Journal of BUON **10:** 337-346, 2005

ORIGINAL ARTICLE

Dose escalation of docetaxel and ifosfamide in patients with advanced breast cancer failing prior anthracyclines: mature results of a phase I-II study

C. Kosmas[1], N. Tsavaris[2], N. Malamos[3], G. Tsakonas[1], A. Gassiamis[1], H. Skopelitis[2], G. Soukouli[1], A. Polyzos[2], N. Mylonakis[1], A. Karabelis[1]

[1]Department of Medical Oncology-B, "Metaxa" Cancer Hospital, Piraeus; [2]Oncology Unit, Departments of Pathophysiology and Propedeutic Medicine, Athens University School of Medicine, "Laikon" General Hospital, Athens; [3]Medical Oncology Unit, "Helena Venizelou" Hospital, Athens, Greece

Summary

Purpose: *Single-agent docetaxel and ifosfamide are clinically active in anthracycline-pretreated advanced breast cancer. We conducted a phase I-II study aiming to define the maximum tolerated dose (MTD), the dose-limiting toxicities (DLTs), and the activity of the docetaxel-ifosfamide combination in this setting.*

Patients and methods: *Cohorts of 3-6 patients with histologically confirmed metastatic breast cancer after prior anthracycline-based chemotherapy were treated at successive dose levels (DLs) with escalated doses of docetaxel (70-100 mg/m^2 over 1 h on day 1), followed by ifosfamide 5-6 g/m^2 divided over days 1 and 2 (2.5-3.0 g/m^2 /day over 1 h), and recycled every 21 days. G-CSF was added once dose-limiting neutropenia was encountered at a certain DL and planned to be incorporated prophylactically in subsequent higher DLs.*

Results: *Sixty-five patients (median age 57 years, range 32-72) and performance status (PS) (World Health Organization–WHO) of 1 (range 0-2) were treated at 5 DLs as follows: 21 in phase I DLs (DL1: 3, DL2: 6, DL3: 3, DL4: 6, and DL5: 3) and the remaining 44 were treated at DL4 (total of 50 patients at DL4), which was defined as the level for phase II testing. All patients were evaluable for toxicity and 62 for response. DLT (with the addition of G-CSF after DL2) was reached at DL5 with 2/3 initial patients developing febrile neutropenia. Clinical response rates (RRs), on an intention-to-treat basis, in phase II were 56% (95% CI 42.2-69.7): complete remission (CR) 4, partial remission (PR) 24, stable disease (SD) 10 and progressive disease (PD) 12. The median response duration was 7 months (range 3-24), the median time to progression (TTP) 6.5 months (range 0.1-26), and the median overall survival (OS) 13 months (range 0.1-33). Grade 3/4 toxicities included neutropenia in 72% of patients-with 60% developing grade 4 neutropenia (≤ 7 days) and 10% of these febrile neutropenia (FN), while no grade 3/4 thrombocytopenia was observed. Other toxicities included grade 2 peripheral neuropathy only in 10% of the patients, grade 1/2 reversible CNS toxicity in 16%, no renal toxicity, grade 2 myalgias in 8%, grade 3 diarrhea in 8%, skin/nail toxicity in 14%, and grade 2 fluid retention in 2%. One patient treated at the phase II part of the study died of acute liver failure after the first cycle.*

Conclusion: *The present phase I-II study determined the feasibility, defined the MTD and demonstrated the encouraging activity of the docetaxel-ifosfamide combination in the phase II part of the study. Therefore, future randomized phase III studies versus single-agent docetaxel or combinations of the latter with other active agents are warranted.*

Key words: breast cancer, docetaxel, ifosfamide, phase I study, phase II study

Received 21-05-2005; Accepted 28-06-2005

Author and address for correspondence:

Christos Kosmas, MD
Department of Medical Oncology-B
"Metaxa" Cancer Hospital
51 Botassi street
185 37 Piraeus
Greece
Tel./Fax: +30 210 99 62 917
E-mail: ckosm@ath.forthnet.gr

Introduction

Docetaxel (Taxotere®) represents a novel antimicrotubule agent that promotes the polymerization of tubulin and thereof stabilizes microtubules by preventing their disassembly. Docetaxel has demonstrated a broad spectrum of activity against a variety of advanced solid tumors, and breast cancer represents the first human cancer in which docetaxel has been

successfully tested [1]. In particular, for patients with prior anthracycline-based therapy, taxanes represent the treatment of choice in the salvage setting, since previously applied agents have demonstrated inferior activity. Taxanes have exhibited a relative lack of cross-resistance with anthracyclines, and they have so far demonstrated fair tolerability in pretreated patients.

