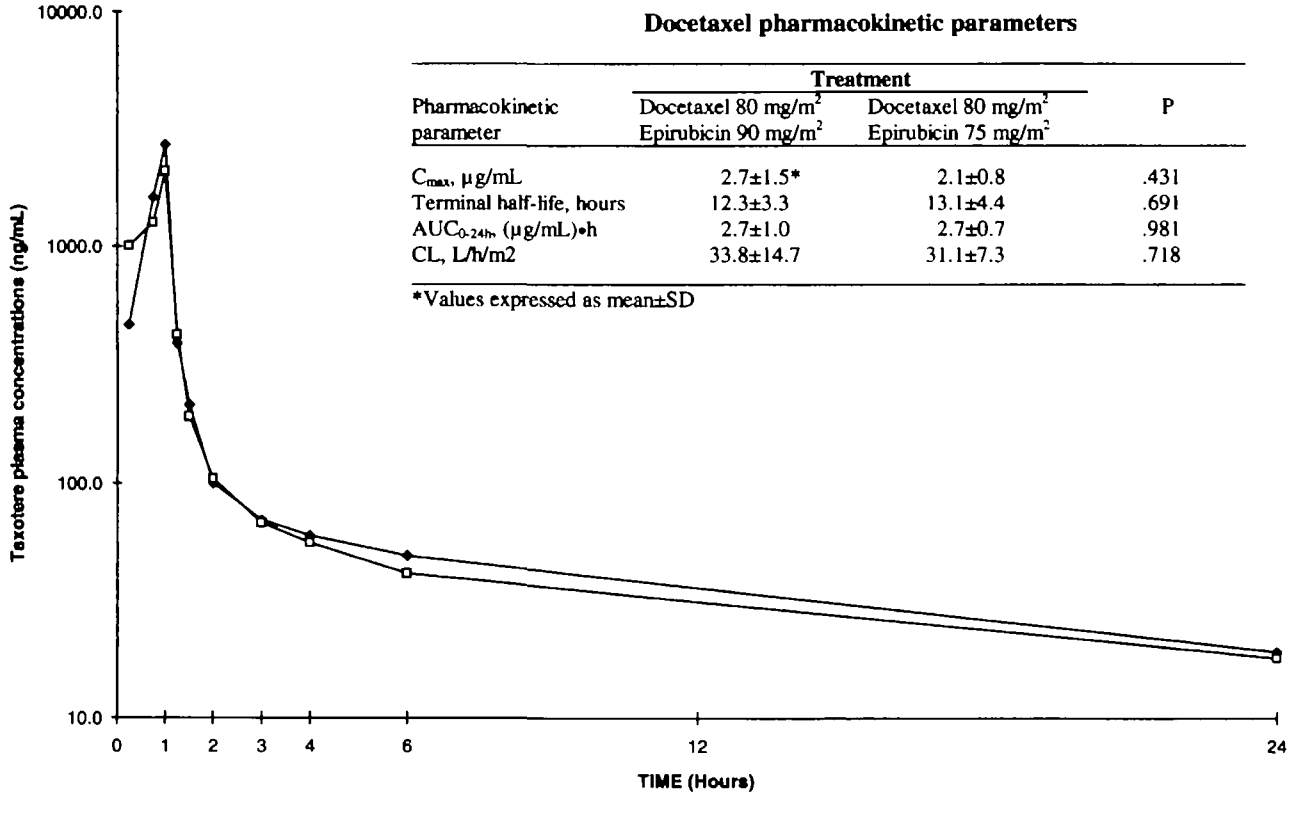

Figure 4. Docetaxel plasma concentration following epirubibin at 75 mg/m^2 (□) or 90 mg/m^2 (◆).

the patients experienced a DLT: one grade 3 skin toxicity, one long-lasting neutropenia, and two febrile neutropenias. The results of our study clearly indicate that the administration of doses of docetaxel >60 mg/m^2 in combination with epirubicin at 90 mg/m^2 requires G-CSF support. The second MTD was identified at a dose of epirubicin 75 mg/m^2 and docetaxel 80 mg/m^2. At these doses, only two out of 13 patients experienced a DLT. The median number of cycles administered was five (range 3–8); dose-reduction was required in only one patient and 93% of the cycles were given without any delay. Febrile neutropenia was reported in 1% of cycles.

This is similar to results of other studies in which the combination of docetaxel and epirubicin, as first-line treatment in advanced breast cancer, was investigated. In these trials, the recommended doses, without G-CSF, were: epirubicin 60 mg/m^2 plus docetaxel 75 mg/m^2 [12] and epirubicin 60 mg/m^2 plus docetaxel 80 mg/m^2 [13]. In the latter study, it was also reported that higher doses (epirubicin 70 mg/m^2 plus docetaxel 90 mg/m^2) could be given whenever drugs were given on two consecutive days. However, at these doses 24% febrile neutropenia was observed [14]. The reduced incidence of febrile neutropenia by using lower doses of docetaxel was also recently confirmed. It occurred in 7% of cycles when both epirubicin and docetaxel were given at 75 mg/m^2 [15]. Conversely, this is in contrast with the results of two other trials in which epirubicin 90 mg/m^2 plus docetaxel 75 mg/m^2 could be given without G-CSF support [16, 17]. The German study was reported only in abstract form. The incidence of febrile neutropenia, dose reduction, and use of G-CSF were not reported. The other study was recently updated [18]. The reported incidence of febrile neutropenia was around 12%. However, G-CSF was required in more than 40% of cycles, and the actual incidence of febrile neutropenia in cycles not supported by G-CSF was as high as 24%. Finally, the median number of cycles administered was only four. Thus these data do not support the routine use of epirubicin and docetaxel at the above indicated doses without G-CSF.

