Annals of Oncology 11: 985–991, 2000.

Original article

Epidoxorubicin and docetaxel as first-line chemotherapy in patients with advanced breast cancer: A multicentric phase I–II study

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Summary

Background: The combination of anthracyclines and taxanes is currently considered the first choice chemotherapy in advanced breast cancer (ABC) and considerable emphasis has been placed on programs exploring the safest and most efficient way to integrate these classes of drugs in both the metastatic and, more recently, the adjuvant setting.

We report here the overall results of the combination of epidoxorubicin (E) 90 mg/m^2 and docetaxel (D) 75 mg/m^2 as first-line chemotherapy in ABC.

Patients and methods: A total of 70 patients were entered in the initial dose-finding study (20 patients) and in the subsequent extended phase II trial (50 patients). Overall 54% of patients had dominant visceral disease and 57% had at least two metastatic sites. Adjuvant anthracyclines were allowed in the phase II part of the study based on the lack of cardiac toxicity observed in the phase I study at a median cumulative E dose of 480 mg/m^2. A maximum of eight cycles of the combination was allowed, and cardiac function was monitored at baseline and after every second course by echocardiography.

Results: Overall, the median number of cycles administered with the combination was 4 (range 3–8). Neutropenia was confirmed to be the main haematological toxicity, with granulocyte colony-stimulating factor (G-CSF) support required in 44% of the cycles. Febrile neutropenia occurred in 12% of cycles of the combination but 52% of the episodes could be managed on an outpatient basis with oral antibiotics. Overall, the median cumulative dose of E, including prior adjuvant anthracyclines, was 495 mg/m^2 (range 270–1020 mg/m^2). One patient who received adjuvant E together with radiotherapy to the left chest wall developed fully reversible clinical signs of cardiotoxicity and a significant decrease of LVEF to 35% after a cumulative E dose of 870 mg/m^2, with four additional patients (6%) developing asymptomatic and transient decline of resting LVEF. The overall response rate (ORR) in 68 evaluable patients was 66% (95% confidence interval (95% CI): 54%–73%). A comparable antitumour activity of 71% was reported in the group of patients with a prior adjuvant chemotherapy with anthracyclines. After an overall median follow-up time of 22 months (range 4–39+), the median time to progression (TTP) was 4.5 months and the median duration of response was 8 months (range 3–16). No pharmacokinetic (Pk) interaction could be demonstrated between E and D when given simultaneously and sequentially with a one-hour interval.

Conclusions: The combination of E and D in a multi-institutional setting is an active and safe regimen in poor-prognosis patients with ABC. New combinations and schedules are worth considering in an attempt to further improve disease response and long-term control of the disease.

Key words: advanced breast cancer, docetaxel, epidoxorubicin

Introduction

First-line metastatic or ABC are the optimal settings for testing new agents and combinations in controlled clinical trials in order to assess their real impact on long-term control of the disease and palliation of its symptoms. Until recently, doxorubicin (Dox) was the most active single agent available and anthracycline-containing regimens have been considered the treatment of choice as first- and second-line therapy of advanced disease [1, 2].

In the 1990s, the taxanes [3], in particular D [4], emerged as the most powerful new single agent in the management of breast cancer [5, 6]: the high ORR confirmed in different studies, the lack of complete cross-resistance and of significant toxicity have prompted the evaluation of various combination regimens of these two classes of drugs [7, 8]. The International Breast Cancer Study Group (IBCSG) conducted a dose-finding phase I trial of E and D as first-line therapy in ABC [9]: the ED combination proved to be an effective and safe regimen in poor-prognosis, anthracycline-naive patients. The lack of both cumulative haematological toxicity and clinical cardiac toxicity after four cycles of the combination led to a phase II trial to evaluate a more protracted treatment with the administration of higher cumulative doses

of ED, also in patients who had received adjuvant anthracyclines. We report the overall results of administration of the ED combination at the recommended dose level of E 90 mg/m^2 and D 75 mg/m^2, established in the dose-finding part of the study.

