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Original article

Dose-finding study of epidoxorubicin and docetaxel as first-line chemotherapy in patients with advanced breast cancer

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Summary

Background: Anthracyclines and taxanes are the most active drugs against breast cancer and the search after their optimal combination is under intensive investigation in both the advanced and early disease settings. A dose-finding study of epidoxorubicin (E) and docetaxel (D) was conducted in advanced breast cancer (ABC) to define the maximum tolerated dose (MTD) of the combination with and without granulocyte colony-stimulating factor (G-CSF) support and to characterise its toxicity and activity profile.

Patients and methods: Forty-two patients who received neither palliative chemotherapy nor adjuvant anthracyclines (55% with dominant visceral disease and 66% with ≥ 2 sites involved) with measurable/evaluable lesions, were treated at four dose levels starting from E 75 mg/m^2 and D 75 mg/m^2 to E 120 mg/m^2 and D 85 mg/m^2. A maximum of four cycles of the combination was given every three weeks and four additional cycles of single agent D were allowed in responding patients. Cardiac function was monitored at baseline and at every second course by echocardiography.

Results: Febrile neutropenia (two patients) and prolonged, severe neutropenia (absolute neutrophil count (ANC) $< 0.1 \times 10^9$/l for more than three days; one patient) defined the MTD of the combination without G-CSF support at E 90 mg/m^2 and D 75 mg/m^2. G-CSF was then routinely administered from the subsequent dose level of E 120 mg/m^2 and D 75 mg/m^2. The MTD with G-CSF support was established at E 120 mg/m^2 and D 85 mg/m^2 (one patient with neutropenic fever together with failure of ANC recovery at day 21, three patients with ANC less than 0.1×10^9/l for more than three days, one patient with both and one patient with grade 4 thrombocytopenia and toxic death from typhlitis while neutropenic). No severe neurotoxicity, mucositis, or fluid retention were observed and there were no clinical signs of cardiotoxicity. Antitumour activity was not a primary endpoint of the study: the overall response rate (ORR) in 40 evaluable patients was 60% (95% confidence interval: 43%–75%, 58% in liver disease, 84% in soft tissue) with no apparent dose-related effect. After a median follow-up of 19 months (range 2–30+), the overall time to progression (TTP) in nine patients without maintenance hormonal therapy was five months.

Conclusions: The combination of E and D proved to be an effective and safe regimen in poor- prognosis patients with ABC. G-CSF support allowed higher doses to be delivered safely but dose escalation did not translate into improved response rates (RR). The MTD without growth factors support was used, in a phase II trial, which also included patients with previous anthracycline-containing adjuvant regimens.

Key words: advanced breast cancer, docetaxel, epidoxorubicin, G-CSF

Introduction

Anthracyclines are among the most active of the first-line drugs in advanced breast cancer (ABC), achieving objective response rates (ORR) of 40%–50% when used as single agents [1] and of up to 70% in combination regimens [2]. In anthracycline-based combinations, doxorubicin (DOX), the most commonly used of these compounds, can be replaced by epirubicin (E) without loss of efficacy [3, 4] and with decreased cardiotoxicity [5].

Nonetheless, the anthracycline-based regimens have not dramatically changed the overall survival of these patients, because of the low complete remission (CR) rate (5%–15%) and the short duration of responses.

Single agent docetaxel (D) has demonstrated high activity as first-line therapy in ABC: with ORRs of 54% to 68% this drug appears to be at least as effective as standard combination therapies [6–9]. Moreover, the ORR of 41% reported in patients with anthracycline-resistant disease [10] is the highest yet seen with a single agent. A recent randomised phase III trial showed also an improved overall survival (11.4 vs. 8.7 months, $P = 0.0097$) as compared to the combination of mitomycin C and vinblastine in patients with metastatic disease who have previously failed an anthracycline-containing regimen [11]. Although both D and the anthracyclines are substrates for MDR-related efflux mechanisms, the differences in their mechanisms of action (microtubular as-

sembly disturbance vs. topoisomerase II inhibition) might explain these results. The 100 mg/m^2 recommended dose of D might be more active than 75 mg/m^2; the apparent dose-response relationship is being investigated prospectively in an ongoing multicenter, randomised trial of D 100 mg/m^2 vs. 75 mg/m^2 as first- or second-line therapy in ABC [7].