Three second-line phase III studies in anthracycline-refractory patients evaluated single-agent docetaxel *versus* salvage regimens thought to be active in this setting, namely mitomycin-C+vinblastine [2], methotrexate+5-fluorouracil (5-FU) [3], and infusional 5-FU+vinorelbine [4]. Two of the above studies [2, 3] demonstrated an advantage in favor of docetaxel with respect to RR and TTP, while only the study of Nabholtz et al. [2] reported so far a significant 3-month prolongation in median OS, while, in contrast, the third study by Monnier et al. [4] did not report any advantage of docetaxel *versus* infusional 5-FU+vinorelbine. Moreover, in a recently reported large phase III randomized trial [5] comparing single-agent docetaxel *versus* doxorubicin in alkylating agent-pretreated metastatic breast cancer patients, a significantly better RR for docetaxel (52 *versus* 37%), without, however, prolongation in median TTP was seen. The other taxane, paclitaxel, has been compared to doxorubicin in 2 recent large phase III studies [6, 7]. The first study conducted by the EORTC compared 3-h infusional paclitaxel 200 mg/m^2 to doxorubicin 75 mg/m^2 in chemotherapy-naïve or alkylator-pretreated advanced breast cancer patients, yielding significantly higher RRs and longer progression-free survival in favor of doxorubicin [6]. The second study, a 3-arm North American trial, compared doxorubicin 60 mg/m^2 *versus* paclitaxel 175 mg/m^2 (24 h infusion) *versus* the combination of doxorubicin 50 mg/m^2 plus paclitaxel 150 mg/m^2 (24 h infusion) and yielded equivalent results in terms of RR, TTP and OS between the doxorubicin and paclitaxel single-agent arms [7].

Ifosfamide, an oxazophosphorine alkylating agent like cyclophosphamide, has demonstrated substantial activity in advanced breast cancer [8]. It is relatively non cross-resistant to cyclophosphamide in a variety of tumors and possesses a different toxicity profile than cyclophosphamide, with ifosfamide causing more urothelial toxicity known to be preventable with mesna and adequate hydration, encephalopathy and renal dysfunction, which are dose and schedule-dependent. However, ifosfamide can be administered at significantly higher doses than cyclophosphamide with considerably much less myelosuppression, thereby permitting for a higher alkylator dose intensity than cyclophosphamide. There have been several phase I/II studies combining ifosfamide with other agents in chemotherapy-naïve or pretreated patients with advanced breast cancer, such as doxorubicin [9], paclitaxel [10], and vinorelbine [11]. These studies have demonstrated the feasibility of administering considerably high ifosfamide doses, as well as substantial activity of the combinations. A single previous phase I study has evaluated the feasibility of the docetaxel-ifosfamide combination without G-CSF in pretreated patients with a variety of advanced solid tumors. Dose-limiting toxicity was reached at docetaxel 85 mg/m^2 on day 1, followed by ifosfamide 5 g/m^2 administered as 24 h infusion and the recommended phase II doses were docetaxel 75 mg/m^2+ifosfamide 5 g/m^2 [12].

Given the encouraging activity of each individual cytotoxic agent and the feasibility of the docetaxel+ifosfamide combination, we elected to conduct a phase I/II study in an attempt to further intensify the above regimen, possibly with the aid of G-CSF, in patients with anthracycline-pretreated metastatic breast cancer and administer it in an outpatient setting by avoiding the 24 h infusion and selecting the fractionated short-over 2 days-infusion of ifosfamide.

Patients and methods

1. Patient selection

Patients with histologically confirmed metastatic breast cancer pretreated with anthracycline-based chemotherapy were enrolled. The following patient categories were formed: (i) patients progressing on anthracycline-based therapy or within 4 months after the end of such a treatment, (ii) or patients treated with neoadjuvant and adjuvant anthracyclines that progressed within 12 months after the end of adjuvant chemotherapy were deemed anthracycline-refractory, (iii) while all other patients were considered potentially anthracycline-sensitive. Patients had to have bi-dimensionally measurable lesions with at least one outside a previously irradiated field, unless definite evidence of progression at this site was observed during a minimum 3-month period. No prior taxanes or ifosfamide were allowed. Patients identified in retrospect (on archive or new biopsy material) to have HER2 (*c-erbB2*) overexpressing tumors by immunohistochemistry and/or FISH analysis, as this became available after the end of 2000, were not offered trastuzumab therapy in combination with the study regimen of docetaxel-ifosfamide until disease progression. Other inclusion criteria were as follows:

age 18 to 72 years; a WHO PS of 0 to 2; life expectancy of at least 3 months; adequate hematopoietic (absolute neutrophil count–ANC ≥ 1500/μL, platelets–PLT ≥ 100.000/μL), liver (bilirubin < 1.5 mg/dl, AST/ALT < 2 × upper normal limit, unless caused by tumor, and serum albumin > 3.0 g/dl), renal (BUN and creatinine < 1.5 × upper normal limit; and creatinine clearance > 50 ml/min), and cardiac function (left ventricular ejection fraction [LVEF] ≥ 50%). Patients with brain metastases were eligible, provided they had been irradiated and had clinical and radiological improvement and were off steroids or receiving tapering doses of steroids. Other exclusion criteria were radiation therapy within 4 weeks from treatment initiation, irradiation of more than 25% of the bone marrow-bearing skeleton, severe infection or malnutrition. The study was approved by the Ethical and Scientific Committees of the participating institutions and informed consent was obtained from each patient before study entry.

2. Treatment schedule

Eligible patients entered the DLs as shown in Table 1. Docetaxel was administered at 70-100 mg/m^2 over 1 h by i.v. infusion on day 1, after premedication consisting of dexamethasone 20 mg, dimethidene maleate (Fenistil®) 4 mg and ranitidine 50 mg, all administered i.v. 30 min before docetaxel. Ifosfamide followed docetaxel and was administered at 5.0-6.0 g/m^2 divided over 2 days (2.5-3.0 g/m^2 per day i.v. over 1 h) together with mesna uroprotection administered at 40% of the ifosfamide dose, within the same solution with ifosfamide [1 L of 1/2 (0.9% normal saline+dextrose 5%) + 20 mEq KCl+30 mEq bicarbonate and 10 mg furosemide], and 80% of the ifosfamide dose divided within the post-ifosfamide hydration fluids which consisted of 2 L [1/2 (0.9% normal saline+dextrose 5%) + 20 mEq KCl+10 mg furosemide] administered over 6 h in the outpatient unit.

Table 1. Docetaxel-ifosfamide dose levels in the phase I part of the study.

	Drug doses			
Dose level	*Docetaxel (mg/m^2)*	*Ifosfamide (g/m^2)*	*G-CSF*	*No. of patients entered*
1	70	5.0	–	3
2	85	5.0	–	6
3	85	5.0	+	3
4	100	5.0	+	6+44 (phase II)
5	100	6.0	+	3

3. Supportive care

Standard antiemetic medication included ondansetron 24 mg i.v. 1 h before chemotherapy on days 1 and 2, and post-chemotherapy 8 mg t.i.d. per os on days 3-5. Dexamethasone 20 mg i.v. was administered 1 h before chemotherapy (on day 1 as docetaxel premedication as well) on days 1 and 2 and post-chemotherapy 4 mg t.i.d. or methylprednisolone 16 mg b.i.d per os on days 3-5 [11].

Hematopoietic growth factors included G-CSF (lenograstim) 150 μg/m^2/day s.c. from day 4 until day 10 or until white blood cells (WBC) ≥ 10.000/μl, whatever came first.

4. Dose escalation schedule, DLTs and dose modifications

DLTs were assessed during the first chemotherapy cycle and were considered to have been reached when one of the following was met: (i) grade 4 neutropenia of > 7 days duration; (ii) any episode of febrile ≥ grade 3 neutropenia; (iii) any episode of grade 4 thrombocytopenia; (iv) any non-hematologic grade 3 or 4 toxicity excluding nausea/vomiting, musculoskeletal-arthritic pain and alopecia.

Cohorts of 3 patients entered at the DLs shown in Table 1. In the case that DLT was encountered (defined above) in 1/3 of the patients at a certain DL, a total of 6 patients were entered at that particular level and if > 2/6 (33%) met the DLT requirements (in total at least 3/6 patients developed the same DLT) no further accrual to the next higher DL was undertaken and the level immediately before the DLT was considered as the MTD. In the case that 2 out of the first 3 patients experienced at a certain level the same DLT, no more patients were accrued at that level and further dose-escalation was stopped. The DL immediately before the one that DLT was reached, i.e. the MTD, was recommended for further phase II testing.

