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Original article

Dose-finding study of paclitaxel and cyclophosphamide in advanced breast cancer

O. Pagani,[1] C. Sessa,[1] G. Martinelli,[3] T. Cerny,[2] J. de Jong,[1] A.Goldhirsch,[3] M. Zimatore [3] & F. Cavalli [1]

[1]*Servizio Oncologico, Ospedale S Giovanni, Bellinzona;* [2]*Medical Oncology, Inselspital, Bern, Switzerland;* [3]*European Institute of Oncology, Milan, Italy*

Summary

Background: The toxicity profile of prolonged infusions of paclitaxel in combination with cyclophosphamide in metastatic breast cancer has already been defined. The objective of this dose-finding study was to determine the maximum tolerable doses (MTDs) of shorter (three-hour) infusions of paclitaxel in combination with i.v. bolus cyclophosphamide in patients who had previously received a maximum of one chemotherapy for advanced breast carcinoma. The MTD of the same regimen with granulocyte colony-stimulating factor (G-CSF) support was then established.

Patients and methods: Eighty women with metastatic breast cancer received a total of 352 fully evaluable courses of therapy. The starting doses were paclitaxel 135 mg/m^2 and cyclophosphamide 750 mg/m^2 given every three weeks. At least three patients were treated at each dose level and if there were dose-limiting toxic effects during the first cycles three additional patients were entered. G-CSF support (5 μg/kg s.c.) was added to the second cycle if specific dose-limiting toxicities had occurred during the first cycle. The MTD was defined as the dose level at which more than two of six patients presented dose-limiting toxicities during the first cycle.

Results: Febrile neutropenia (n = 4) and severe thrombocytopenia (n = 1) defined the MTDs of paclitaxel as 200 mg/m^2 and of cyclophosphamide as 2,000 mg/m^2 with or without G-CSF in patients with and, respectively, without prior chemotherapy for advanced disease. Non-hematologic toxicity was moderate. Recommended doses were 200 mg/m^2 of paclitaxel and 1,750 mg/m^2 of cyclophosphamide with or without G-CSF in patients with and, respectively, without prior chemotherapy. The overall response rate was 25% and 50%, respectively, in patients with and without prior chemotherapy for metastatic disease. Complete remissions (9%) were reported only in patients without prior chemotherapy; antitumour activity in women with anthracycline-resistant disease, with an 8% response rate (95% CI: 1%–26%), was poor.

Conclusions: Paclitaxel at 200 mg/m^2 and cyclophosphamide at 1,750 mg/m^2 can be safely administered every three weeks to women with advanced breast cancer. The moderate antitumour activity observed with the schedule tested argues against its use as initial therapy for advanced breast cancer.

Key words: breast cancer, cyclophosphamide, G-CSF, paclitaxel

Introduction

Paclitaxel (P) has shown good antitumor activity in metastatic breast cancer, with results comparable to those achieved with anthracyclines [1, 2]. As first-line therapy, treatment with P given over 24 hours at doses between 200 and 250 mg/m^2 resulted in an overall response rate of 50%–60%, and a response rate of 20%–30% has been reported in patients treated at dosages between 175 mg/m^2 and 250 mg/m^2 as 3-hour or 24-hour infusions [3, 4]. Several trials were then designed to develop synergistic combinations with agents known to be active in breast cancer. The most extensively studied and thus far most promising of these is the one with doxorubicin. The observation that grade 3–4 mucositis was more frequent when P preceded doxorubicin, first reported by Holmes with P given as 24-hour infusion [5], was confirmed in subsequent studies [6], where an overall response rate between 50% and 80% was reported. Gehl et al. [7] and Gianni et al. [8] then reported response rates exceeding 80% in patients receiving P as a three-hour infusion in combination with bolus doxorubicin as initial treatment for metastatic breast cancer. The observation that the sequence of administration had no significant effect on the toxicity profile [8] and that severe cardiotoxicity with congestive heart failure occurred in 25% of patients after a cumulative dose of 480 mg/m^2 of doxorubicin, raised the issue of the cumulative dose and optimal scheduling of the anthracycline.