Several trials on the combination of paclitaxel (P) (given by $\geqslant$ 24-hour infusion) with DOX (given by bolus or by prolonged infusion) in ABC suggested a sequence-dependent tolerability, with higher MTDs when DOX was administered before P than with the opposite schedule [12–14]. PK analysis showed that, when P was given before DOX, the elimination phase of DOX was prolonged and the maximum concentration and the area under the concentration-time curve (AUC) were increased [15]. This observation was not confirmed by Gianni et coworkers who found a PK interference between P (given over three hours) and DOX, with increased plasma concentrations of DOX and its metabolite doxorubicinol, with both sequences of administration [16]. On the contrary, P seems to be associated with an increased urinary excretion of E, the pharmacodynamic relevance of which is currently under investigation [17]. The available clinical data indicate so far that the sequence DOX and P is the one associated with the best tolerability.

As a result of the high antitumour activity and toxicity profile reported with P and DOX [12–14, 18–21] with 20% congestive heart failure (CHF) after cumulative doses of DOX $>$ 360 mg/m^2 [19], a phase I–II trial in 42 patients with D and DOX as first-line chemotherapy in ABC was designed and conducted by Dieras et al. [22]. The MTD was reached at DOX 50 mg/m^2 and D 85 mg/m^2 with sepsis as the dose-limiting toxicity (DLT). Antitumour activity was seen at all dose levels with an ORR of 81% and an objective RR of 83% in patients with liver involvement. The recommended doses, without G-CSF support, were DOX 50 mg/m^2 and D 75 mg/m^2, or 60 mg/m^2 of both drugs. No cases of CHF or significant decrease in left-ventricular ejection fraction (LVEF) were observed at a median cumulative dose of DOX of 392 mg/m^2.

As a consequence of an almost two-fold faster elimination and, thus, a 40% smaller area under the curve than equimolar doses of DOX, E might be given at higher doses. In fact, the MTD was established at 180–150 mg/m^2 in untreated and previously treated patients respectively [23, 24] and in several phase II trials E could be safely administered as single agent at doses ranging from 120 mg/m^2 to 150 mg/m^2 every three weeks [25].

Three randomised trials in ABC showed that higher doses of E, either alone or in combination, induced a significantly greater RR, suggesting a clinically relevant dose threshold for E ($\geqslant$ 90 mg/m^2) [26–28].

The combining of P with E has been motivated primarily by the potential for decreasing the cardiac toxicity observed after high cumulative doses of DOX in combination with P [19]. These trials have thus far shown good cardiac tolerability and significant antitumour activity, the latter being somewhat lower than that reported with the equitoxic combination with DOX [29–31].

The International Breast Cancer Study Group (IBCSG) conducted a dose-finding phase I trial of E and D as first-line therapy in ABC. The primary aim of the study was determine the MTDs of the combination given every three weeks with and without G-CSF support. Secondary aims were the evaluation of the toxicity profile and of the antitumour activity of the combination.

Patients and methods

Patients with histologically or cytologically documented metastatic or locally advanced breast cancer who had received no prior chemotherapy for metastatic disease were eligible. Neoadjuvant chemotherapy completed at least six months prior to study entry and not containing anthracyclines was allowed. Prior hormonal therapy for advanced disease was allowed. Criteria for inclusion were as follows: adequate hematologic (ANC $\geqslant 2.0 \times 10^9$/l, platelet count $\geqslant 100 \times 10^9$/l) renal, hepatic (liver function tests currently recommended for treatment with docetaxel) [32] (and cardiac function (LVEF $\geqslant$ 50% by echocardiography), measurable or evaluable disease, written informed consent.

