ANTICANCER RESEARCH *25*: 1211-1218 (2005)

Sequential Administration of Epirubicin and Paclitaxel for Advanced Breast Cancer. A Phase I Randomised Trial*

C. FOCAN[1], M.P. GRAAS[1], M. BEAUDUIN[2], J.L. CANON[3], J.P. SALMON[4], G. JERUSALEM[5], D. FOCAN-HENRARD[1], J.P. LOBELLE[6] and D. SCHALLIER[7]

[1]CHC Clinique Saint-Joseph, Liège; [2]CH Jolimont, Haine Saint-Paul; [3]Clinique Notre Dame Reine Fabiola, Charleroi; [4]CH Peltzer La Tourelle, Verviers; [5]CHU-Sart-Tilman, Liège; [6]Pfizer Oncology (Benelux); [7]Academic Hospital VUB – Jette, Belgium

Abstract. *Forty-six previously untreated patients with advanced breast cancer were eligible for the present randomised phase I study. It aimed to evaluate the toxicity and activity of a therapeutic sequence with epirubicin on day 1 followed by paclitaxel on day 2 (sequence A) or the reverse sequence, i.e., paclitaxel on day 1 followed by epirubicin on day 2 (sequence B). The starting doses of epirubicin and paclitaxel, administered either according to sequence A or B, (level 1 cohort) were 90 mg/m^2 and 175 mg/m^2, respectively. Per cohort of 3 patients, the dose of paclitaxel was increased by 25 mg/m^2 (levels 2 and 4) and of epirubicin by 10 mg/m^2 (levels 3 and 5). Treatment was repeated with 3-week intervals. The maximal tolerated dose (MTD) was achieved at level 1 in sequence B (paclitaxel first) and level 3 (epirubicin100 mg/m^2 followed by paclitaxel 200 mg m^2) in sequence A. Dose limiting toxicity (DLT) was neutropenia (+/- febrile) in both sequences. Cardiac events occurred in 28% of the patients; significant decrease in left ventricular ejection function (LVEF) was observed in 8/33 and in 2/13 patients in sequence A and B, respectively. This was associated with 5 and 1 cardiac heart failure (CHF), respectively. In 43 evaluable patients, 10 CR and 25 PR were observed (overall response rate 81%). In the 20 patients with locally advanced disease (LABC), the respective numbers were 7 CR and 11 PR; in the 23 metastatic (MBC) patients, 3 CR and 14 PR were recorded. The median survival of the both groups was not reached at 33 + months. In conclusion , the combination of epirubicin and paclitaxel has significant activity in breast cancer. The recommended sequence of both drugs in combination therapy, mainly to avoid neutropenia, is epirubicin day 1 followed by paclitaxel on day 2. Cardiac toxicity remains problematic in either sequence of administration.*

*Partly presented at the San Antonio Breast Cancer Symposium, December 2000.

Correspondence to: C. Focan, M.D., Ph.D., CHC-Clinique Saint-Joseph, Rue de Hesbaye 75, 4000 Liege, Belgium. Tel: 00 32 4 224 89 90, Fax: 00 32 4 224 89 91, e-mail: Christian.focan@CHC.be

Key Words: Breast cancer, epirubicin, paclitaxel, sequence.

Advanced breast cancer (BC) is of major public health concern as it represents the second cause of cancer related-death for American and European women. Despite all available hormonal and chemotherapeutic agents, metastatic breast cancer (MBC) remains largely incurable with less than 10% disease-free patients 5 years after diagnosis (1, 2). However, the patients more likely to have a prolonged survival (and perhaps even cure) are those having achieved a complete tumoral response in the early phase of their disseminated disease (1, 2).

The most important anticancer agents available up to the mid 1990's were the anthracyclines (doxorubicin and epirubicin) (3, 4). These were the cornerstone of any palliative regimen for advanced BC for two decades. They were proven to be superior to combinations not including anthracyclines in randomised trials (3, 4). A dose-response relationship was also clearly established (5); however, despite frequent improvements in response rate, response duration or time to progression, no clear improvement in overall survival could be observed in individual trials (5). Nevertheless, a recent meta-analysis emphasized the relevance of the response quality (complete, partial or none) as a surrogate endpoint of survival (1).

