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ORIGINAL ARTICLE

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Paclitaxel administration on days 1 and 8 every 21 days in anthracycline-pretreated metastatic breast cancer patients. A multicenter phase II trial

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Abstract Paclitaxel is now included in second- and even first-line regimens in advanced breast cancer. The optimal dose and schedule of this drug, however, still remain a matter of investigation. A group of 57 consecutive patients with advanced breast cancer previously treated with anthracycline-containing regimens were submitted to treatment with single-agent paclitaxel administered at 130 mg/m^2 on days 1 and 8 every 21 days. Of the 57 patients, 56 were fully evaluable, and of these 25 had an absolute anthracycline resistance, 14 a relative resistance and 17 were potentially sensitive. The median age of the patients was 57 years (range 33–71 years), their median performance status was 1 (0–3), and 27 (47%) had liver involvement, 17 (30%) lung involvement, 30 (53%) bone involvement and 15 (26%) skin/lymph node involvement. Toxicity was recorded in 295 cycles. This scheme was well tolerated, the dose-limiting toxicities being hematological and neurological. Grade 3/4 leukopenia was observed in 20% of patients at nadir, while grade 3 leukopenia was observed in 3% of patients at recycle. Only one patient experienced febrile neutropenia. Grade 2/3 neurotoxicity was observed in 26% of patients, leading to drug withdrawal in three. The treatment was given on an outpatient basis in all patients and the median relative dose intensity of 86.6 mg/m^2 per week was 100% of the planned dose (range 75–100%). Three patients (5%) attained a complete clinical response and 12 (21%) a partial response for an overall response rate of 26% (95% confidence interval 18–38%), while 30 (53%) attained disease stabilization and 11 progressed (19%). Time to progression in responding patients was 10.3 months, and the median overall survival of the entire population was 15.4 months. To conclude, paclitaxel administration on days 1 and 8 every 21 days was active and manageable in advanced breast cancer patients previously treated with anthracyclines. The response obtained was durable.

Key words Paclitaxel · Breast cancer · Anthracyclines · Second-line chemotherapy

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Introduction

Breast cancer still remains the leading cause of death from cancer among women in Italy [35]. There is no known treatment that appears to substantially prolong disease-free survival or overall survival of patients with advanced disease. The main goal of therapy is the palliation of symptoms [14]. Cytotoxic chemotherapy

has become established as a key element in multimodality treatment. To date anthracyclines, notably doxorubicin and epirubicin, are the most active agents, yielding excellent response rates both as single agents and in combination therapy [6, 8, 23, 34]. Objective response rates to second- or third-line therapy with other cytotoxic agents, such as cisplatin, mitomycin-C and mitoxantrone, in patients previously exposed to anthracyclines are rare (15–20% on average) and the median duration of response is generally very short [5, 21, 27]. Anthracyclines are now increasingly employed in an adjuvant setting and this represents a hindrance, leading to limitation of their use in relapsed patients. Patients who relapse or have progressive disease during or immediately after adjuvant anthracycline treatment have a poor prognosis and a low chance of achieving an objective response when treated with other cytotoxic agents [17, 21].

New active agents and strategies are therefore needed. Recent studies have suggested that a new class of drugs, the taxanes, have the ability to elicit responses in patients with anthracycline-resistant tumors. Paclitaxel is the prototype of these chemotherapeutic agents. It has a unique mechanism of action: promoting intracellular tubulin polymerization and stabilizing abnormal microtubule structures [19]. In phase I/II studies, this drug has shown significant activity in metastatic breast cancer, with a response rate of 30–62% in patients with no prior exposure to cytotoxic agents and 21–30% in heavily pretreated patients [1, 11, 15, 24, 29, 30]. Short paclitaxel infusion (3 h) has been found to be well tolerated using an appropriate premedication [18, 29, 30]. In the majority of the trials, the drug was delivered in a 1-day schedule of administration using various doses ranging from 135 to 250 mg/m^2 every 21 days. Randomized trials comparing different doses administered in a 3-week schedule, however, have failed to demonstrate a dose/response relationship, while higher doses have been associated with a greater degree of toxicity [24, 37].

More recently, the administration of paclitaxel in a weekly or biweekly schedule has been shown to be very active in the treatment of advanced breast cancer [9, 31]. The rationale of such an approach is found in Norton's concepts of cell kinetics and tumor growth [26]. These suggest that reducing the interval between treatments should minimize the appearance of drug-resistant cell clones and regrowth, providing a greater opportunity for log tumor cell kill. The delivery of lower, more frequent doses of paclitaxel has been found to alter the toxicity profile. Sensory neuropathy has proven to be the dose-limiting toxicity, whereas myelosuppression is modest [7, 28, 31]. The optimal dose and schedule for delivering the drug on a substantial weekly schedule is still a matter of investigation. In this multicenter phase II trial we evaluated the activity and the safety of single-agent paclitaxel administered on days 1 and 8 every 21 days in anthracycline-pretreated breast cancer patients.