In addition we report the absence of any Pk interaction between E and D given simultaneously or sequentially with a one-hour interval.

Patients and methods

Patients with histologically or cytologically documented metastatic or locally advanced breast cancer without prior chemotherapy for metastatic disease were eligible. Neo/adjuvant chemotherapy completed at least 12 months prior to study entry was allowed, a previous treatment with anthracyclines qualified patients for the phase II trial provided the total cumulative dose of Dox or E did not exceed 240 mg/m^2 or 430 mg/m^2, respectively, taking a conversion factor for cardiotoxicity of 1.8, as previously discussed [9]. Prior hormonal therapy for advanced disease was allowed. Eligibility criteria included adequate hematologic (absolute neutrophil count (ANC) $\geq 2.0 \times 10^9$/l, platelet count (Pt) $\geq 100 \times 10^9$/l) renal, hepatic (liver function tests currently recommended for treatment with D) [10] and cardiac function (LVEF $\geq 50\%$ by echocardiography), measurable or evaluable disease, and written informed consent.

Baseline evaluation was performed during the four weeks before study entry and included patient history, physical examination, chest X-ray, complete blood cell count (CBC), biochemistry, electrocardiogram (ECG) echocardiogram (ECHO) and radiological imaging of indicator lesions (CT scan, bone scan and/or X-rays of hot spots). 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 ECHO) were repeated after every other course. Treatment was discontinued in instances of CHF of any grade and/or of a significant reduction in LVEF ($\geq 10\%$ decrease from baseline associated with a decline to a level $\leq 50\%$) confirmed by an ECHO performed one week later.

In the dose-finding part of the trial patients were allowed a maximum of four cycles of the combination followed by four cycles of single-agent D in case of response. Based on the observed lack of significant cardiac toxicity, in the phase II study responders could receive a total of eight cycles of the combination, up to a maximum cumulative dose of E of 970 mg/m^2 (corresponding to 540 mg/m^2 of Dox).

Response was defined according to WHO criteria [11]. Imaging of all cases was reviewed by two external radiologists. 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 Aventis as a concentrated sterile solution containing 40 mg/ml = 80 mg/2 ml/vial in polysorbate 80 (Tween® 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 1-hour interval by D given as a 1-hour infusion on Day 1. A 3-day prophylactic medication with oral dexamethasone (8 mg b.i.d) 13 hours, 7 hours and 1 hour before D and then on days 1 and 2 was routinely administered in combination with oral cimetidine (300 mg) once daily. Prophylactic antiemetic treatment was given according to the investigators' routine practice. Prophylactic oral antibiotics were strongly recommended in instances of ANC below 0.5×10^9/l. Therapy was administered in the outpatient clinic every three weeks, provided the ANC was $\geq 2.0 \times 10^9$/l and the Pt count was $\geq 100 \times 10^9$/l on the day scheduled for retreatment. If recovery had not occurred after a maximum delay of three weeks patients were withdrawn from the study.

Toxicity was recorded according to the NCI–Common Toxicity Criteria (CTC). Each cycle was considered fully evaluable for haematological toxicity only in cases of an at least twice weekly CBC assessment.

G-CSF support (150 μg/m^2/day subcutaneously from day 2–11) was initiated in individual patients at the subsequent cycle in instances of febrile neutropenia (ANC $< 0.5 \times 10^9$/l and single elevation in oral temperature to > 38.5 °C during a 24-hour period) [12] or failure of ANC recovery by the day of retreatment. The E dose was decreased to 75 mg/m^2 in instances of grade 4 thrombocytopenia, grade ≥ 3 non-haematological toxicity (except for alopecia, nausea/vomiting, musculoskeletal pain), persistence of grade ≥ 2 nonhematologic toxicity at scheduled retreatment or febrile neutropenia despite G-CSF support

Pharmacokinetics

Pk of both E and D when given in combination was investigated in a subset of 12 patients who were randomly allocated to receive the combination according to two different schedules: group A: E 90 mg/m^2 given first, followed after one hour, by D 75 mg/m^2; group B: E given as above, immediately followed by D. The one-hour interval between the two drugs (group A) was selected to assess the potential influence of a delay in the administration of D on the Pk profile of both drugs. With this purpose, E, its major metabolite 13-hydroxy-epidoxorubicin (epidoxorubicinol) and D were measured in plasma at the following time points: T_0 (pretreatment), end of the anthracycline infusion and at 0.25, 0 5, 1, 1.5, 2, 3, 4, 8, 24 and 48 hours after the end of E administration.