The following guidelines were applied with respect to dose reductions for toxicity: (i) for neutropenia and thrombocytopenia meeting the aforementioned criteria, docetaxel and ifosfamide doses were reduced by 20% in subsequent cycles and if toxicity reappeared after a total of 40% reduction from the starting dose in consecutive cycles, treatment was stopped but the patient was evaluable for toxicity and response; (ii) for ≥ grade 3 mucositis the doses of docetaxel and ifosfamide were reduced by 20% in subsequent cycles; (iii) for ≥ grade 3 neuropathy treatment was interrupted; (iv) for ≥ 3 grade renal toxicity (serum creatinine elevation > 3 × normal)

treatment was withheld until recovery (serum creatinine < 1.8 mg/dl) with ifosfamide administered with more posthydration and hospitalization in subsequent cycles. If the creatinine clearance dropped to < 40 ml/min, ifosfamide was omitted in subsequent cycles; (v) for ≥ grade 3 CNS toxicity (ifosfamide encephalopathy) the dose of ifosfamide was reduced by 20% and more hydration with bicarbonates was anticipated in subsequent cycles. In the case that encephalopathy reappeared, then ifosfamide was omitted from subsequent cycles. In the case that blood counts had not recovered to ANC ≥ 1.500/μl and PLT ≥ 100.000/μl on the day of therapy, treatment was withheld until recovery, and after a maximum delay of 2 weeks (day 35) no further therapy was administered in case that counts did not return to normal.

5. Patient evaluation

Baseline evaluations included: patient history, physical examination, chest x-rays, complete blood count with differentials and platelet count, serum biochemistry, ECG, and echocardiography or multigated angiogram (MUGA) scan with LVEF measurement. Computed tomography (CT) scans of the chest, abdomen, pelvis and bone scintigraphy were performed at study entry and CT scan of the brain whenever clinically indicated. Complete blood counts with differentials and platelet counts were performed twice weekly or daily in case of grade 3/4 neutropenia, thrombocytopenia or febrile neutropenia until hematologic recovery; serum biochemistry and physical examination were performed every 3 weeks. Toxicities were evaluated according to the NCI common toxicity criteria (NCI-CTC).

Responses were evaluated according to WHO response criteria [13]. CR was defined as the disappearance of all signs and symptoms of disease for at least 1 month, with documented disappearance of all known lesions by physical examination, x-rays, CT scans, with no development of new lesions. PR was defined as a decrease of 50% or greater (compared with pre-treatment measurements) in the sum of the products of the two largest perpendicular diameters of all measurable lesions without development of new lesions for at least 1 month. Also, no deterioration of symptoms or PS unless secondary to drug toxicity. SD was defined as a decrease of less than 50% or an increase in tumor size less than 25% over the original measurements. Also, no deterioration of symptoms or PS unless secondary to drug toxicity. PD was defined as an increase of 25% or greater over the original measurements in the sum of the products of the two largest perpendicular diameters of any measurable lesions or the appearance of new lesion (s). Relapse was defined as occurring following a period of CR or PR when a former lesion reappeared or enlarged as above or a new lesion appeared in case of previous CR. Patients were evaluated before each cycle for lesions assessable by physical examination or chest x-ray; however, all patients were evaluated by the appropriate imaging studies indicative of the measurable target lesions every 3 chemotherapy cycles. Patients with disease regression or stabilization received up to 6 chemotherapy cycles. Patients with PD were withdrawn from the study. The duration of response was measured from the first documentation of response to PD.

6. Statistical analysis

Patients who received at least 2 cycles of treatment were evaluable for response and patients who received at least 1 cycle of treatment were evaluable for toxicity. Toxicity and DLTs analysis was carried out regarding patients entering the phase I evaluation, and after the recommended DL for phase II testing was defined, analysis of toxicity in the phase II part of the study was done separately. Response duration was measured from the day of its initial documentation until confirmed PD; TTP was calculated from study entry until evidence of PD; OS was measured from the day of entry until last follow-up or death. In the phase II part of the study, the 95% confidence intervals (CI) for response rates were calculated from the binomial distribution [14]. Median duration of response, median TTP, and actuarial OS were estimated by the product-limit method of Kaplan-Meier [15].

According to Simon's two-stage mini-max design [16] for phase II studies, a sample size of 50 patients has approximately 90% power to accept the hypothesis that the true response rate (RR) is >50%. At the first stage if less than 7 responses occur out of the first 24 patients, the study will conclude that the anticipated RR is < 30% and will terminate.

Results

1. Patient characteristics

Sixty-five patients entered the phase I-II study of docetaxel-ifosfamide combination between March 1997 and December 2001. Patients entered at 5 consecutive DLs in the phase I part of the study (Table 1) as follows: 21 were treated in phase I DLs (DL1:

3, DL2: 6, DL3: 3, DL4: 6, and DL5: 3) and the remaining 44 were treated at DL4, which was defined as the level for phase II testing. In total, 50 patients were treated at DL4 that was defined as the MTD (see below). Patient characteristics are demonstrated in Table 2. All patients were evaluable for toxicity (n=65) and 48/50 patients entering at DL 4 were evaluable for response in the phase II part of the study. The median age was 57 years (range 32-72) and the median WHO PS was 1 (range 0-2). Thirty-five (54%) patients were anthracycline-refractory and 30 (46%) were potentially anthracycline-sensitive according to the definitions. The median number of prior chemotherapy regimens, including adjuvant and/or anthracycline-based treatment, was 1 (range 1-3). The median interval from the end of the last chemotherapy regimen was 8 months (range 1.5-45). All patients received at least one chemotherapy cycle and were therefore evaluable for toxicity, while 62 out of 65 patients received at least two chemotherapy cycles and were therefore evaluable for response. DLT was reached at DL5 with 2/3 of the initial patients developing febrile neutropenia.