Baseline evaluation was performed within four weeks before study entry and included history, physical examination, chest X-ray, complete blood cell count (CBC), biochemistry, electrocardiogram (ECG) and radiological imaging of indicator lesions (CT scan, bone scan and/or bone selected segments). During therapy, CBC was performed at least twice weekly and biochemistry before each cycle. Tumour response of measurable and evaluable sites of disease and cardiac function monitoring (ECG and echocardiography) were repeated after every second course. Treatment was discontinued in case of CHF of any grade and/or of a significant reduction in LVEF ($\geqslant$ 10% associated with a decline to a level $\leqslant$ 50%) confirmed one week later.

Patients were allowed a maximum of four cycles of the combination: four additional cycles of single-agent D at the same dose level were available to those who responded. Response was defined according to WHO criteria [33]. The imaging of all cases was reviewed by an independent radiologist. The duration of response was calculated from first demonstration of response to documented disease progression. TTP was dated from initial treatment to progression, last contact or start of further antitumour therapy. Osteolytic lesions were considered evaluable, but not measurable, while sclerotic metastases were deemed not evaluable.

D (Taxotere) (RP 56976) was supplied by Rhône-Poulenc Rorer as a concentrated sterile solution containing 40 mg/ml = 80 mg/2 ml/vial in polysorbate 80 (Tween Æ 80). The appropriate solvent for the premix solution of D was also supplied as a sterile solution in vials of 6 ml containing ethyl alcohol 95% : water 13 : 87 (W : W).

E (farmorubicin RTU) is supplied in vials containing 10 mg, 20 mg, and 50 mg of epidoxorubicin hydrochloride as a ready to use solution.

E was administered intravenously as a 15-minute infusion followed after one-hour interval by D given as a one-hour infusion on day 1. A three-day prophylactic medication with oral dexamethasone (8 mg) 13 hours, 7 hours and 1 hour before D and then twice daily on days 1 and 2 was routinely administered in combination with oral cimetidine (300 mg) once daily. Prophylactic antiemetic treatment was given according to investigators' routine practice. Prophylactic oral antibiotics were recommended in case of ANC below 0.5 $\times 10^9$/l. Therapy was administered in the outpatient clinic every three weeks, provided the ANC was $\geqslant 2.0 \times 10^9$/l and the platelet count was $\geqslant 100 \times 10^9$/l the day scheduled for retreatment. If recovery had not occurred after a maximum delay of three weeks patients were withdrawn from the study.

The starting dose of E and D was 75 mg/m^2 and was selected on the basis of the data on tolerability of the combination of DOX and D [22].

At least three patients had to be treated at each dose level and if a DLT occurred in one of them during the first cycle, a total of six patients had to be entered at the same dose. Toxicity was recorded according to the NCI Common Toxicity Criteria (CTC). Each cycle was considered fully evaluable for haematological toxicity only in case of at least a twice weekly CBC assessment. DLTs were ANC less than 0.5×10^9/l for more than seven days, ANC less than 0.1×10^9/l for more than three days, febrile neutropenia (ANC $< 0.5 \times 10^9$/l and single elevation in oral temperature to > 38.58 °C during a 24-hour period) [34], grade ≥ 3 mucositis and failure of ANC recovery at day of retreatment.

G-CSF support (150 μg/m^2/day subcutaneously from day 2 to day 19) was initiated in the individual patient at the subsequent cycle in case of DLT and at the next higher dose level if two or more of three patients or three or more of six patients presented a DLT for which the administration of G-CSF was indicated. This dose was defined to be the MTD without G-CSF support.

The MTD with G-CSF support was defined as the one at which, during the first cycle, more than two of three or three of six patients suffered a DLT in spite of receiving G-CSF support or a DLT for which G-CSF was not indicated, ie grade 4 thrombocytopenia, grade ≥ 3 nonhematologic toxicity (except for alopecia and nausea and vomiting) or persistence of grade ≥ 2 nonhematologic toxicity at scheduled retreatment. The recommended phase II dose was defined as the MTD without G-CSF support and its evaluation was expanded in 20 additional patients.