More recently, the taxanes, paclitaxel and docetaxel, have been approved for the treatment of MBC (6, 7). The taxanes are microtubule inhibitors that are reversibly bound to the beta subunit of tubulin, inducing microtubule polymerization and inhibiting microtubule depolymerization, leading to cell arrest at the G_2/M-phase of the cell cycle (6, 7). The taxanes also induce apoptosis in cancer cells and inhibit tumor angiogenesis (6, 7). Paclitaxel, as a single agent, produced

equivalent survival compared to the previously common combination of cyclophosphamide, methotrexate, fluorouracil and prednisone in untreated MBC patients (6); response rates in these comparisons were usually similar, as well. In monochemotherapy, paclitaxel displayed a dose-response relationship in a randomised comparison of two different dosages (8). This drug was combined with doxorubicin, first using prolonged infusions in the early trials (*i.e.*, 24- to 72-h infusion for paclitaxel and 48- to 72-h for doxorubicin) (9-11), and afterwards in combined or sequential scheduling (12, 13). These combinations led to impressive response rates (sometimes ≥90%) but also to severe toxicity, *i.e.*, cardiac toxicity and neutropenia with a risk of congestive heart failure (CHF) in ≥20% of patients (13, 14).

In 1997, at a time when no consensus existed regarding the appropriate sequence of administration of paclitaxel and the presumed least cardiotoxic anthracycline epirubicin in a combination schedule (4), a randomised phase I trial was initiated to determine the MTD of both drugs given 24 h apart, starting with epirubicin followed by paclitaxel or the reverse sequence. Detailed cardiac and hematological monitoring was performed during the trial. The determination of tumoral outcome was a secondary objective.

Materials and Methods

The study was conducted as a multicenter trial. It was performed in accordance with the Helsinki Declaration on Human Rights and after individual approval from the medical ethical committee of each individual institution.

Women aged 18 to 60, with a histologically proven diagnosis of locally advanced breast cancer (LABC) (stages IIIA or IIIB) or recurrent MBC (stage IV), were eligible for the study. The following conditions were required: WHO performance status ≤2, life expectancy ≥3 months, no prior chemotherapy for MBC or LABC, no prior adjuvant high-dose intensified chemotherapy with autologous bone marrow or stem cell rescue, adjuvant chemotherapy stopped at least 6 months before the study entry, no concomitant hormonotherapy, adequate bone marrow (granulocytes ≥2, 000/mm^3; platelets ≥150, 000/mm^3), kidney (creatinine ≤16 mg/l) or liver functions (SGOT, SGTP, total bilirubins ≤1.5 and/or alkaline phosphatase ≤2.5 upper normal limits in absence of bone metastases).

If patients had previously received an anthracycline or an anthracenedione as adjuvant treatment, a maximum cumulative dose of ≤300 mg/m^2 doxorubicin, ≤480 mg/m^2 epirubicin and ≤60 mg/m^2 mitoxantrone was allowed. Prior radiotherapy was permitted provided it was not performed on measurable or evaluable lesions.

Normal left ventricular ejection function (LVEF) (≥55% by isotopic or ultrasound testing) was required before starting the treatment. Patients with an active cardiac event within the previous 6 months, as well as patients suffering from an actual severe and/or active heart disease (class III or IV heart failure according to the New York heart association) or with active central nervous system (CNS) metastases, were excluded. Patients had to present at least one measurable or evaluable lesion according to WHO as assessed by a work-up including a general biology with tumor markers (CEA, CA 15.3), a recent mammography, CT scans of thorax and abdomen and a bone scintigraphy.

After informed consent, patients entered into the phase I study. They were stratified according to the centre and to the type of advanced disease (either locally advanced or recurrent metastatic) and randomised to receive chemotherapy according to sequence A (epirubicin day 1, paclitaxel day 2) or sequence B (paclitaxel day 1, epirubicin day 2). In order to determine the MTD for each sequence, according to the most recent recommendations on the management of phase I trials, cohorts of 3-6 cases were allocated either to sequence A or to sequence B (15). Successive dose-levels were foreseen: in sequence A, epirubicin preceded paclitaxel at the respective dose-levels of 90/175, 90/200, 100/200 and 100/225 mg/m^2, while in sequence B, the reverse sequence, at the respective dose levels of 175/90, 200/90, 200/100 and 225/100 mg/m^2, was programmed. Epirubicin was administered as a short infusion (30 min) and paclitaxel as a 3-h infusion with standard pre- and post-medication. Paclitaxel was kindly supplied for the study by Bristol Myers Squibb, Belgium.

Courses were repeated every 21 days. Prophylactic administration of 5HT3-antagonists was standard, while that of growth factors was excluded during the first 2 courses.