Cyclophosphamide (C) is the other candidate for combination studies with P because it is the standard alkylating agent used in both the adjuvant and the palliative settings, no mechanisms of cross-resistance with P are known, and neutropenia, the major overlapping toxic effect of the two drugs, could be ameliorated by the use of colony-stimulating factors. Results of two phase I trials evaluating the combination of P and C in metastatic breast cancer have already been

published. In the Johns Hopkins trial, P was given over 24 hours with intravenous bolus C and G-CSF support to patients with at least one prior chemotherapy for metastatic disease [9]. Neutropenia and typhlitis were dose-limiting (DLT) and the maximum tolerable doses (MTDs) were 200 mg/m^2 of P and 1,250 mg/m^2 of C. Sequence-dependent toxicities were observed, the sequence P/C being associated with deeper neutropenia and higher admission rate for neutropenic fever; pharmacokinetic interactions between the two drugs were not observed.

In the study conducted at the NCI by Tolcher et al., P was given over 72 hours with high-dose C, spread over three consecutive days, and G-CSF to patients mostly pretreated for metastatic disease with C and/or an anthracycline-containing regimen [10]. Myelosuppression was DLT and MTDs were established at 160 mg/m^2 of P and 2,700 mg/m^2 of C.

The primary objective of this study was to determine the MTD of the combination of P given by three-hour infusion and C in patients with advanced breast cancer. In a subsequent phase of the study the MTD of the same combination with G-CSF support was determined. The evaluation of the antitumor efficacy was a secondary endpoint of this trial, which was primarily a dose-finding study.

Patients and methods

Eligibility criteria

Patients with histologically or cytologically documented metastatic breast cancer who had received no more than one therapy regimen for advanced disease were eligible. One additional adjuvant treatment was acceptable if the time interval between the adjuvant and the chemotherapy for metastatic disease was longer than one year. Prior hormonal therapy for advanced disease was allowed if it had been discontinued at least four weeks before study entry. Eligibility criteria also included age younger than 75 years, an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less, adequate hematologic function (absolute neutrophil count ANC $\geq 2.0 \times 10^9$/l, platelet count $\geq 100 \times 10^9$/l), and normal renal and hepatic function. With respect to prior anthracyclines, a cumulative dose of ≤ 550 mg/m^2 doxorubicin or an equivalent dose of another anthracycline, anthrapyrazole or anthracene, was permitted. Written informed patient consent was required. Pre-existing motor or sensory neuropathy of World Health Organisation (WHO) grade ≥ 2 and a history of arrhythmias or congestive heart failure, even if medically controlled, were considered exclusion criteria.

Study treatment

Paclitaxel was supplied by the Bristol-Myers Squibb Company as 5 ml vials containing a concentrated sterile solution 6 mg/ml in polyoxyethylated castor oil 50% and dehydrated alcohol USP 50%. The calculated amount was diluted in 500 ml 0.9% saline solution and administered as a three-hour infusion. For administration, in-line filters (0.2 μ) (IVEX-2; Abbott Laboratories, Abbott Park, IL), glass containers, and polyethylene-lined nitroglycerin tubing were used. Premedication consisted of dexamethasone 20 mg orally 12 and 6 hours before administration plus ranitidine 50 mg and dimethindene 8 mg i.v. 30 minutes before P. Cyclophosphamide was administered diluted in 250 ml of 0.9% saline solution as a 30 min infusion following P. At least 1,500 ml of 0.9% normal saline was given as post-treatment hydration after a dose of C of at least 1,500 mg/m^2. Prophylaxis against hemorrhagic cystitis with mesna was not routinely applied. Prophylactic antiemetic treatment was given according to investigators' routine practice; the recommended regimen included i.v. $5HT_3$ antagonists and steroids the day of treatment followed by oral metoclopramide or thiethylperazine for the prevention of delayed emesis. G-CSF was provided by Amgen (Thousand Oaks, CA) as a 1 ml vial 300 μg/ml aqueous solution. When indicated, G-CSF 5 μg/kg/d was given s.c. from day 2 until day 19 or until the ANC was at least 2.0×10^9/l on two consecutive occasions, or until the ANC was 5.0×10^9/l, whichever occurred first. Prophylactic oral antibiotics, started whenever the ANC fell below 0.5×10^9/l and continued until the ANC had recovered to at least 1.0×10^9/l, were recommended. Ciprofloxacin 500 mg b.i.d. was the most frequently used treatment. Chemotherapy was repeated every three weeks provided the ANC was $\geq 2.0 \times 10^9$/l and the platelet count was $\geq 100 \times 10^9$/l. If recovery had not occurred after a treatment delay of a maximum of three weeks patients were withdrawn from the study.