Results

From July 1996 to September 1997, a total of 42 patients with metastatic or locally ABC entered the trial (Table 1), 28 patients in the dose-escalating part of the study and 14 in the phase II part at the recommended dose. Twenty-three patients (55%) had dominant visceral disease and 28 (66%) had at least two metastatic sites. A total of 235 courses of therapy were administered at four different dose levels:

Dose level	Epirubicin (mg/m^2)	Docetaxel (mg/m^2)
1	75	75
2	90	75
3[a]	120	75
4[a]	120	85[a]

[a] G-CSF support from cycle 1.

Sixty-seven percent of the cycles (159) were fully evaluable for hematologic toxicity as no dose reductions were applied and no G-CSF support was added (Table 2). Treatment delay occurred in 17 patients due to logistic problems only, whereas a reduction to the lower dose level was applied to eight patients, as a consequence either of febrile neutropenia (six patients), or of grade 3 stomatitis and diarrhoea (one patient each). All patients were evaluable for non-haematological toxicity (Table 3). One patient died due to typhlitis and small bowel perforation while neutropenic after the first cycle at the highest dose level. Twelve responding patients received the allowed four additional cycles of single-agent T at the same dose delivered when in combination.

Table 1. Patients characteristics.

	Number of patients
Entered	42
Age	
Median	51.5
Range	32–68
ECOG performance status 0–1	42
Oestrogen receptors	
Positive	18
Negative	14
Unknown	10
Prior chemotherapy	13
Prior hormonal treatment	16
Metastatic	5
Dominant disease site	
Viscera (liver)	23 (12)
Soft tissue	4
Loco-regional	8
Bone	7
Number of metastatic sites	
1	14
≥ 2	28

Hematologic toxicity

Grade 4 neutropenia was universal and represented the main hematologic toxicity (Table 2): overall, the use of G-CSF allowed higher doses to be delivered with similar depth and duration of ANC nadirs which lasted a median of four days at all dose levels with a maximum of 10 days. Among six patients treated at the lowest dose level (E 75 mg/m^2 and D 75 mg/m^2) without G-CSF support, only one patient experienced a DLT after the first cycle (ANC less than 0.5×10^9/ *and* less than 0.1×10^9/l for more than seven days). At the subsequent level of dose (E 90 mg/m^2 and D 75 mg/m^2), three out of six patients required G-CSF support after the first cycle (neutropenic fever in two patients and ANC less than 0.1×10^9/l for more than three days in one patient) thus defining the MTD without G-CSF support. Thereafter, G-CSF was added from the first cycle in all patients entering the highest dose level. At E 120 mg/m^2 and D 75 mg/m^2 (third dose level) two out of seven patients suffered a DLT (one neutropenic fever and one ANC less than 0.1×10^9/l for more than three days): in the first patient the dose of E was reduced to 90 mg/m^2 according to protocol while in the second patient the investigator decided to continue at the same doses with no major hematologic toxicity observed at the subsequent cycles. At the fourth level of dose (E 120 mg/m^2 and D 85 mg/m^2) six out of nine patients experienced a DLT thus defining the MTD (one with neutropenic fever together with failure of ANC recovery at day 21, three with ANC less than 0.1×10^9/l for more than three days, one with both). Dose reductions according to protocol were implemented in the two patients with febrile neutropenia while the remaining three patients continued to receive the same amount of E with signs of cumulative myelosuppression in only one of them. The sixth patient with DLT died from typhlitis while neutropenic after the first

Table 2. Overall incidence of neutropenia and neutropenic fever.