During the first course, patients were followed twice weekly for hematological (WBC, granulocytes, platelets) and weekly for clinical evaluation. As from course 2, hematological and clinical controls were scheduled once between days 10-14.

Dose-limiting toxicities (DLT) were defined as follows: granulocytes ≤500/mm^3 for at least 7 days; granulocytes ≤100/mm^3 for at least 3 days; granulocytes <1,000/mm^3 at retreatment day (21); febrile neutropenia (fever with granulocytes ≤500/mm^3); grade 4 thrombocytopenia (platelets ≤25,000/mm^3); any grade 3 non-hematological toxicity, in particular grade 3 mucositis ≥5 days; alopecia and tiredness were excluded. If no DLT was recorded among 3 patients treated at a given dose-level, the following patients were enrolled at the next dose-level and this separately for sequence A or B. If at least one DLT was recorded among 3 patients treated at a given dose-level in a given sequence, 3 more patients had to be enrolled at that dose-level.

MTD was defined as the epirubicin-paclitaxel or paclitaxel-epirubicin dose at which ≥2 patients out of 6 from a particular dose-level cohort reported DLT after the first course. Another cohort of 6 patients had to be entered for confirmation of that dose-level in the case that MTD was already reached at dose-level 1; otherwise, a confirmatory cohort of 6 patients had to be recruited at the previous inferior dose-level.

If a patient developed a DLT, she had to leave the study and the clinician was free to choose further treatment and/or any dose adaptation. Treatment had to be stopped in case of a drop in LVEF below 55% and/or ≥15% with respect to the baseline determination. LVEF determination by cardiac echography or MUGA scan was foreseen every 2 courses.

In this phase I study, patients could receive a maximum of 8 courses with epirubicin and paclitaxel and, if necessary, 4 additional courses with paclitaxel alone. Tumor evaluation was recommended every 2 courses. In cases of documented CR, PR or no change after 4 courses, eligible patients could be oriented to intensification protocols with peripheral stem cell rescue according to the decision of the investigator or could receive 2 more courses. After 6 courses, clinicians were free to choose further treatment (*i.e.*, surgery +/- radiotherapy in LABC, further identical treatment with a maximum

Table I. *Patients' characteristics.*

Number		46
Age:	mean	48
	range	32 – 69*
Stage:		
	- T (1/2/3/4/x)	10/11/6/13/6
	- N (0/1/2/3/x)	13/16/5/2/10
	- IIIA	11
	- IIIB	10
	- IV (M1)	24
	- unspecified	1
Previous adjuvant chemotherapy		11
Previous anthracyclines		10

*1 case >60y in the expanded access cohort

Table II. *Dose-limiting toxicity (DLT) at cycle 1. Number of patients.*

	Sequence A		Sequence B	
	Nb Included	Nb DLT	Nb Included	Nb DLT
Level 1	7	1	6	2
Level 2	7	0	0	-
Level 3	6	0	0	-
Level 4	3	2	0	-
Confirmation				
Level 1	-	-	7	3
Level 3	6	0	-	-
Expanded access				
Level 3	4	0	-	-
Total	33	3	13	5

Details of DLT C1
Sequence A: Level 1: 1 neutropenia
Level 4: 2 febrile neutropenia
Sequence B: Level 1: 1 neutropenia
4 febrile neutropenia

of 8 courses including epirubicin followed by courses with paclitaxel as single agent, alternative chemotherapy and/or hormonotherapy). The evolution of the patients with respect to progression and survival was recorded; actuarial survivals (progression-free and overall) were computed by the Kaplan Meier estimates for the whole group.

Due to the specific nature of this study, registration procedures, case report form (CRF) completion and data management collection were performed with pro-active exchange of information through fax communication.

Results

Patients' characteristics. Forty-six patients were entered in the trial from 02/17/1997 to 02/14/2000. Their main characteristics are presented in Table I. Eleven patients had received adjuvant chemotherapy 10 times including anthracyclines or anthracenedione. Four patients received the treatment outside the frame of the study (paclitaxel free of charge as an expanded access cohort) at the previously defined MTD, but were fully evaluated; one of those patients with excellent performance status was older than 60 years.

Toxicity and MTD. Tables II and III present the toxicity at cycle 1 for each dose-level in both sequences as well as the number of DLT recorded. The total number of cycles administered was 224, 145 in sequence A and 79 in sequence B. The mean number of cycles per patient was 5.9 (range 2-9) in sequence A and 6.8 (range 1-9) in sequence B. The main side-effect which occurred in both sequences was grade 3 or 4 granulocytopenia accompanied by febrile events. No toxic death was observed. Alopecia (grade 2) was universal. While MTD was only reached above level 3 in sequence A, MTD was already observed and confirmed at level 1 for sequence B. Therefore, with respect to myelosuppression, sequence A (E→P) was definitively better tolerated than sequence B (P→E).