Study design

The starting doses of P and C were 135 mg/m^2 and 750 mg/m^2, respectively. The dose of 135 mg/m^2 of P was selected on the basis of the available data on tolerability and antitumor activity of monochemotherapy in previously treated patients. The dose of C of 750 mg/m^2 was within the recommended range (600 to 1,000 mg/m^2) for this agent when administered in combination with antitumour drugs such as doxorubicin and/or 5-fluorouracil. Doses of both drugs were escalated sequentially by 15% increments in each successive cohort of new patients. Intra-individual dose escalation was not permitted. At least three patients had to be treated at each dose level, and if DLTS were observed in the three weeks following the first administration, three additional patients had to be entered at the same dose level. If DLTs were overall reported in more than two of six patients the MTD was considered to have been reached and dose escalation was discontinued. WHO criteria for toxicity were applied [11].

Dose modifications and G-CSF support

In all patients, G-CSF support was added at the next cycle in instances, during the previous course, of an ANC $< 0.5 \times 10^9$/l for more than seven days or an ANC $< 0.1 \times 10^9$/l for more than three days, febrile neutropenia requiring i.v. antibiotics, WHO $\geq$ grade 3 mucositis for more than seven days, or failure of ANC recovery by day 28. If in more than two of six patients there was the indication to add G-CSF support, because of occurrence of those DLTs in the three weeks following the first administration, G-CSF was given routinely already at the first cycle in patients being treated for the first time at the next higher dose level; at this stage, the second phase of the study, aiming at defining the MDT with G-CSF support, began. The doses of P and C were decreased by one level during subsequent cycles if a patient presented one of the DLTs for which G-CSF support was not indicated or if the patient, despite G-CSF support, again presented a DLT for which G-CSF support was indicated.

Definition of MTD

The MTD was reached if after the first cycle more than two patients presented a DLT that required G-CSF support or a DLT for which G-CSF was not indicated (i.e., platelet count $< 25 \times 10^9$/l requiring platelet transfusion, WHO $\geq$ grade 3 nonhematologic toxicity except for alopecia, nausea and vomiting, and grade 3 musculoskeletal pain) or persistence of WHO $\geq$ grade 2 nonhematologic toxicity (with the exception of alopecia, nausea and vomiting, and musculoskeletal pain) at scheduled retreatment. Identical criteria were applied to define the MTD of the second phase of the study with G-CSF support.

Disease evaluation and treatment duration

It was required that baseline evaluations, including history, physical examination, complete blood cell count, biochemistry, electrocardiogram, chest X-ray, and radiologic imaging of indicator lesions, be carried out within two weeks prior to study entry. Echocardiography was performed in patients with a cumulative doxorubicin dose $\geqslant 300$ mg/m^2. During therapy, complete blood cell counts were performed at least twice weekly and biochemistry evaluations before each cycle. Assessment of tumour response was performed after the first two cycles in the absence of clinical evidence of early tumour progression, and every two courses thereafter. The WHO criteria for response were applied [11]. Responses had to be confirmed by a subsequent evaluation performed after at least four weeks. Patients with progressive disease went off study, while in responders treatment had to be continued until relapse, unacceptable toxicity, or for four cycles after achievement of complete (CR) or partial response (PR). To avert cumulative non-hematologic toxicity, a maximum of 10 cycles was given. In patients with stable disease (SD) treatment could be continued for up to six cycles at the discretion of the investigator. The duration of response was calculated from the start of treatment.