Table 2. Patient characteristics

Characteristic	*No. of patients*	*%*
Total patient number	65	100
Age (years)		
Median	57	
Range	32-72	
Performance status (WHO)		
0-1	54	83
2	11	17
Menopausal status		
Pre-menopausal	23	35
Post-menopausal	42	65
Histology		
Ductal	50	77
Lobular	6	9
Not specified	9	14
Hormone receptors		
ER -/PR-	14	22
ER+/PR-	12	19
ER+/PR+	23	35
ER -/PR+	10	15
Not done	6	9
No. of prior regimens		
1	39	60
2	24	37
3	2	3
Type of chemotherapy		
Adjuvant CAF	9	14
Neoadjuvant	8	12
Metastatic disease	30	46
Adjuvant+metastatic	18	28
Anthracycline sensitivity		
Sensitive	30	46
Refractory	35	54
Metastatic sites		
1	32	49
2	28	43
≥3	5	8

2. Toxicities

(i) Phase I

Five DLs were evaluable for toxicity in the phase I part of the current study. No DLTs were observed at DL1. At DL2 3/6 patients developed febrile neutropenia after the first cycle. The same DL was repeated with the addition of prophylactic G-CSF as DL3, and none of the 3 patients entered developed DLT. At DL4 1/6 patients entered developed febrile neutropenia. At DL5 2/3 of the initial patients developed febrile neutropenia and one of these sepsis and grade 3 diarrhea, managed successfully by broad spectrum antibiotics and other supportive care measures; neither further accrual of patients was undertaken nor further dose escalation was attempted beyond DL5 according to our preset definitions. No other important hematologic or non-hematologic grade 3/4 DLTs were observed in phase I (Table 3).

(ii) Phase II

Hematologic and non-hematologic toxicities encountered in the present study were evaluated in all patients and cycles and are shown in Tables 4 and 5, respectively. In brief, grade 3/4 toxicities included neutropenia (36/50, 72%) with 30/50 (60%) developing grade 4 neutropenia (≤ 7 days) and 5 (10%) of these febrile neutropenia. All were managed successfully with broad spectrum antibiotics. One patient with extensive liver metastases but no pretreatment deterioration of liver function (according to eligibility criteria) developed severe metabolic acidosis, liver enzyme and bilirubin elevation 16 h after the first dose of docetaxel and ifosfamide and died as a result of that complication 48 h later from multiorgan failure; her death could be attributed either to drug-related hepatic toxicity or acute tumor lysis syndrome or a combination of these factors. No other treatment-related deaths were observed. No grade 3 or 4 thrombocytopenia was observed. Anemia was cumulative in nature and 6/50

Table 3. Results of phase I docetaxel-ifosfamide dose escalation

DL	*No. of patients*	*No. of treatment cycles*	*DLT*	*Toxicity (Grade [Gr] 3 & 4)*
1	3	18	0/3	None
2	6	29	3/6	3 pts with Gr4 FN
3	3	15	0/3	1 pt with Gr4 neutropenia of < 7 days duration
4	6	32	1/6	1 pt with Gr4 FN
5	3	16	2/3	2 pts with Gr4 FN (1 with sepsis and Gr3 diarrhea)

DL: Dose level, DLT: dose-limiting toxicity (after 1st cycle), FN: febrile neutropenia, pt: patient

(12%) patients required packed red blood cell transfusions for grade 3 anemia. Grade 1 peripheral neuropathy was encountered in 11/50 (22%) patients, grade 2 in 5/50 (10%), while grade 3 peripheral neuropathy did not occur. Grade 1 and 2 only CNS toxicity attributed to ifosfamide was seen in 4/50 (8%) and 3/50 (6%) patients, respectively, and was rapidly reversible. The one patient progressing to coma after developing liver failure soon after docetaxel and ifosfamide could not be categorized as ifosfamide-related CNS toxicity. Moreover, no renal toxicity was seen, 4 patients developed grade 2 myalgias, while 6 patients developed grade 2 and 3 patients grade 3 diarrhea. Grade 3 nausea and vomiting was seen in 2 patients. No dose reductions or schedule modification were required for renal toxicity in any patient on study. Skin and nail toxicity due to docetaxel were mild in general; grade 2 nail toxicity occurred in 7/50 (14%) patients, consisting of limited onycholysis. Acute hypersensitivity reactions during docetaxel infusion occurred in only 3 patients, mainly in the form of facial flashing that resolved rapidly after temporary interruption of the infusion, with no further side-effects upon reinstitution of drug administration. Fluid retention taking the form of mild (grade 1) ankle edema occurred in 16/50 (32%) patients and was cumulative in nature, usually after the 5th or 6th cycle, while 1 patient developed grade 2 edema with small bilateral pleural effusions after the end of treatment, that resolved after a brief course of diuretics.