Drug concentrations were assayed in plasma by high-performance liquid chromatography (HPLC) after solvent extraction for the anthracyclines, and after solid phase extraction for D [13, 14] The limit of quantitation (LOQ) for E and D were 2 and 15 ng/ml, respectively.

The Pk parameters were obtained by fitting the concentration-time data for both drugs on a non-linear fitting program [15], calculating the experimental area under the curve of the plasma concentration *versus* time (AUC) by the trapezoidal method from 0 to the last time point available (Cz) with concentration above the LOQ, plus the extrapolated portion of the curve to infinity obtained dividing Cz by the elimination phase konstant (Kel).

Results

From October 1996 to May 1998, a total of 70 patients with metastatic or locally ABC were treated with E 90 mg/m^2 and D 75 mg/m^2, 20 in the phase I part of the study and 50 in the extended phase II program. The median follow-up time is 22 months (range 4–39+). The patients' characteristics (Table 1) were similar in the two studies, with the results of the phase I having already been reported [9]. Overall, 38 patients (54%) had dominant visceral disease and 40 (57%) had at least two metastatic sites. A total of 417 courses of therapy were administered, of which 369 (88%) were with the combination and 48 (12%) with single-agent D; 326 cycles with ED (88%) were fully evaluable for haematological toxicity, as no dose reductions were applied and a twice weekly CBC was performed. Treatment delays occurred in 12% of cycles (32 patients), most of them because of

Table 1. Patient characteristics.

		Number of patients (%)
Entered and evaluable		70
Age		
Median	50	
Range	21–68	
Dominant disease site		
Viscera (liver)		38 (25)
Locoregional		21
Soft tissue		5
Bone		6
Oestrogen receptor		
Pos		33
Neg		24
Unknown		13
Number of metastatic sites		
1		30
$\geqslant 2$		40
Prior adjuvant chemotherapy		29
With anthracyclines		7
Prior hormonal treatment		20
Metastatic		3

Table 2. Overall neutropenia and related complications.

	No. of cycles (eval)	No. of cycles ED (eval)	Median nadir ANC (10^9/l) (range)	ANC <0.5, median duration (days) (range)	Febrile neutropenia (% cycles)	Grade 4 ANC (% cycles)
	417 (371)	369 (326)	0.28 (0.01–3 57)	3 (0–12)	12	64
No G-CSF	234 (200)	192 (161)	0.16 (0.01–2 37)	4 (0–12)	24	88
With G-CSF	183 (171)	177 (165)	0.66 (0.03–3.57)	0 (0–8)	3	41

Table 3 Grade $\geqslant 2$ non-hematologic toxicities.

	Nausea/ vomiting (% cycles)	Asthenia (% cycles)	Mucositis (% cycles)	Myalgia (% cycles)
Phase I	7	7	9	2
Phase II	11	8	8	3

logistical problems (77%), followed by haematological (12%), or non-haematological (4%) toxic effects, or other causes (7%). G-CSF was given during 183 cycles (44%) in 47 patients due mainly to haematological toxicity (febrile neutropenia and prolonged G4 neutropenia in 73% and 21% of cases, respectively). E dose reduction was applied to six patients (14 cycles) as a consequence of either febrile neutropenia despite G-CSF support (3 patients), or of grade 3 stomatitis and diarrhoea (2 and 1 patients each). E was definitively stopped in 10 patients after 4 cycles (cumulative dose reached in 2 patients, investigator's decision in the remaining 8). A total of 13 patients in the dose-finding part of the study (9 achieving a PR and 4 with SD) received additional cycles of single-agent D (4 and 2 cycles in 5 and 8 patients, respectively). Overall, the median number of cycles administered (including those with single-agent D) was 6 and the median number of cycles with the combination was 4.