Results

From September 1992 to June 1996, 80 patients with advanced breast cancer entered the study (Table 1). Their median age was 49.5 years (range 27 to 70 years), and in 91% the performance status was 0–1. Dominant site of disease, defined as the metastatic site most relevant in the evaluation of antitumour efficacy, was liver in 43%; 52% of the patients had at least two metastatic sites and 43% had already received one chemotherapy regimen for advanced disease. One young patient, treated with P at 200 mg/m^2 and C at 1750 mg/m^2, had received adjuvant high-dose chemotherapy with peripheral stem cell transplantation 11 months before entering the protocol. Only 16 patients had received no prior chemotherapy. Forty-three percent of the patients had undergone radiotherapy, either complementary to primary surgery or for metastatic disease, and 56% had received previous hormonal therapy, in 82% for metastatic disease.

Of 49 patients (61%) pretreated with anthracyclines, 25 were considered anthracycline-resistant because of tumour relapse within six months from the last doxorubicin administration (10 patients), tumour progression after an initial response (seven patients) and tumour progression while on anthracycline without an intervening response (eight patients). Forty-nine patients (61%) were pretreated with C.

A total of 382 courses of therapy were administered, of which 352 (92%) were fully evaluable for hematologic toxicity. The doses of P and C were escalated through 10 dose levels from 135 to 200 mg/m^2 of P and 600 mg/m^2 to 2,000 mg/m^2 of C (Table 2). The median number of cycles administered to all patients was 5 (range 1 to 10); two patients discontinued treatment after one cycle due to early progression of disease, one patient died of toxicity after the first cycle and one patient refused therapy after the first course. All patients were evaluable for toxicity.

Table 1 Patient characteristics.

	No. of patients
Entered	80
ECOG performance status	
0–1	73
2	7
Dominant disease site	
Liver	35
Lung	24
No. of metastatic sites	
1	38
2	31
$\geqslant 3$	11
Prior CT	
Adjuvant only	28
Metastatic disease only	17
Both	19
Prior anthracyclines	49
Anthracycline-resistant	25

Table 2 Dose escalation.

Dose level	P/C dose (mg/m^2)	Prior CT[a] pts/cycles	No prior CT[a] pts/cycles	Total eval. pts/cycles
1	135/750	3/8	0/0	3/8
2	155/750	5/17	1/4	6/20
3	175/600	3/8	1/4	4/12
4	175/750	4/11	3/24	7/35
5	200/750	3/13	6/28	9/41
6	200/1000	3/19[b]	6/30	9/36
7	200/1250	3/15	3/17	6/31
8	200/1500	3/17	5/26	8/36
9	200/1750	6/31	14/81	20/97
10	200/2000	6/27	2/12	8/36

[a] CT – chemotherapy for advanced disease.
[b] G-CSF given from the first cycle.

Hematologic toxicity

Neutropenia was the main toxicity, with an overall median ANC nadir of 0.4 × 10^9/l (range 0 to 9 × 10^9/l) and a median time to ANC nadir of 12 days (range 5 to 32 days). Grade 4 neutropenia occurred at all dose levels; overall, febrile neutropenia occurred in 5% of cycles and the incidence of febrile neutropenia was similar at all dose levels except at the highest (P/C 200/2,000 mg/m^2), where 20% of cycles were associated with neutropenic fever. Documented infections were uncommon and never severe.

The most relevant features of hematologic toxicity per dose level in patients pretreated or non-pretreated with chemotherapy for advanced disease are reported in Tables 3 and 4, respectively.

No distinctions were made at the lowest dose levels between patients pretreated or not for advanced disease. Of six patients treated at dose level 2 (P/C 155/750 mg/m^2), two had an ANC below 0.1 × 10^9/l for more than three days, one after the first cycle and one after the second cycle. In the first patient, a 70-year-old pre-

Table 3 Hematologic toxicity in patients pretreated with chemotherapy for advanced disease.