Table III. *Toxicity at cycle 1 (grade 3+4). Number of patients.*

	Level 1	Level 2	Level 3	Level 4
Sequence A	7	7	16	3
Hb	0	0	1	0
WBC	4	3	8	3
Granulocytes	7	6	12	3
Platelets	0	0	1	0
NV (gr 3)	1	0	0	0
Stom/Diar/Cut	0	0	0	0
Sequence B	13			
Hb	0			
WBC	8			
Granulocytes	12			
Platelets	0			
Stom (gr 3)	1			
NV/Diar/Cut	0			

Abbreviations: Hb: hemoglobin; WBC: leucocytes; NV: nausea-vomiting; stom: stomatitits; diar: diarrhea; cut: cutaneous.

The results of detailed monitoring of cardiac function are presented in Figure 1. Significant cardiac events (significant drop in LVEF and/or cardiac heart failure (CHF) occurred irrespective of the sequence*:* sequence A*:* 8/33 (24% with 5 CHF); sequence B*:* 2/13 (15% with 1 CHF). CHF occurred

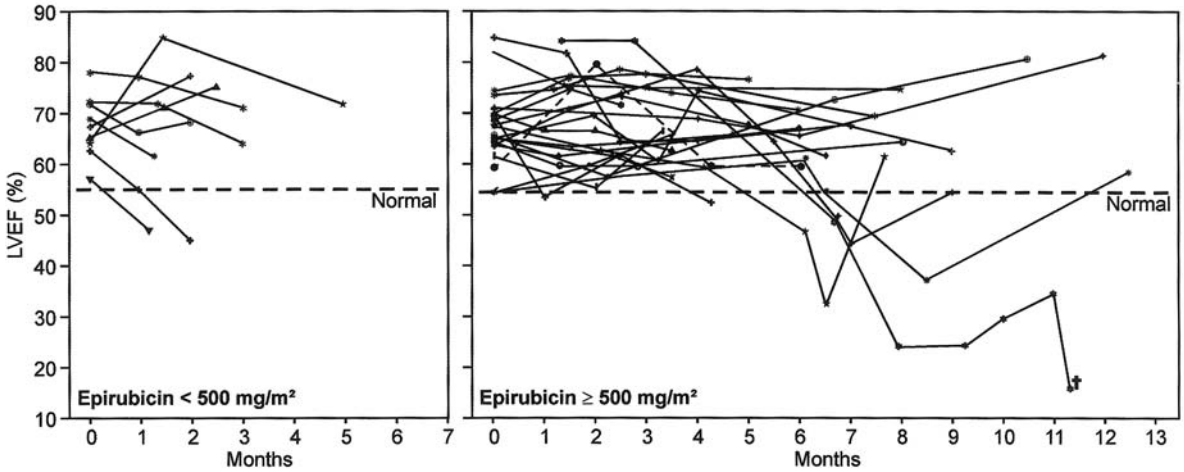

Figure 1. *Evolution of left ventricular ejection fractions (LVEF) along time. Left: cumulative dose epirubicin <500mg/m^2. Right: cumulative dose epirubicin ≥500mg/m^2*

mainly in patients having received ≥7 courses (after a median cumulative dose of epirubicin of 625mg/m^2, range 90 to 900 mg/m^2). Unexpectedly, one patient developed CHF after one cycle of epirubicin in sequence B. Moreover 4/10 of these patients had previously received anthracyclines as adjuvant treatment. Table IV details these observations.

Tumor outcome. Although the evaluation of antitumoral activity was not a primary end-point, response could be evaluated in 43/46 patients (3 patients were unassessable, 1 for previous surgical removal of the target and 2 for early withdrawal from the study). As represented in Table V, a high response rate was observed (81%) in both arms and was seemingly influenced by previous adjuvant anthracycline treatment [1 CR + 4PR/10 (50%) in patients previously treated with anthracyclines *versus* 9 CR + 21 PR/33 (91%) in anthracycline-naïve patients]. Clinical complete response occurred in 10/43 patients (23.3%), with 13% (3/23 patients) in MBC *versus* 35% (7/20 patients) in LABC. Confirmed pathological CR (pCR) was less common in LABC and observed only in 3 patients. Four other cases could also be considered as 'almost' pCR with only residual intra-canalicular carcinoma in 2, a small residual millimetric carcinoma in 1 and atypical cells altered by chemotherapy and not necessarily neoplastic in another patient.