Haematological toxicity

Grade 4 neutropenia represented the main haematological toxicity (Table 2) and occurred in about 60% of cycles. The administration of G-CSF significantly reduced the incidence of both Grade 4 neutropenia, which was reported in 41% and 88% of cycles with and without G-CSF, respectively, and febrile neutropenia. Overall, febrile neutropenia complicated 12% of cycles with ED (44 cycles) and in 56% of cases occurred after the first cycle, thereby confirming the overall incidence reported in the phase I study (13%), but it was short lasting and uncomplicated in the majority of patients; 52% of the febrile episodes did not require hospitalisation and were treated with oral antibiotics. G-CSF seemed to prevent neutropenic fever when administered to patients who had developed profound and long-lasting neutropenia in previous cycles: in the group of G-CSF treated patients the incidence of febrile neutropenia was 3%. Grade 3–4 anemia and thrombocytopenia occurred in only four patients and two patients, respectively, and were of no clinical significance.

Non-haematological toxicity

All patients were evaluable for non-haematological toxicity. Nonhematological toxicity was generally mild to moderate, aside from alopecia which was complete and universal (Table 3). Asthenia was common and occasionally severe, especially in the early days following corticosteroid interruption. Mucositis, neurotoxicity, fluid retention, arthralgia and myalgia were present in some patients but severe in $<10\%$ of cycles. Two patients experienced Grade 3–4 diarrhoea, in association with grade 2 stomatitis and febrile neutropenia in one of them.

Cardiac toxicity

Overall, the median cumulative dose of E, including prior adjuvant anthracyclines, was 495 mg/m^2 (range 270–1020 mg/m^2). The median LVEF assessed at baseline was 63%; the echocardiographic evaluation was repeated at the end of treatment in 93% of patients and showed no alterations in the overall median determinations (60%). Four patients (6%) developed a grade 2 asymptomatic and transient decline of resting LVEF by more than 20% after cumulative doses of E ranging from 360 mg/m^2 to 720 mg/m^2 (Table 4 and 5) with a persistent absolute fall below 50% in only one patient. One further patient who three years earlier had received adjuvant E (420 mg/m^2) together with radiotherapy to the left chest wall developed atrial fibrillation and acute lung oedema in association with a significant decrease of

Table 4. Cardiac function according to CTC.

	No. of patients (evaluable)	Mean Epi (mg/m^2)	0 (%)	I (%)	II (%)	III (%)
Phase I	20 (18)	380	10 (56)	7 (39)	1 (5)	0
Median no. of cycles	6		6	6	NA (4)	NA
Phase II	50 (47)	560	22 (47)	21 (45)	3 (6)	1 (2)
Median no. of cycles	6		6	6	6	NA (5)

Abbreviation: NA – not applicable

Table 5. Characteristics of patients with grade ≥ 2 cardiac toxicity.

	Age	Risk factors[a]	Pre-th LVEF (%)	Post-th LVEF (%)	Total E (mg/m^2)	Months from start	Follow-up LVEF (%) (months)
Phase I	59	No	65	*47*	360	3	46 (7)
Phase II	57	No	65	51	525	5	57 (13)
	45	No	69	51	720	6	64 (12)
	64	No	80	60	360	5	> 60 (20)
	56	Yes	60	58	870	8	*35* (8)
							60 (16)

[a] Risk factors (left chest wall radiotherapy, advanced age, diabetes).

Table 6. Antitumour activity.

	Phase I (%)	Phase II (%)
Entered/evaluable	20/19	50/49
CR	0	3 (6)
PR	11 (58)	31 (63)
SD	7 (37)	9 (19)
PD	1 (5)	6 (12)
Overall	19 (100)	49 (100)

LVEF to 35% after a cumulative E dose of 870 mg/m^2. The clinical picture completely recovered under medical treatment and LVEF returned to pretreatment values.