Dose level	Dose P/C (mg/m^2)	Evaluable pts/ cycles	ANC nadir median	× 10^9/l range	Days ANC <0.5 (median)	Pts with G3/4 neutropenia (all cycles)	Plt nadir median	× 10^9/l range	Pts with G3/4 thrombopenia (all cycles)	DLTs (cycle 1)	DLTs (all cycles)
2	155/750	5/17	0.26	0.01–2.1	2	1/3	134	15–331	0/1	1[b]	
3	175/600	3/8	0.18	0.05–1.5	3.5	0/2	192	90–292	0/0		
4	175/750	4/11	0.35	0 04–0.8	4	1/3	197	163–305	0/0		
5	200/750	3/13	0.32	0.01–2.6	2	0/3	157	105–230	0/0	2[c]	3
6	200/1000	3/9	2.7[a]	0.2–5.7	0	0/1	91	46–150	1/0		
7	200/1250	3/14	1.1[a]	0.13–3.7	0	0/2	151	38–216	1/0		
8	200/1500	3/15	1.2[a]	0.06–9.0	0	1/1	171	57–248	0/0		
9	200/1750	6/27	0.3[a]	0.01–2.3	1	1/5	134	42–230	1/0		2
10	200/2000	6/24	0.35[a]	0–3.0	3	0/6	81	9–211	1/2	3[d]	4

Abbreviation: DLT – dose-limiting toxicity.
[a] G-CSF given from the first cycle.
[b] ANC $<0.1 \times 10^9$/l >3 days.
[c] Febrile neutropenia and ANC $<0.1 \times 10^9$/l $>$ 3 days in 1 pt each.
[d] Febrile neutropenia in 2 pts and grade 4 thrombocytopenia in 1 pt.

Table 4. Hematologic toxicity in patients non-pretreated with chemotherapy for advanced disease.

Dose level	Dose P/C (mg/m^2)	Evaluable pts/ cycles	ANC nadir median	× 10^9/l range	Days ANC <0.5 (median)	Pts with G3/4 neutropenia (all cycles)	Plt nadir median	× 10^9/l range	Pts with G3/4 thrombopenia (all cycles)	DLTs (cycle 1)	DLTs (all cycles)
1	135/750	3/8	0.3	0.2–1.2	4.5	0/3	163	77–269	0/0		
2	155/750	1/3	0.9	0.7–1.6	0	1/0	174	166–413	0/0		
3	175/600	1/4	0.26	0.09–0.3	3	0/1	137	125–155	0/0		
4	175/750	3/24	0.59	0.13–2.6	0	0/3	202	115–340	0/0		
5	200/750	6/28	0.51	0.01–4.0	0	2/4	235	75–340	0/0		
6	200/1000	6/27	0.5	0.02–2.2	0	2/4	228	143–289	0/0		
7	200/1250	3/17	0.55	0.1–2.2	0	1/2	195	152–271	0/0		
8	200/1500	5/21	0.5	0–1.8	0	1/4	231	130–350	0/0		1
9	200/1750	14/70	0.3	0–1.6	4.5	0/14	170	15–304	0/2	1[a]	2
10	200/2000	2/12	0.31	0.02–2.8	3	0/2	141	57–383	0/0	2[b]	

Abbreviation: DLT – dose-limiting toxicity.
[a] Toxic death during grade 4 neutro- and thrombocytopenia.
[b] Febrile neutropenia in 2 pts.

treated woman with bone metastasis, severe myelotoxicity developed after the third cycle despite the addition of G-CSF during the second cycle as per protocol. The patient presented acute dyspnea and died nine days after P with grade 4 anemia, neutropenia and thrombocytopenia, without clinical signs of infection or bleeding; post-mortem examination was not performed, and myocardial infarction or lung embolism could not be ruled out.

Because of the neutropenia observed, the dose of P was escalated to 175 mg/m^2 while C was decreased to 600 mg/m^2 at dose level 3, without the occurrence of hematologic DLTs. At dose level 5, two of three patients pretreated for advanced disease required G-CSF support at the second cycle (due to febrile neutropenia in one case and to an ANC below 0.1×10^9/l for more than three days in the other) (Table 3); G-CSF was added during the first cycle in pretreated patients from dose level 6 (P/C 200/1,000 mg/m^2). It was also decided not to escalate further the dose of P to avoid cumulative neurotoxicity. No DLTs were encountered up to a C dose of 2,000 mg/m^2 (dose level 10) where three of six patients developed DLTs consisting of febrile neutropenia in two cases and grade 4 thrombocytopenia in 1.