Table 4. Hematologic toxicities (phase II part of the study)

	NCI-CTC grade (% of patients, all cycles)				
Toxicity	*0*	*1*	*2*	*3*	*4*
Leukopenia	12	4	6	42	36
Neutropenia	12	4	12	12	60
Thrombocytopenia	62	34	4	0	0
Anemia	8	28	58	14	0
Febrile neutropenia	10%				

3. Compliance to treatment

In the phase I part of the study, 6 patients that developed DLTs continued with 20% dose reduction (Table 3).

In the phase II (including all patients entered at DL4), a total of 238 treatment cycles were administered (median 6, range 1-6), with a mean of 4.76 cycles per patient. Eighteen patients did not complete the planned 6 cycles due to the following reasons: 12 patients because of PD (1 after cycle 1, 7 after cycle 2, and 4 after cycle 3), 1 because of toxic death (liver failure) after cycle 1, and 5 after cycle 4 because of personal choice. Thirteen (7%) treatment cycles were delayed for 2-14 days (median 7) for the following reasons: 7 due to patient's own choice or logistic reasons of travelling from distant areas; 4 due to transfusion for grade 2/3 anemia; and 2 due to neutropenia (with ANC < 1500/μL) on the day of treatment.

Table 5. Non-hematologic toxicities (phase II part of the study)

	NCI-CTC grade (% of patients, all cycles)				
Toxicity	*0*	*1*	*2*	*3*	*4*
Nausea & vomiting	54	28	14	4	0
Mucositis	44	36	18	0	0
Myalgia/arthralgia	72	20	8	0	–
Neurologic					
Peripheral	68	22	10	0	0
CNS	84	8	6	0	2
Infection	98	2	0	0	0
Diarrhea	48	34	12	6	–
Hypersensitivity reactions	94	6	0	0	0
Alopecia	0	0	100	0	0
Skin/nail	43	43	14	0	0
Fluid retention	66	32	2	0	–
Asthenia/fatigue	32	38	20	10	–
Cardiac	100	0	0	0	0
Pulmonary	96	2	0	2	0
Renal	100	0	0	0	0
Hematuria	98	2	0	0	0

4. Dose intensity analysis

The administered median dose intensities for each drug of the docetaxel/ifosfamide combination in the phase II part of the study were as follows: for docetaxel 30.75 mg/m^2/wk (range 24.2-33.3), and for ifosfamide 1.54 g/m^2/wk (range 1.24-1.67), i.e. 92% (range 72.6-100%) of the planned dose intensities for both drugs.

5. Response to treatment and survival

In total, 62 patients were evaluable for response when both phase I and II parts of the study (all dose levels) were considered. Overall, 7 CRs and 28 PRs were recorded, for a 54% RR (95% CI 42-66%) on intention-to-treat (Table 6). When RRs were divided according to prior anthracycline sensitivity, 16/30 (56.5%; 95% CI 35.5-71.2) of anthracycline-sensitive patients *versus* 19/35 (54.3%; 95% CI 37.8-70.7) of anthracycline-resistant patients responded, the difference being not significant. Overall, median duration of response was 7 months (range 3-24), median TTP 6.5 months (range 0.1-26) and median OS 13 months (range 0.1-33). Median duration of response, median TTP and median OS for anthracycline-sensitive patients were 9 months (range 3-24), 6.5 months (range 0.2-26), and 13 months (range 1-33), respectively, while for anthracycline-refractory patients they were 6.5 months (range 3-14), 5 months (range 0.1-16), and 12 months (range 0.1-28), respectively. None of these values showed statistical significance.

Clinical RRs, on an intention-to-treat basis, in phase II (MTD) were as follows: 28/50 (56%; 95% CI 42.2-69.7) patients responded (4 CRs, and 24 PRs), 10 showed SD and 12 developed PD (Table 7). Again, no difference in RRs was observed between anthracycline-sensitive and anthracycline-refractory patients. The patient who died as a result of toxicity and the patient with rapid progression, both after the first cycle, were considered as PD. The median response duration was 7 months (range 3-24), median TTP 6.5 months (range 0.1-26), and median OS 13 months (range 0.1-33).