Overall, all these studies reported neutropenia and neutropenic fever as the main dose-limiting events. In our study the addition of G-CSF allowed higher doses of both drugs without worsening the hematological toxicity. Chemotherapy was well tolerated among the patients who received G-CSF. Grade 4 neutropenia occurred in 31% of the cycles, and was complicated by fever in only 3% of the cycles. Dose reductions were seldom required. Pagani et al. reached the MTD with routine G-CSF support at the dose level of epirubicin 120 mg/m^2 plus docetaxel 85 mg/m^2, with six out of nine patients experiencing a hematological DLT. The recommended dose was epirubicin 120 mg/m^2 plus docetaxel 85 mg/m^2. In our study, two patients experienced a DLT (febrile neutropenia, grade 3 myalgia) at level eight (epirubicin 90 mg/m^2 plus docetaxel 100 mg/m^2). Epirubicin and docetaxel can then be given safely with G-CSF support, both at the recommended dose of 90 mg/m^2 (seventh level).

Apart from hematological toxicity, our trial showed that the combination was generally well tolerated. No grade 4 adverse events were observed, and the adverse events in the majority of the cases were mild or moderate. Only three patients experienced grade 3 mucositis, one patient developed grade 3 skin reaction, and one patient treated at level 8 with G-CSF developed grade 3 myalgia. Only 7 out of 58 patients discontinued treatment before six cycles due to toxicities. Two patients died due to treatment-related complications. Both patients were treated with 90 mg/m^2 of epirubicin. One death occurred in a patient who presented with severe abdominal pain and diarrhoea. This may be related to the fact that docetaxel as a single agent or in combination has been reported to result in an inflammatory bowel syndrome, with acute abdominal pain possibly associated with neutropenia, fever, diarrhoea, oral mucositis or a combination of these symptoms, with the possibility of pancolitis and the potential for an abdominal catastrophe [19]. The second one developed febrile neutropenia and died at home, probably of septicaemia.

Concerns have been raised about cardiac toxicity observed with the use of taxanes with anthracyclines combination. By using paclitaxel plus doxorubicin, some authors reported an incidence rate of CHF of approximately 20% [20, 21]. However, limiting the cumulative doses of doxorubicin to 360–380 mg/m^2 led to a decreased incidence of CHF. Due to its lesser cardiotoxicity, epirubicin has replaced doxorubicin in recent clinical trials. Actually, the incidence of CHF was lower than that reported with doxorubicin and paclitaxel, but still present. A 6% incidence of CHF was observed [22, 23]. At the cumulative dose of anthracycline delivered in our study (median 450 mg/m^2, range 90–720), the association of epirubicin and docetaxel had a very low cardiotoxicity potential. No episode of CHF was observed, and only two patients showed a decline of LVEF to less than 50%. The different cardiotoxicity profile of the association of anthracyclines and either paclitaxel or docetaxel, may be in part explained by different pharmacokinetic behaviors. The interaction between doxorubicin and paclitaxel, leading to an increased bioavailability of both doxorubicin and its metabolite doxorubicinol, offers an explanation for the increased cardiotoxicity [24]. Docetaxel, on the other hand, has been found to have no effect on the pharmacokinetics of doxorubicin when it is given as a one-hour infusion at either 1 hour or 15 minutes after an injection of doxorubicin [25, 26]. On the contrary, doxorubicin seemed to have some influence on the pharmacokinetics of docetaxel. It was reported that AUC of docetaxel significantly increased when its infusion was preceded by the administration of doxorubicin [27]. Pharmacokinetic interaction between docetaxel and epirubicin was also investigated without showing any pharmacokinetic interaction between the parent compound epirubicin [28]. In the present study, we explored the pharmaco-

kinetics of docetaxel in patients exposed to two different doses of epirubicin. Increasing the doses of epirubicin by 20%, from 75 mg/m^2 to 90 mg/m^2, did not significantly influence any pharmacokinetic parameter of docetaxel. However, while our data can exclude a dose-dependent effect of epirubicin on the pharmacokinetics of docetaxel, because of the lack of a control group treated with docetaxel alone, we cannot rule out an effect of epirubicin on pharmacokinetic parameters of docetaxel, as a whole.

As planned three different recommended doses were identified: epirubicin 90 mg/m^2 and docetaxel 60 mg/m^2, epirubicin 90 mg/m^2 and docetaxel 90 mg/m^2 plus G-CSF, epirubicin 75 mg/m^2 and docetaxel 80 mg/m^2. Although this dose-finding study was not designed to select the best dose to be recommended among the three MTDs identified, we think that our level 3-bis (epirubicin 75 mg/m^2, docetaxel 80 mg/m^2) may be chosen for further studies. At these doses the combination was well tolerated, and the majority of patients received full doses of chemotherapy. G-CSF support was required in only 3% of cycles. Some may argue that the dosage of epirubicin we recommend is low; however, there is no clear evidence of increased activity of epirubicin at 90 mg/m^2 as compared to 75 mg/m^2, whereas the activity of docetaxel increases at doses above 60 mg/m^2. In our study, increasing the doses of epirubicin did not lead to a significant difference in response rate, nor in pharmacokinetic parameters of docetaxel that may be associated with activity (Cmax, AUC). As a corollary, at the dose level that we recommended 12 out of 13 patients responded to the therapy. Eventually, 75 mg/m^2 of epirubicin more or less corresponds to 50 mg/m^2 of doxorubicin. At this dose the combination of doxorubicin and docetaxel has been proven to be more active than the standard regimen AC (doxorubicin and cyclophosphamide). In conclusion, the combination of epirubicin and docetaxel at the recommended doses indicated by our study warrants further exploration in phase III studies.

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