In patients non-pretreated for advanced disease (Table 4) the dose of C was increased without the addition of G-CSF up to 2,000 mg/m^2 where the first two patients suffered at the first cycle DLTs for which G-CSF was indicated. The MTDs of P and C were therefore 200 mg/m^2 and, respectively, 2,000 mg/m^2 of C with or without G-CSF in patients with and, respectively, without prior chemotherapy; the recommended doses of P and C were 200 mg/m^2 and, respectively, 1,750 mg/m^2, with G-CSF support only in pretreated patients.

A total of 20 patients, either pretreated or not were then entered at the recommended dose to better define toxicity and antitumour activity. Thrombocytopenia was of lower degree than neutropenia and more pronounced in patients who had previously received chemotherapy

(Tables 3 and 4). A 65-year-old patient with lung metastasis previously untreated with chemotherapy developed dizziness and confusion after the first cycle at dose level 9 associated with grade 4 neutro- and thrombocytopenia. No signs of infection or septic shock were present, renal and liver function test results were within the normal ranges, while an uncontrolled diabetes mellitus was treated without objective improvement. CNS bleeding was clinically diagnosed but the patient died before any further examination could be performed; postmortem examination was not permitted by the family.

Overall, hematologic toxicity was not cumulative without a significant increase of DLTs after repeated administrations.

RBC transfusions were administered to 12 patients during 18 cycles (5%); the rate of RBC transfusions was similarly distributed among all dose levels.

Table 5. Grade 2 or greater non-hematologic toxicities.

Dose level	Dose P/C (mg/m^2)	Peripheral neuropathy pts/cycles with toxicity	Myalgia pts/cycles with toxicity	Mucositis pts/cycles with toxicity	Evaluable pts/cycles
1	135/750	0/0	1/2	1/1	3/8
2	155/750	1/2	1/1	1/1	6/20
3	175/600	3[a]/5	4/4	0/0	4/12
4	175/750	0/0	3/4	0/0	7/35
5	200/750	2/2	5/11	0/0	9/41
6	200/1000	6/11	5/9	1/1	9/36
7	200/1250	2[b]/5	2/3	0/0	6/31
8	200/1500	1/3	8/17	0/0	8/36
9	200/1750	4/6	6/8	1/1	20/97
10	200/2000	2/2	3/3	0/0	8/36

[a] DLT in 2 pts.
[b] DLT in 1 pt.

Non-hematologic toxicity

Paclitaxel-related myalgia and peripheral neuropathy were the most common non-hematologic toxicities (Table 5) together with alopecia, which was universal at all the dose levels tested. Mild to moderate myalgia, sometimes in association with neuropathy, was frequent, especially for doses of P >175 mg/m^2; myalgia appeared during the week following treatment and was usually controlled with nonsteroidal anti-inflammatory drugs.

Peripheral neuropathy was first seen at dose level 2 (with P dose of 155 mg/m^2): it was generally mild and mostly sensory, restricted to distal extremities. Peripheral neuropathy of grade 2 or greater occurred in 23% of patients treated with P at 200 mg/m^2. The majority of these patients (58%) developed peripheral neuropathy after two to three cycles (median 3, range 2–8). Two patients treated at dose level 3 (with P at 175 mg/m^2 and C at 600 mg/m^2) and one patient treated at dose level 7 (with P at 200 mg/m^2 and C at 1,250 mg/m^2) developed grade 3 peripheral neuropathy, associated with weakness and impairment of function, which was dose limiting and required treatment discontinuation after three (total P dose: 900 mg), four (total P dose: 1,320 mg) and six (total P dose: 1,950 mg) cycles. Motor polyneuropathy slowly improved but peripheral paresthesia was still present 11, 9 and 6 months after the last P administration.

Other non-hematologic toxicities were uncommon; nausea and vomiting, probably because of the high-dose glucocorticosteroids administered as premedication, was rare, mucositis was infrequent and of only mild to moderate degree.

One patient with a single liver metastasis, treated with P at 200 mg/m^2 and C at 1,500 mg/m^2, developed severe liver toxicity with jaundice after the second course of therapy: hepatitis tests all yielded negative results while liver biopsy demonstrated diffuse hepatocytic damage with intrahepatic cholestasis, compatible with drug-induced toxicity. The patient was receiving prophylactic oral ciprofloxacin and ketoconazole which had not been given at the first cycle. The causal relationship with study drug was classified as possible.