Table 6. Response to docetaxel-ifosfamide (all levels); n=56 patients

DL	*No. of assessable patients*	*No. of responses* *CR*	*PR*	*SD*	*PD*	*ORR(%)*
1	3	1	0	1	1	33
2	6	0	3	2	1	50
3	3	2	0	1	0	67
4 (phase II)	50	4	24	10	12	56
5	3	0	1	1	1	33
Total	56	7	28	15	15	54

CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease, ORR: overall response rate

Discussion

The rationale for combining taxanes (paclitaxel or docetaxel) with ifosfamide derives from both *in vitro* data and theoretical assumptions based on the properties of each individual cytotoxic agent to mediate its cellular damage. Most *in vitro* data exist with paclitaxel. In brief, paclitaxel inhibits the energy-dependent enzymatic reactions, by disengaging activated intracellular phosphate (eg, ATP and GTP), required for the repair of the DNA damage induced by cisplatin (causing kinking of the DNA double helix) and oxazaphosphorine (cyclophosphamide and ifosfamide) alkylating agents (prevention of DNA strand separation and unwinding). These different types of DNA lesion caused by cisplatin and oxazaphosphorine cytostatics are repaired by the nucleotide excision repair pathway (ERCC and XP genes) and the mismatch repair pathway (HNPCC gene) [17]. *In vitro* synergism has been demonstrated between paclitaxel and hydroperoxy-ifosfamide, an activated ifosfamide metabolite, against cisplatin-sensitive and resistant OC cell lines when paclitaxel preceded hydroperoxy-ifosfamide or during concurrent exposure, whereas the reverse sequence exhibited clear antagonism [18,19]. This might explain the importance of administering paclitaxel or docetaxel before the DNA-damaging agent.

Based on these preclinical *in vitro* experimental data, we believe that the sequence and infusion times regarding docetaxel and ifosfamide, as applied in the present study, might lead to potential *in vivo* synergism between these two drugs [20]. Moreover, our prior experience with paclitaxel-ifosfamide-cisplatin or docetaxel-ifosfamide-cisplatin combinations has demonstrated their feasibility in phase I and II studies in advanced solid tumors and lung cancer in particular [21-24].

If the above considerations regarding sequence-dependent interactions for optimal drug scheduling are important in order to maximize efficacy, of equal importance are the effects of drug sequencing related to bone marrow toxicity. Data from phase I clinical studies of the paclitaxel/cyclophosphamide combination employing different schedules of drug administration demonstrated variable hematologic toxicity. The highest

degree of hematologic toxicity was encountered when paclitaxel was administered by 24 h or 72 h continuous infusion with high doses of cyclophosphamide [25, 26]. However, when paclitaxel, given by 3 h infusion, was followed by cyclophosphamide, bone marrow toxicity was of much less severity [27]. Toxicity with the paclitaxel/cyclophosphamide combination appears to be lessened when paclitaxel follows cyclophosphamide. In contrast, with the docetaxel/ifosfamide combination, the schedule of administering the taxane first led to less hematologic toxicity and a higher MTD than did the reverse drug sequence [12]. It is therefore realistic to consider that the sequence of administration of docetaxel followed by ifosfamide could account for the tolerable hematologic toxicity, i.e. neutropenia and thrombocytopenia, encountered in our study up to high individual drug doses, that were achieved at DL4. Moreover, as grade 4 neutropenia and febrile neutropenia represented the only significant toxicities in our study, the 10% incidence of the latter appears rather low and compares favorably to that of single-agent docetaxel at 100 mg/m^2 with G-CSF support. The phase I study of Pronk et al. [12], that has evaluated the feasibility of the docetaxel-ifosfamide combination without G-CSF in pretreated patients with a variety of advanced solid tumors, determined the DLT of the combination being mainly neutropenia at the following doses: docetaxel 85 mg/m^2 on day 1 followed by ifosfamide 5 g/m^2 administered as 24 h infusion, and the recommended phase II doses were docetaxel 75 mg/m^2+ifosfamide 5 g/m^2 [12]. A subsequent pharmacokinetic analysis of the regimen by the same investigators found that the sequence of drug administration did not affect the clearance and the area under the curve (AUC) of docetaxel. However, there was a decrease in the AUC of ifosfamide in the schedule of docetaxel→ifosfamide compared with the reverse sequence, resulting from an increase in the clearance of ifosfamide. The authors suggested that the increase of ifosfamide clearance when it is given after docetaxel might be due to pretreatment with corticosteroids [28]. It is also possible that ifosfamide might yield a decreased AUC when administered by 24 h continuous infusion compared to short 1-2 h infusions fractionated over 2 or more days. Eventually, this might represent the major cause of reduced antitumor activity observed by prolonged infusions of ifosfamide compared to short 1-2 h fractionated daily administration of the same dose [29].