The median time to progression was 15.4 months for the whole group (14.2 for metastatic and 33.4+ months for loco-regional disease). Median survival for both sub- groups was not reached at 33.3+ months.

Discussion

Anthracyclines and taxanes are among the most active agents for the treatment of breast cancer. The optimal way of combining both drugs, either concomitantly in a combination or sequentially as single agent, is still being debated. The objective of the present study was to explore the optimal sequence of administration of both drugs in a combination in previously untreated patients with LABC or MBC.

The present study demonstrated that the sequence of administration of paclitaxel and epirubicin both given as a short intravenous infusion, 24 hours apart, is crucial with respect to hematological toxicity. Higher doses of both drugs could be delivered in sequence A (E→P) than in sequence B (P→E). The DLT was (febrile) neutropenia in both sequences, but this occurred at dose level 1 in sequence B (paclitaxel 175/m^2 followed by epirubicin 90mg/m^2) and at dose level 3 in sequence A (paclitaxel 200 mg/m^2 preceded by epirubicin 100 mg/m^2). Interestingly, significant cardiac events (decrease of LVEF and/or CHF) were recorded in both sequences.

On reviewing the available *preclinical* literature about the combination of taxanes and anthracyclines for the treatment of human cancer, it is clear that no unanimous consensus has been reached. On the one hand, some preclinical experiments suggest the benefit of sequencing both drugs, favoring the administration of paclitaxel first (16), while in another, the reverse sequence appeared better (17). In other experiments, only additive or even antagonistic interactions were observed, especially with simultaneous exposure (18-21).

Early *clinical* trials incorporating prolonged infusion of both paclitaxel (24 to 72h) and doxorubicin (48 to 72h) resulted in severe hematological and non-hematological toxicity (10, 11). Sequencing paclitaxel after doxorubicin and reducing the duration of infusion of both largely reduced the hematological toxicity, while still leading to a high incidence of cardiac toxicity (14).

Table IV. *Cardiac events.*

Sequence A	8/33	(24%)	5 CHF
Sequence B	2/13	(15%)	1 CHF

Sequence A:

Level	1 # 3	CHF during further ABMT; had received 8 courses. Survived (CDE: 718 mg/m^2)
	# 7	LVEF drop 84→50/25% + CHF post C7; exitus (CDE: 718 mg/m^2)
	# 11	Died in CHF and anthracycline cardiomyopathy but - received only 3 courses (CDE: 284 mg/m^2) - end therapy 11/97, death 07/98 - received previous anthracyclines and further mitoxantrone, - no precise follow-up of LVEF
Level	2 # 20	LVEF drop 85→64% post C4 (CDE: 540 mg/m^2) Epirubicin stopped after C7; asymptomatic
	# 24	LVEF progressive drop 63 → 55 → 45% (C3) (CDE: 267 mg/m^2)
	# 27	CHF 3 months post C8 (LVEF 38%). Previous anthracyclines. Survived (CDE: 531 mg/m^2)
Level	3 # 39	LVEF drop 57→52% post C2; asymptomatic (CDE: 191 mg/m^2)
Level	4 # 37	LVEF drop 44% post C8 – CHF (CDE: 900 mg/m^2) Previous irradiation of left thorax: survived

Sequence B

Level	1 # 13	LVEF drop 71→57 → 62→53% post C6 (CDE: 720 mg/m^2) no clinical symptom. Previous anthracyclines
	# 14	CHF post C1; previous anthracyclines (CDE: 90 mg/m^2) Outcome unknown

Comments: cardiac problems in previous anthracyclines: 4/10
CHF occurred generally after ≥7 courses

Abbreviations: CHF: Cardiac Heart Failure
ABMT: Autologous Bone Marrow Transplantation
CDE: Cumulative Dose Epirubicin
LVEF: Left Ventricular Ejection Fraction

Table V. *Response per disease category and per sequence.*

	CR	PR	NC	PD
Sequence A				
All (32)	8	18	4	2
	81.3%			
M1 (16)	1	11	2	2
	75.0%			
M0 (16)	7	7	2	0
	87.5%			
Sequence B				
All (11)	2	7	2	0
	81.8%			
M1 (7)	2	3	2	0
	71.4%			
M0 (4)	0	4		
	100%			
Both sequences				
All (43)	10	25	6	2
	81.4%			
M1 (23)	3	14	4	2
	73.9%			
M0 (20)	7	11	2	0
	90.0%			

Note: 3 cases unevaluable (1 no target in sequence A; 2 study withdrawals post C1 for febrile neutropenia in sequence B)

Abbreviations: CR: complete remission; PR: partial remission; NC: no change; PD: progressive disease; MO: locally advanced breast cancer; M1: metastatic disease.