Four patients treated at dose levels 9 and 10 (with C at 1,750 mg/m^2 and 2,000 mg/m^2) developed hemorrhagic cystitis requiring mesna administration and increased post-treatment hydration.

Antitumor efficacy

Two patients were not evaluable for response because of toxic death in one case and refusal of treatment in the other, both after the first cycle. Among 78 evaluable patients, the overall response rate was 38% (95% CI: 28%–50%) with 38% of patients showing tumour progression. Of 63 patients with measurable disease, 35% achieved partial and 6% complete responses, for an overall response rate of 41% (95% CI: 29%–54%). Major responses were documented at a variety of sites including liver (10 patients), lung (12 patients) and soft tissue (14 patients).

The response rate in 36 patients receiving P and C as salvage therapy was 25% (95% CI: 12%–42%) while it was 50% (95% CI: 34%–66%) with 9% of complete remissions in 42 evaluable patients who received it as initial treatment. In the latter group of patients, the antitumour efficacy seemed to be lower in patients receiving less than 200 mg/m^2 of P, with no response among eight patients treated, while a higher response rate of 60% was reported in patients receiving P at 200 mg/m^2. In addition, the response rate was comparable in the group treated with C at dosages of up to 1500 mg/m^2 or higher, while in patients pretreated with chemotherapy a lower response rate was reported in those receiving less than 1500 mg/m^2 of C (16% vs. 50%). Overall, the median time to progression in responders was 7.5 months (range 4 to 21+) with no difference in duration of response between patients pretreated or non pretreated with chemotherapy. The antitumor efficacy in patients resistant to anthracyclines was poor, with

objective responses in 2 of 25 patients (8%; 95% CI: 1%–26%), while the response rate in patients who received anthracyclines as adjuvant therapy was 37%.

Discussion

A variety of multidrug regimens with paclitaxel (P) are currently under evaluation in different stages of breast cancer. The high complete response rate achieved with P and doxorubicin in patients with metastatic disease [8] has established this combination as thus far the most effective in advanced disease, and has prompted its evaluation as adjuvant treatment. On the other hand, the reported antitumour activity of P in patients resistant to anthracyclines suggested that combinations with P and C might be of value in this setting, as well as in tumour types other than breast which are sensitive to both antitumour agents.

The results of the present study indicate that P and C can be given together without G-CSF at doses of 200 mg/m^2 as a three-hour infusion and, respectively, 1750 mg/m^2 i.v. bolus, to patients without prior chemotherapy for metastatic disease. The addition of G-CSF from the first course of therapy allowed the delivery of the same doses also to patients with one prior regimen for advanced disease. As in the other studies where the combination was evaluated in pretreated patients, neutropenia was dose-limiting [9, 10]. In the present study, however, the use of a shorter infusion of three hours of P and of a single i.v. bolus of C, instead of the one-hour infusion or of the three daily consecutive doses of C, was associated with a lower incidence of febrile neutropenia requiring i.v. antibiotics. Overall, only 5% of cycles were complicated by febrile neutropenia, increased to 20% at the MTD but without documented severe infections or toxic deaths. In the NCI study in which a 72-hour infusion schedule was used, a higher incidence of febrile neutropenia requiring i.v. treatment was observed, possibly related to the higher number of pretreated patients as well as to the incidence of cumulative diarrhea and damage to the intestinal mucosa [10].