Dose level (mg/m²)	No. of pts	Total cy/eval[a]	Median ANC nadir (range)	Febrile neutropenia		G3–4 ANC	DLT
				Number of patients	Number of cy (%)	% cy	
D 75 E 75	6	29/24	0.21 (0.03–2.34)	1	1 (3)	92	1[b]
D 75 E 90	20	116/62	0.26 (0–1.5)	9	10 (16)	87	3[c]
D 75 E 120[d]	7	41/34	0.30 (0–2.28)	2	2 (5)	83	2[e]
D 85 E 120[d]	9	49/39	0.31 (0–3.15)	5	8 (20)	88	6[f]

[a] Excluded cycles with G-CSF support and modified dose.
[b] ANC $< 0.5 \times 10^9$/l *and* $< 0.1 \times 10^9$/l > 7 days.
[c] Febrile neutropenia (two patients), ANC $< 0.1 \times 10^9$/l > 3 days (one patient).
[d] G-CSF support from cycle 1.
[e] Febrile neutropenia (one patient), ANC $< 0.1 \times 10^9$/l > 3 days (one patient).
[f] Febrile neutropenia *and* failure of ANC recovery at day 21 (one patient), ANC $< 0.1 \times 10^9$/l > 3 days (three patients), both (one patient), typhlitis (one patient)

Table 3. Grade ⩾2 non-hematologic toxicities.

Dose level (mg/m²)	Nausea/vomiting (% cy)	Neurotox (% cy)	Mucositis (% cy)	Asthenia (% cy)
D 75 E 75	7	0	7	3
D 75 E 90	7	2	9	7
D 75 E 120[a]	2	5	5	0
D 85 E 120[a]	14	6	2	10

[a] G-CSF support from cycle 1.

Table 4. Impairment of cardiac function.

⩾10% LVEF decrease

Patient	D/E dose level	Cycle number	LVEF decrease in units	Cumulative E (mg/m²)
A	2	2	13	180
B	2	4	14	360
C	2	2	10	180
D	2	6	11	540[a]
E	2	2	14	180
F	2	4	16	360
G	3	4	11	480

[a] Patient received six cycles of the combination by investigator's decision.

cycle for a locally advanced disease: the patient presented one week after treatment with abdominal pain and grade 4 neutropenia and thrombocytopenia. She was admitted to the hospital and suddenly developed a septic shock with large bowel perforation and blood cultures positive for *Clostridium septicum*. The patient underwent three subsequent bowel resections with a picture of a diffuse, acute ischemic colitis requiring first a total colectomy followed by repeated jejunal perforations. Tumour infiltration, vasculitis, septic emboli or atheromatosis could not be found in the pathologic specimens. Post mortem examination was not performed.

Overall, febrile neutropenia occurred in 13% of cycles (Table 2) but was associated with complications in only one patient at the highest dose level. Its incidence increased with the increase of E doses (3% and 16% of cycles at first and second dose level, respectively, without G-CSF support). G-CSF seemed to allow higher doses to be delivered with unaltered occurrence of febrile neutropenia when E doses were concerned (5% of cycles at the third dose level) but not when D doses were increased too (20% of cycles at the fourth dose level with one toxic death). In the group of 14 patients treated in the second part of the study at the dose defined as MTD without G-CSF support (E 90 mg/m² and D 75 mg/m²) the overall incidence of febrile neutropenia was 9%.

Grade 3–4 anemia and thrombocytopenia occurred only in 4% of cycles at the highest dose level and were of no clinical significance.

Non-hematologic toxicity

Non-hematologic toxicity was generally mild to moderate, aside from universal alopecia (Table 3). Asthenia was common, occasionally severe, especially in the early days following corticosteroid interruption. Mucositis, neurotoxicity, fluid retention, arthralgia, myalgia and fluid retention were present in some patients, with no significant difference in incidence and severity at the highest dose levels, and were generally not severe. Grade 4 diarrhoea in association with grade 2 stomatitis and febrile neutropenia was experienced by one patient only treated at E 90 mg/m² and D 75 mg/m².

In patients receiving four additional cycles of D, no signs of cumulative neurotoxicity, fluid retention, arthralgia, myalgia or skin toxicity were reported.

Cardiac toxicity

No clinically evident cardiac toxicity has been seen so far. Overall, the cumulative E dose ranged from 120 mg/m² to 540 mg/m² with a median of 480 mg/m². Six patients treated at E 90 mg/m² and D 75 mg/m² and one at E 120 mg/m² and D 75 mg/m² developed a >10% transient and asymptomatic decrease in LVEF after cumulative doses of E ranging from 180 mg/m² to 540 mg/m² (Table 4) with no absolute fall below 50%. In none of these patients a known predisposing factor to anthracycline cardiotoxicity was evident.