Antitumour activity

Of the 70 patients entered, two were not evaluable for response because of an absence of measurable/evaluable disease and 65 of 68 who were evaluable for response had at least one measurable lesion. The ORR was 66% (95% confidence interval (95% CI): 54%–73%) with three patients (5%) achieving a complete remission (CR) and seven patients (10%) showing tumour progression (PD) (Table 6). The median time to best response was 83 days and the overall TTP was 4.5 months. Duration of response was censored in 32 of 45 responders due to the addition of maintenance hormonal therapy (20 patients), surgical treatment (4 patients), different chemotherapy (2 patients), combined chemo-hormonotherapy (2 patients), surgery followed by endocrine therapy (3 patients) and alternative therapy (1 patient). In the remaining 13 patients the median duration of response was 8 months (range 3–16 months). Adjuvant chemotherapy did not seem to affect antitumour activity: overall, in the 29 patients with prior adjuvant treatment completed at least 12 months before starting ED (median 29 months, range 6–180), the ORR was 76%; of 7 patients who had received prior anthracyclines, none has showed a PD while on treatment, 3 have achieved a PR and 2 a CR for an ORR of 71%. All sites of disease responded to treatment; overall there was an ORR in visceral disease of 71%, (64% and 76% in patients with lung and liver involvement, respectively) and 1 CR of 14 months' duration in 1 patient with liver metastases. When E and D were given as neoadjuvant treatment in locally advanced disease (12 patients) a PR was achieved in 58%, after a median number of five cycles administered (range 3–6). In the phase II study responders could receive up to 8 cycles of the combination; in only 6 (18%) of the 34 patients who received more than 4 cycles of ED the response improved under prolonged therapy, while in 18 (40%) of 45 responding patients a PR was already achieved after the first 2 cycles.

After a median follow-up time of 22 months (range 4–39+) 28 patients (40%) had died and 42 (60%) are still alive: the two-year survival is 60%.

Pharmacokinetics

A comparison between the mean ± SD plasma decay curves of E and epidoxorubicinol in 12 patients receiving the treatment with two sequences of administration (groups A and B) is shown in Figure 1a and 1b. A similar comparison is reported for D in Figure 2: the mean Pk profile of D is shown in 11 patients only, due to the insufficient amount of plasma available in 1 patient. No significant differences in patients' characteristics which could possibly interfere with the Pk profile of both drugs (i.e., disease extent, concomitant medications, kidney and liver function) were present.

E disappeared from plasma following the usual three open compartment model showing no difference between the two sequences of treatment of drug and metabolite plasma levels. Main Pk parameters of E (mean ± SD) Cmax, AUC and terminal half-life were 5.62 ± 1.60 μg/ml, 3.32 ± 0.61 μg/ml/h and 20.9 ± 9.1 hours, after treatment A, and 5.64 ± 1.7 μg/ml, 3.21 ± 0.64 μg/ml/h and 20.2 ± 6.8 hours, after treatment B. Similarly, no difference was found in the Pk profile of epidoxorubicinol, with an AUC and a terminal half life of 1.0 ± 0.48 μg/ml/h and 22.2 ± 7.9 hours, in group A, and 1.0 ± 0.33 μg/ml/h and 20.6 ± 7.0 hours, in group B.

The main Pk parameters of D were similar when the drug was administered one hour after E or simultaneously with it. Cmax, AUC and T/2 were 2.0 ± 0.6 μg/ml, 2.55 ± 0.78 μg/ml/h and 10.6 ± 4 hours in group A and 1.8 ± 0.69 μg/ml, 2.82 ± 1.0 μg/ml/h and 12 ± 6 hours in group B.