Pharmacokinetic studies revealed that the administration of paclitaxel 3 to 24 h before doxorubicin or epirubicin reduced the hepatic clearance and increased the peak plasma drug concentration (C max) and Area Under the Curve (AUC) of the latter (22-28). Also, the active anthracycline metabolites, *e.g.* doxorubicinol and epirubicinol, which are potentially more cardiotoxic, were increased (29). In addition, an inverse correlation between the AUC of epirubicin and neutrophil recovery was reported (30). Finally, a reduction of the renal clearance of epirubicin and epirubicinol has been related to the interference with paclitaxel and/or its vehicle cremophor (31, 32). The effect of paclitaxel appears dose- and schedule-dependent. In order to reduce myelosuppression in the paclitaxel – epirubicin combination, it seems logical to give epirubicin first followed by paclitaxel with an interval of at least 24 h (26, 27). It is less obvious to recommend any strategies, based on pharmacokinetic or pharmacodynamic observations, to reduce cardiac toxicity. Indeed, in our study, cardiac toxicity occurred in both sequences; at level 1 of sequence A, in which the least cardiac events were to be expected, 3 out of 7 patients developed CHF after cumulative dose of epirubicin (CDE) of 284, 718 and 718mg/m^2.

Other strategies to decrease the incidence of cardiac toxicity could be the use of the liposomal formulation of doxorubicin, the limitation of the doxorubicin or epirubicin dose to 50mg/m^2 or 75mg/m^2 per course or to 360mg/m^2 or 480mg/m^2 cumulative dose, respectively (26, 27, 33). Also the use of the cardioprotectant dexrazoxone (33) or the use of even longer administration intervals could be suggested (28).

Another way of overcoming potential troublesome pharmacokinetic interferences and potential toxicities could be not to combine paclitaxel and epirubicin at all, but rather to use both drugs as single agents sequentially with 3-week intervals (6). Sledge *et al*. have shown that sequential treatment with single agent paclitaxel and doxorubicin produced identical survival results in metastatic breast cancer patients compared to the combination of both (9). In the latter study, the response rate and time to treatment progression were, however, in favor of the combination therapy (9).

The present trial indicates that the combination of epirubicin and paclitaxel is active. A high response rate in the protoadjuvant situation and/or in anthracycline-naïve patients was achieved. The CR rate observed in the present trial was almost double the standard epirubicin-based treatment employed by our group in a previous trial (5). This may represent a real improvement if one considers that only complete responders to treatment may have a chance of prolonged survival and even cure (2). Nevertheless, when the CR in the LABC setting were carefully analyzed, the pCR remained low, in the present report as well as in others (6).

In the metastatic setting, four recently published or reported trials compared an epirubicin-paclitaxel arm to standard anthracycline-cyclophosphamide (34-37). In only one study was a significant difference in response rate, time to progression and survival favoring the anthracycline-paclitaxel arm observed (34-37).

Therefore, since toxicity is a relevant problem in these patients, probably alternative approaches for the majority of patients, including previously established combinations or sequential use of anthracyclines and taxanes, have to be considered.

Conclusion

Our trial has defined the MTD and the optimal sequence of administration of epirubicin and paclitaxel in the first-line treatment of advanced breast cancer. The sequence of epirubicin on day 1 followed by paclitaxel on day 2 was the better tolerated one, and the doses recommended for further phase II or III studies, without growth factors, are, respectively, 100 and 200 mg/m^2.

Pharmacokinetic studies published elsewhere support the conclusion that the paclitaxel effect on epirubicin metabolism explains the enhanced toxicity in the sequence in which paclitaxel is administered first.

An interesting response rate was observed, quite in accord with most recent data on anthracycline-taxane associations. The importance of this finding for the final outcome of the patients remains to be established.

Finally, the observation of cardiac events leading to potentially harmful CHF limits the application of such therapy to younger patients, unexposed to anthracyclines. In addition, we recommend limiting the number of courses to 6 in this patient population.

Acknowledgements

This study was supported in part by grants from Pfizer and Bristol Myers Squibb, Belgium.