Even though the impact of drug sequencing upon toxicity was not an objective of this study, a sequence analysis was undertaken in the six patients treated at dose level 2 (with P at 155 mg/m^2 and C at 750 mg/m^2). The first three patients at each dose level received P immediately before C at cycle 1 and C before P at cycle 2; the ANC and Plt nadirs were 0.2 X 10^9/l (range 0.1 to 1.2 × 10^9/l) and 110 × 10^9/l (range 95 to 245 × 10^9/l). In the subsequent three patients who received the alternate sequence, the ANC and Plt nadirs were 0.9 × 10^9/l (range 0.01 to 1.4 × 10^9/l) and 160 × 10^9/l (range 79 to 166 × 10^9/l). These preliminary observations confirm the results of the John Hopkins study where a higher admission rate for fever and a lower average nadir ANC were observed in the courses in which P was given before C [9]. Peripheral neuropathy was the main non-hematological toxicity; it was mainly sensory, cumulative and occurred in 23% of patients receiving P at 200 mg/m^2; because of the higher incidence of peripheral neuropathy observed with higher doses of P, rising to 26% and 40% of grades 2 or 3 toxicity at 225 mg/m^2 and 250 mg/m^2 as a three-hour infusion [4, 12] and of the still unproven higher efficacy of greater doses of P, it was decided to keep the dose of P at 200 mg/m^2 and to escalate further only the dose of C. Nevertheless, three patients developed severe motor polyneuropathy, which was dose limiting and required treatment discontinuation, after cumulative doses of 900, 1320 and 1950 mg/m^2.

In the present study, the overall response rate in 78 evaluable patients was 38% (95% CI: 28%–50%). The overall response rate in patients non-pretreated for metastatic disease was 50% (95% CI: 34%-66%) with 9% complete remissions while it was 25% in patients with one prior regimen for advanced disease. These results, like those of Kennedy et al. [9] who reported an overall response rate of 28% in a population of heavily pretreated anthracycline refractory patients, are comparable to those achieved with a similar dose of P given as a three-hour infusion in patients with [3, 4, 13] or without prior chemotherapy [12]. This suggests that the addition of single i.v. doses of C does not improve the antitumour activity of P when given at 200 mg/m^2 as first-line therapy; the observation of an apparently higher antitumour activity in the group of pretreated patients receiving C at dosages equal or greater than 1500 mg/m^2 (50% vs. 16%) suggest that significant doses of C should be used in this subgroup. This observation is also partly supported by the higher antitumour activity of 55% reported in the NCI study where P was given as a 72-hour infusion and C was administered at the highest dose tested of 2700 mg/m^2 in patients mostly pretreated with alkylating agents and/or anthracycline-containing regimen [10].

The results achieved in studies assessing the antitumour efficacy of P in patients with anthracycline-resistant tumours are difficult to evaluate because of the limited number of patients, differences in characteristics of the disease, differences in prior treatment and in the definition of resistance to anthracyclines. In this study, the response rate in anthracycline-resistant patients was disappointingly low (8%) and comparable to the 9% reported with single-agent P given as a three-hour infusion [13]. It may be that prolonged infusions are associated with better antitumour activity, as already reported, with similar response rates in patients resistant or not to anthracycline [3]. The small sample size of these studies, however, does not permit ruling out a true difference; this needs to be confirmed in further studies. Preclinical *in vitro* data [14] in human breast carcinoma cell lines suggest that maximal cytotoxicity may result from prolonged paclitaxel infusions: two ongoing randomized studies in metastatic breast cancer will definitely clarify the characteristics of toxicity and activity of 3-, 24- or 96-hour infusions [15] and will define the optimal schedule of P.

In conclusion, this study demonstrates that P by three-hour infusion can be given safely in combination with significant doses of C on an outpatient basis; however, the 50% overall response achieved in patients non-pretreated for metastatic disease does not support its use as first-line therapy due to the availability of other more active combinations. The combination might be of some benefit in those patients who received adjuvant anthracyclines and developed tumour recurrence at least six months after the completion of treatment; in this group of patient the overall response rate was 37%. The 25% overall response rate and the acceptable profile of toxicity observed at doses of P and C of 200 mg/m^2 and 1750 mg/m^2 in pretreated patients indicate that this regimen might represent a valuable salvage treatment, not only in breast cancer but also in other tumor types sensitive to P and alkylating agents, such as ovary and lymphoma, provided C is given at doses of at least 1500 mg/m^2. The good PBSC mobilisation produced by P and C followed by G-CSF suggest a further development of this combination in sensitive neoplasia [16, 17] as cytoreductive treatment before high-dose chemotherapy with stem cell rescue.

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Correspondence to.
Dr. Cristiana Sessa
Division of Oncology
Ospedale San Giovanni
6500 Bellinzona, Switzerland