Discussion

The previously published results of the phase I study showed that the combination of E and D could be given

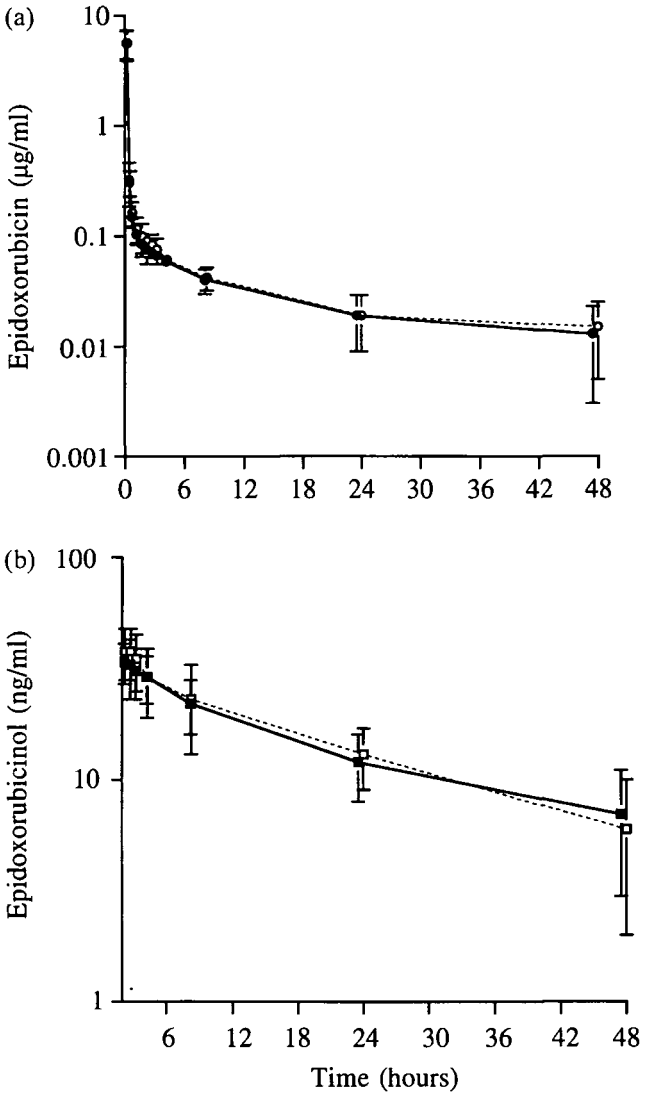

Figure 1. Mean (± SD) plasma decay curves of E (a) and epidoxorubicinol (b) determined in 12 patients who received E and D given simultaneously (open symbol) or sequentially with a one-hour interval (closed symbol).

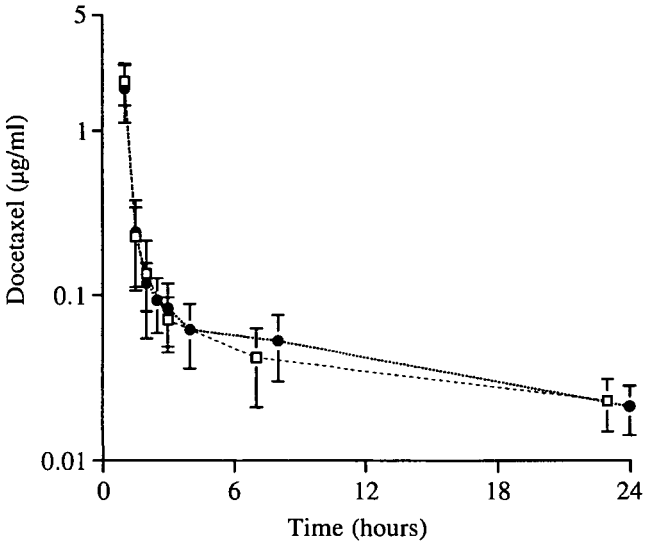

Figure 2 Mean (± SD) plasma decay curves of D determined in 11 patients who received E and D given simultaneously (open symbol) or sequentially with a one-hour interval (closed symbol).