References

1 Del Mastro L, Sormani M, Venturini M *et al*: Tumor response as surrogate end-point for survival in metastatic breast cancer patients*:* a meta-analysis. J Clin Oncol 2005 (in press).
2 Greenberg PAC, Hortobagyi GN, Smith TL *et al*: Long-term follow-up of patients with complete remission following combination chemotherapy for metastatic breast cancer. J Clin Oncol *14*: 2197-2205, 1996.
3 Gluck S: The expanding role of epirubicin in the treatment of breast cancer. Cancer Control *9(2 Suppl)*: 16-27, 2002.
4 Ormrod D, Holm K, Goa K *et al*: Epirubicin*:* a review of its efficacy as adjuvant therapy and in the treatment of metastatic disease in breast cancer. Drugs Aging *15*: 389-416, 1999.
5 Focan C, Andrien JM, Closon MT *et al*: Dose-response relationship of epirubicin-based first-line chemotherapy for advanced breast cancer*:* a prospective randomized trial. J Clin Oncol *11*: 1253-1263, 1993.
6 Di Leo A and Piccart MJ: Paclitaxel activity, dose, and schedule: data from phase III trials in metastatic breast cancer. Semin Oncol *26 (3, suppl 8)*: 27-32, 1999.
7 Nabholtz JM, Reese DM, Lindsay MA *et al*: Docetaxel in the treatment of breast cancer*:* an update on recent studies. Semin Oncol *29*: 28-34, 2002.
8 Nabholtz JM, Gelman K, Bontenbal M *et al*: Multicenter, randomized comparative study of two doses of paclitaxel in patients with metastatic breast cancer. J Clin Oncol *14*: 1858-1867, 1996.
9 Sledge GW Jr, Robert N, Sparano JA *et al*: Paclitaxel (Taxol)/doxorubicin combinations in advanced breast cancer*:* the Eastern Cooperative Oncology Group experience. Semin Oncol *21(5, suppl 8)*: 15-8, 1994.
10 Berg SL, Cowan KH, Balis FK *et al*: Pharmacokinetics of taxol and doxorubicin administered alone and in combination by continuous 72-hour infusion. J Natl Cancer Inst *86*: 143-145, 1994.
11 Holmes FA, Valero V, Walters RS *et al*: Paclitaxel by 24-hour infusion with doxorubicin by 48-hour infusion as initial therapy for metastatic breast cancer*:* phase I results. Ann Oncol *10*: 403-411, 1999.
12 Conte PF, Baldini E, Gennari A *et al*: Dose-finding study and pharmacokinetics of epirubicin and paclitaxel over 3 hours*:* a regimen with high activity and low cardiotoxicity in advanced breast cancer. J Clin Oncol *15*: 2510-7, 1997.