Antitumour activity

Two patients were not evaluable for response because of toxic death after the first cycle in one case and lack of measurable/evaluable disease in the other. Among 40

Table 5. Antitumour activity.

Dose level (mg/m^2)	Number of patients (evaluable)	CR (%)	PR (%)	SD (%)	PD (%)
D 75/E 75	6 (6)	0	3 (50)	1 (17)	2 (33)
D 75/E 90	20 (19)[a]	0	11 (58)	7 (37)	1 (5)
D 75/E 120	7 (7)	0	4 (57)	1 (14)	2 (29)
D 85/E 120	9 (8)[b]	1 (2.5)	5 (64)	1 (12)	1 (12)

[a] One patient not evaluable due to lack of measurable/evaluable disease.
[b] One patient not evaluable due to toxic death after the first cycle.

Table 6. Tumour response by disease site.

Site	Total	Evaluable	CR (%)	PR (%)	NC (%)	RR (%)
Liver	12	12	0	58	33	58
Lung	11	11	0	64	27	64
Locoregional	15	12	0	50	50	50
Soft tissue	19	19	11	74	16	84
Bone	21	16	0	6	75	6

patients evaluable for response, 38 patients had at least one measurable tumour parameter. The ORR was 60% (95% CI: 43%–75%) with CR in one patient (2.5%), tumour progression (PD) in 15% of patients and no differences in response rate among the different dose levels (Table 5). Median time to best response at the different dose levels ranged from 1.2 to 2.9 months. Overall, the addition of four cycles of single-agent D did not improve the antitumour activity achieved with the initial four cycles of the combination: only one patient with stable disease in liver and bone achieved a PR at the end of a total of eight cycles. Adjuvant chemotherapy did not seem to affect antitumour response; among 13 patients who completed adjuvant treatment at least six months prior the inclusion in the present trial (median 28 months, range 4–180) seven achieved a PR and one a CR with an ORR of 61.5%. All disease sites responded to the combination, irrespective of the dose administered (Table 6). The RR of the combination given as neoadjuvant treatment in locally advanced disease (12 evaluable patients) was 50%. The presence of bone metastases did not significantly affect disease response evaluation: in two patients with impressive shrinkage of locoregional disease the difficulty of bone disease assessment impaired the overall response determination.

At a median follow-up time of 19 months (range 2–30+) 14 out of 23 patients with a PR were censored without evidence of disease due to maintenance hormonal therapy (10 patients), surgical treatment (3 patients) or chemotherapy (1 patient); in the remaining 9 patients the median duration of response was seven months (range 3–19+) and the overall TTP was five months. The only CR observed was achieved in one patient with lung and mediastinal metastases and carcinomatous lymphangitis who subsequently developed bone metastases. Median survival has not been reached: 14 patients have died (33%) and 28 (67%) survive.

Discussion

Several trials exploring the combination of anthracyclines and taxanes in breast cancer have been recently conducted or are under way both in the advanced and in the adjuvant disease setting.

Four phase I studies evaluated the combination of E and D as first-line treatment in ABC [35–38], with a total of 196 patients enrolled (Table 7). The toxicity profile was comparable between trials, with grade 4 neutropenia almost universal, rarely complicated, and lack of clinically significant cardiac toxicity.

As regards antitumour response the ORR ranged from 52% in the Greek trial [38] to 69% and 76% (8% and 14% CRs) in the French [35] and the Italian trial [36] respectively, with sustained activity at all disease sites. The recommended dose without G-CSF support is not yet established in the Greek study and varied from E 100 mg/m^2/D 75 mg/m^2 [35] to E 60 mg/m^2/D 75 mg/m^2 [37] in the trials with mature results.

Table 7. Phase I studies of docetaxel/epirubicin in ABC.