safely at doses of 90 mg/m^2 and, respectively, 75 mg/m^2, with neutropenia as the dose-limiting toxicity (DLT) [9]. Those findings are confirmed in the present cumulative series: 44% of cycles required the administration of G-CSF, motivated in two-thirds of the patients by the occurrence of febrile neutropenia which complicated 12% of cycles but was easy to handle with no septic deaths. The prophylactic administration of oral antibiotics during grade 4 neutropenia, the biweekly laboratory assessment and the careful clinical evaluation in experienced cancer centres may explain this favourable clinical outcome. G-CSF significantly reduced haematological complications and might be advisable for administration of the combination in the general population. Adjuvant chemotherapy might influence the severity of neutropenia with 76% of patients requiring G-CSF support (86% and 73% of patients with and without prior anthracycline-containing regimens), as compared with 61% in chemotherapy-naïve patients.

At the median cumulative dose of E of 495 mg/m^2 (range 270–1020 mg/m^2) and with a median number of cycles of the combination of 4, only one patient with a previous history of both adjuvant anthracyclines and radiotherapy to the left chest wall developed clinical signs of cardiotoxicity together with a transient decline in LVEF. Although prolonged observation indicates that effects on myocardial contractility are reversible after the end of combination therapy with Dox and paclitaxel (P) [16], its potentially significant cardiotoxicity [17] has introduced the concept of decreasing the safe cumulative dose of Dox from the classical 500–550 mg/m^2 to 360 mg/m^2 when used with P given over three hours. The identification of baseline risk factors (i.e., left chest wall radiotherapy, advanced age, diabetes) [18, 19] could help in both identifying the optimal patient population and in implementing guidelines for appropriate dose reductions. Several strategies to prevent cardiotoxicity are also under evaluation [20, 21] and will likely allow higher cumulative doses of P in combination with Dox to be delivered.

Previous studies by Gianni et al. showed that the combination of P and Dox was complicated by a significant incidence of cardiac toxicity, possibly due to a Pk interaction [22, 23]. In preclinical studies we showed that tissue cardiac levels of Dox and E were significantly increased in mice treated with P over those treated with Dox alone [13]. It was therefore speculated that P could inhibit the MDR-related efflux mechanism mediated by P-glycoprotein or other proteins known to be involved in anthracyclines efflux, thereby increasing the tissue distribution. This hypothesis led us to investigate the possible Pk interaction between E and D, when E was given immediately or one hour before D. The one-hour interval was considered adequate to allow anthracycline distribution without interference by the taxane.

The data obtained in this study, however, showed the

same Pk profile of both E and its metabolite epidoxorubicinol, when E was given simultaneously or one hour after D. Noteworthy is the fact that the levels were also comparable to those reported in patients receiving E alone at the same dose [24]. The lack of Pk interaction between D and E is also supported by some recent data obtained in mice showing that E distribution in several tissues, including heart, was not affected by D [25].

The contrasting ability of P and D to interact with E was also recently reported by Esposito et al. who found in breast cancer patients much greater metabolic changes of E when given with P rather than with D [26].

The ORR of 66% in 68 evaluable patients, treated in a multi-institutional setting involving 6 centers, compares favourably with the most recent data published on the ED combination [27, 28] which used E doses ranging from 60–80 mg/m^2. As regards Dox-D combinations the ORR of published data [29–33] ranged from 55%–78% with slightly higher CR rates (5%–21%) at roughly comparable dose levels (Dox from 40–60 mg/m^2, D from 50–75 mg/m^2). However, in the only published study [33], despite a reported longer overall TTP (11.5 months vs. 4.5 months in the present population), the two-year survival is comparable (66% vs. 60% in the present study). A direct comparison between the two combinations in a randomised phase II trial could be of interest.

In an attempt to further improve long-term control of the disease and the toxicity profile a dose-finding study is ongoing to combine fluoropyrimidines with weekly ED.

Acknowledgements

This study was supported by Aventis, Antony, France and Pharmacia & Upjohn, Milan, Italy. We thank the patients who participated, and the nurses and the data managers who contributed their technical expertise to the conduct of the study.

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Received 4 April 2000; accepted 26 June 2000.

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