13 Gianni L, Munzone E, Capri G *et al*: Paclitaxel by 3-hour infusion in combination with bolus doxorubicin in women with untreated metastatic breast cancer: high antitumor efficacy and cardiac effects in a dose-finding and sequence-finding study. J Clin Oncol *13*: 688-99, 1995.
14 Gianni L, Dombernowsky P, Sledge G *et al*: Cardiac function following combination therapy with paclitaxel and doxorubicin: an analysis of 657 women with advanced breast cancer. Ann Oncol *12*: 1067-1073, 2001.
15 Dent SF and Eisenhauer EA: Phase I trial design: are new methodologies being put into practice? Ann Oncol *7*: 561-566, 1996.
16 Akutsu M, Kano Y, Tsunoda S *et al*: Schedule-dependent interaction between paclitaxel and doxorubicin in human cancer cell lines *in vitro*. Eur J Cancer *31A*: 2341-2346, 1995.
17 Frassineti GI, Zoli W, Tienghi A *et al*: The sequential administration of combined doxorubicin and paclitaxel in the treatment of advanced breast cancer. Semin Oncol *23(5 suppl 12)*: 22-8, 1996.
18 Hahn SM, Liebmann JE, Cook J *et al*: Taxol in combination with doxorubicin or etoposide. Possible antagonism *in vitro*. Cancer *72*: 2705-2711, 1993.
19 Koechli OR, Sevin BU, Perras JP *et al*: Characteristics of the combination paclitaxel plus doxorubicin in breast cancer cell lines analyzed with the ATP-cell viability assay. Breast Cancer Res Treat *28*: 21-27, 1993.
20 Konecny G, Untch M and Slamon D *et al*: Drug interactions and cytotoxic effects of paclitaxel in combination with carboplatin, epirubicin, gemcitabine or vinorelbine in breast cancer cell lines and tumor samples. Breast Cancer Res Treat *67*: 223-33, 2001.
21 Viallet J, Tsao MS and Gallant G: Etoposide and doxorubicin antagonize the *in vitro* activity of paclitaxel in human non-small cell lung cancer cell lines. Lung Cancer *15*: 93-101, 1996.
22 Colombo T, Parisi I, Zucchetti M *et al*: Pharmacokinetic interactions of paclitaxel, docetaxel and their vehicles with doxorubicin. Ann Oncol *10*: 391-395, 1999.
23 Grasselli G, Vigano L, Capri G *et al*: Clinical and pharmacologic study of the epirubicin and paclitaxel combination in women with metastatic breast cancer. J Clin Oncol *19*: 2222-31, 2001.
24 Holmes FA and Rowinsky EK: Pharmacokinetic profiles of doxorubicin in combination with taxanes. Semin Oncol *28*: 8-14, 2001.
25 Danesi R, Innocenti G, Fogli S *et al*: Pharmacokinetics and pharmacodynamics of combination chemotherapy with paclitaxel and epirubicin in breast cancer patients. Br J Clin Pharmacol *53*: 508-18, 2002.
26 Razis ED and Fountzilas G: Paclitaxel: epirubicin in metastatic breast cancer - a review. Ann Oncol *12*: 593-8, 2001.
27 Venturini M, Lunardi G, Del Mastro L *et al*: Sequence effect of epirubicin and paclitaxel treatment on pharmacokinetics and toxicity. J Clin Oncol *18*: 2116-25, 2000.
28 Moreira A, Lobato R, Morais J *et al*: Influence of the interval between the administration of doxorubicin and paclitaxel on the pharmacokinetics of these drugs in patients with locally advanced breast cancer. Cancer Chemother Pharmacol *48*: 333-337, 2001.
29 Minotti G, Saponiero A, Licata S *et al*: Paclitaxel and docetaxel enhance the metabolism of doxorubicin to toxic species in human myocardium. Clin Cancer Res *7*: 1511-1515, 2001.
30 Esposito M, Venturini M, Vannozzi MO *et al*: Comparative effects of paclitaxel and docetaxel on the metabolism and pharmacokinetics of epirubicin in breast cancer patients. J Clin Oncol *17*: 1132-40, 1999.
31 Rischin D, Webster LK, Millward MJ *et al*: Cremophor pharmacokinetics in patients receiving 3-, 6-, and 24-hour infusions of paclitaxel. J Natl Cancer Inst *88*: 1297-1301, 1996.
32 Webster LK, Cosson EJ, Stokes KH *et al*: Effect of the paclitaxel vehicle, cremophor EL, on the phamacokinetics of doxorubicin and doxorubicinol in mice. Br J Cancer *73*: 522-524, 1996.
33 Sparano JA: Use of dexrazoxane and other strategies to prevent cardiomyopathy associated with doxorubicin-taxane combinations. Semin Oncol *25(4, Suppl 10)*: 66-71, 1998.
34 Luck HJ, Thomssen C, Untch M *et al*: Multicentric phase III study in first line treatment of advanced metastatic breast cancer (ABC). Epirubicin/paclitaxel (ET) *vs* epirubicin/cyclophosphamide (EC). A study of the AGO Breast Cancer Group. Proc Am Soc Clin Oncol *19*: 73a (abstr 280), 2000.
35 Biganzoli L, Cufer T, Bruning P *et al*: Doxorubicin and paclitaxel *versus* doxorubicin and cyclophosphamide as first-line chemotherapy in metastatic breast cancer: the European Organization for Research and Treatment of Cancer 10961 multicenter phase III trial. J Clin Oncol *20*: 3114-3121, 2002.
36 Carmichael J: UKCCR trial of epirubicin and cyclophosphamide (EC) *vs* epirubicin and taxol (ET) in the first line treatment of women with metastatic breast cancer (MBC). Proc Am Soc Clin Oncol *20*: 22a (abstr 84), 2001.
37 Jassem J, Pienkowski T, Pluzanska A *et al*: Doxorubicin and paclitaxel *versus* fluorouracil, doxorubicin, and cyclophosphamide as first-line therapy for women with metastatic breast cancer: final results of a randomized phase III multicenter trial. J Clin Oncol *19*: 1707-15, 2001.

Received September 29, 2004
Revised February 2, 2005
Accepted February 16, 2005