Ifosfamide combinations in advanced anthracycline-pretreated breast cancer have been applied in recent years. Combination of ifosfamide with vinorelbine demonstrated RR of 56% in a group of patients with no or minimally pretreated metastatic breast cancer [11]. The regimen proved to be tolerable at doses of vinorelbine of 35 mg/m^2 on days 1+15 and ifosfamide 2 g/m^2/day × 3 days in the outpatient setting. The combination of a fixed dose of doxorubicin 20 mg/m^2/day × 3 days with escalating doses of ifosfamide (1.2-2.75 g/m^2/day for 5 days) with G-CSF support in a phase I study focusing in stage IV chemotherapy-naïve breast cancer patients has yielded the feasibility of a quite high dose of ifosfamide 12.5 g/m^2 (total) with a RR of 83% of which 33% were CRs [9].

Moreover, ifosfamide has been combined with paclitaxel in a phase I study in patients with advanced heavily pretreated predominantly breast and ovarian malignancies including 13 patients with advanced anthracycline-pretreated breast cancer [10]. While the MTD reached for paclitaxel was 190 mg/m^2 by 24 h infusion and for ifosfamide 3.0 g/m^2/day for 3 days (total dose: 9.0 g/m^2), no major toxicities were encountered with this quite high dose of ifosfamide administered by short non-continuous daily infusion, while RR in breast cancer patients was almost 62% with 31% CRs in this study [10].

Another phase II study evaluating docetaxel and ifosfamide in women with heavily pretreated anthracycline- and hormone-refractory breast cancer led to early disappointment in view of no responses seen in the first 10 patients entered, with the authors concluding that antagonism between docetaxel and ifosfamide might be a plausible explanation. However, these data should be deemed rather premature and the schedule and doses administered were largely suboptimal; docetaxel 50 mg/m^2 on day 1 and ifosfamide 1.2 g/m^2/day × 3 days [30], compared to those defined in the study of Pronk et al. [12], as well as in the present study.

In the aforementioned phase I-II study of Pagani et al. [27], evaluating the paclitaxel/cyclophosphamide doublet, a dose-response effect was suggested for pretreated patients, with a lower RR reported for those receiving < 1500 mg/m^2 of cyclophosphamide [27]. Since equivalent cytotoxic alkylator doses of ifosfamide are anticipated at 4.5-6.0 g/m^2, the recommended phase II dose derived from our study regarding ifosfamide might represent an optimal alternative to cyclophosphamide with less hematologic toxicity. The preliminary activity of the paclitaxel/cyclophosphamide combination in the study of Pagani et al. [27] was rather poor in patients with prior anthracycline exposure (RR 25%). In contrast, an almost equivalent important clinical activity for anthracycline-sensitive *versus* - refractory disease was observed in our study, implying that either the incorporation of ifosfamide as a partially non cross-resistant agent to cyclophos-

phamide, or the activity of docetaxel *per se*, or both, might underlie that observation.

The value of ifosfamide in relapsed anthracycline-pretreated advanced breast cancer as single agent or in combination, despite promising phase II results, cannot currently be defined in the absence of randomized data. As the combination of docetaxel+ifosfamide in the phase II part of the present study yielded a 56% RR, it can be argued that similar results might have been obtained with single-agent docetaxel. However, the almost 55% RRs obtained with single-agent docetaxel in the early phase II studies [31,32] should be regarded as preliminary, since these have been based in small numbers of patients and subsequent randomized studies of single-agent docetaxel *versus* mitomycin-C+vinblastine or *versus* methotrexate+5-FU in anthracycline-refractory or heavily pretreated patients yielded RRs of 30% and 42%, respectively, for docetaxel [2,3].

Therefore, randomized phase III studies of single-agent docetaxel at 100 mg/m^2 *versus* the combination of docetaxel+ifosfamide, as defined in the present study, might address the value of adding ifosfamide to docetaxel, as well as the issue of cost-effectiveness of such a combination, since it is well appreciated that ifosfamide administration is rather cumbersome, even in the outpatient setting, expensive and requires multiple admissions (over 2-5 days) for each cycle. At present, our results can be viewed as having defined the MTD, the recommended phase II doses and RR of the docetaxel+ifosfamide combination. All these warrant further randomized phase III comparisons to docetaxel monotherapy or other active combinations of docetaxel with newer agents, such as gemcitabine, capecitabine or vinorelbine.

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