Study	Number of patients	Design	G-CSF	DLT	MTD (mg/m^2)	ORR (%)
Pagani	42	E+D (one hour later)	From third level	Febrile neutropenia Prolonged neutropenia	D75/E90 (no G-CSF) D85/E120 (+ G-CSF)	60
Kerbrat [35]	65	Concomitant E+D	No	G4 neutropenia	D75/E110	69
Venturini [36]	25	Concomitant E+D	No	Febrile neutropenia Prolonged neutropenia	D60/E90 D80/E75	76
Trudeau [37]	19	E+D (one hour later)	No	Febrile neutropenia Prolonged neutropenia GI toxicity	D75/E75	NA
Panagos [38]	45	1 × concomitant E+D 2 × E+D (one day later)	At MTD	Febrile neutropenia G4 neutropenia	1 × D80/E70 2 × D90/E80 (ongoing)	52 (27 patients)

The results of the present phase I trial show that haematological toxicity represents the DLT of the combination and confirm that E and D can be given safely without G-CSF support at doses of 90 mg/m^2 and 75 mg/m^2, respectively. No indications of cumulative toxicity emerged in the 159 evaluable cycles. The addition of G-CSF allowed higher doses of both drugs to be delivered without a significant worsening in hematological toxicity, in particular as regards depth and duration of ANC nadir. The incidence of febrile neutropenia was quite high (13%) but it was short lasting and uncomplicated in the majority of patients: 60% of the febrile episodes did not require hospitalisation and could be resolved with oral antibiotics. Routine administration of oral prophylactic antibiotics during grade 4 neutropenia and the careful clinical and laboratory evaluation in experienced cancer centres may partly explain this favourable clinical outcome.

At the cumulative dose of anthracycline delivered in this study, E/D did not cause any clinically significant cardiac toxicity, as compared to the 20% of CHF previously reported for a median cumulative dose of DOX of 480 mg/m^2 [19]. These data confirm the lack of enhanced cardiotoxicity reported with DOX/D, despite median cumulative doses of DOX exceeding 360 mg/m^2 [22] and the good cardiac tolerability of E/P [29–31]. It should be noticed, however, that in the present trial patients could receive a maximum of four cycles of the combination, up to a maximum cumulative dose of E of 480 mg/m^2 at the highest dose levels, significantly lower than the dose of 360 mg/m^2 recommended for DOX in combination with P; taking a conversion factor for cardiotoxicity of 1.8, this should correspond to a dose of E of 650 mg/m^2.

Preclinical studies have shown that the concentrations of E in serum and tissues (heart, kidney and liver) are significantly higher in mice receiving P as compared to E alone [39]. More recent studies in mice treated with P, D and DOX suggest that both taxanes might increase the concentration of DOX in many tissues, including hearth [40].

The lack of both cumulative hematological toxicity and clinical cardiotoxicity after four cycles of the combination justifies the evaluation of more prolonged treatments with the administration of higher cumulative doses of E/D.

In the present study the ORR in 40 evaluable patients was 60%: this result is comparable to those achieved both in the French Anti-Cancer Centres [35] and in the Italian single centre study [36] but seem somewhat lower than those reported by some authors when DOX is combined either with P [19, 21] or D [22], mainly as regards the CR rate.

Different patient characteristics and the small sample size of most of these studies may partly explain these different results: the difficulty to assess tumour response in bone, where both osteolytic and sclerotic lesions often coexist, could possibly affect the ORR in our series, where bone disease was present in 47% of patients.

Tumour response was similar at all dose levels: dose escalation of E was apparently associated with a slightly higher RR (67% ORR with E at 120 mg/m^2 vs. 56% ORR with E at 75 mg/m^2 to 90 mg/m^2) but the different dose levels were not designed to address this specific question and the number of patients is too small to draw any significant conclusion. This observation seem to confirm the data recently published on the comparable ORR and OS for doses of E $\geqslant$90 mg/m^2 [41] and prompted us to evaluate the combination of E 90 mg/m^2 and D 75 mg/m^2 without G-CSF in an extended phase II study recently completed.

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