Patients and methods

Eligibility criteria

To be eligible for this study, patients had to meet the following criteria: age more than 18 years and less than 75 years; histologically confirmed breast cancer with clinical evidence of progressive metastatic disease; presence of measurable disease; previous exposure to an anthracycline regimen, either in an adjuvant setting (providing that they had relapsed within 12 months of completion of chemotherapy) or for advanced disease, or as a contraindication to further anthracycline therapy for a prior cumulative doxorubicin dose of 550 mg/m^2 or for a prior cumulative epirubicin dose of 1000 mg/m^2; ECOG performance status of 0–3; estimated life expectancy 12 weeks or more; adequate bone marrow function (absolute neutrophil count ≥2000 cells/μl, hemoglobin count ≥10 g/dl and platelet count > 100,000/μl); normal hepatic and renal function (total serum bilirubin < 1.5 mg/dl and serum creatinine < 1.5 mg/dl).

All patients were allowed to have received prior radiotherapy if it had been completed 4 weeks or more before study entry. An assessable target lesion should not have been irradiated. Hormonal agents, either as adjuvant treatment or as therapy for metastatic disease were allowed, but they had to have been discontinued at least 4 weeks before study entry.

Exclusion criteria were the presence of symptomatic brain metastases; history of primary malignant neoplasm other than curatively treated basal cell or squamous cell carcinoma of the skin or in situ carcinoma of the cervix surgically cured; history of myocardial infarction within the past 6 months; documented coronary artery insufficiency; chronic congestive heart failure; severe infections; previous history of grade 2–3 peripheral neuropathy of any etiology; previous treatment with taxanes. Each patient provided informed consent to the treatment.

Assessment of response and toxicity

Pretreatment evaluation included a complete medical history and physical examination, hematological tests and blood biochemistry, electrocardiogram and a baseline echocardiogram, chest radiograph, bone scan, liver ultrasound. A computed tomographic scan was performed only when indicated to evaluate bidimensionally measurable disease (i.e. liver metastases). A complete blood count was performed before every paclitaxel administration (on days 1 and 8) but was optional on the 15th day. A repeat history and physical examination with documentation of toxicity were performed before each cycle. Baseline laboratory studies as earlier were repeated on day 1 of each cycle.

Antitumor activity was evaluated every three courses on all measurable lesions and all patients were scheduled for at least two cycles in order to be eligible for assessment of tumor response. In patients with tumor response or stable disease, the treatment was continued up to a maximum of six cycles. Tumor response was classified according to the WHO criteria [22] and documented with appropriate scan or examinations by two investigations 6 weeks a part. Response was defined as complete response (CR, disappearance of all measurable disease), partial response (PR, ≥50% reduction in the sum of the products of two perpendicular diameters of all measurable disease), stable disease (SD, < 25% change in measurable disease) or progressive disease (PD, ≥25% increase in any measurable disease site or the appearance of new lesions). In cases of multiple measurable lesions, response assessment was limited to the four or five best indicator lesions. Toxicity was re corded according to WHO criteria [22].

The level of resistance to anthracyclines was classified according to the definitions listed in Table 1. Time to disease progression was defined as the period between the first day of treatment and the date at which disease progression was documented or death occurred for whatever reason. Overall survival was defined as the period from the first day of chemotherapy to the patient's death.

Table 1 Level of anthracycline resistance (*TFI* treatment-free interval)

Level of resistance	Definition
Absolute	Relapse within 6 months after adjuvant anthracycline
	Progression following or no response to first-line anthracycline for metastatic disease
Relative	Relapse between 6 and 12 months after adjuvant anthracycline
	TFI ≤ 6 months after an objective response to first-line anthracycline for metastasis
Potentially sensitive	Relapse ≥12 months following adjuvant anthracycline
	TFI > 6 months after an objective response to first-line anthracycline for metastasis

Treatment plan and dose modification

Chemotherapy consisted of paclitaxel (Taxol; Bristol Myers Squibb, Rome, Italy) at a dose of 130 mg/m^2 on days 1 and 8, given as a 3-h infusion in 500 ml saline solution. Cycles were repeated every 3 weeks. To prevent hypersensitivity reactions, all patients were pretreated with prednisone 25 mg orally 12 h before paclitaxel, and with hydrocortisone 250 mg intravenously, cimetidine 300 mg intravenously and chlorphenamine 10 mg intramuscularly 30 min before paclitaxel. G-CSF (granulocyte colony-stimulating factor) was not planned to be used systematically.

On days 1 and 8 of each cycle, patients had to have an absolute neutrophil count of ≥1500/μl and a platelet count of ≥100,000/μl. In cases of leukopenia/thrombocytopenia, the day 1 administration was postponed by 1 or 2 weeks until acceptable blood values returned, and the day 8 administration was omitted. Patients requiring a delay of more than 2 weeks in day 1 treatment were withdrawn from the study. Paclitaxel administration was planned to be stopped in cases of grade 4 extrahematological toxicities and for neurotoxicity of WHO grade 3 or more.

Statistical analysis

According to the optimal two-stage phase II study design of Simon [33], the samples size was assessed in order to refuse response rates ≤ 15% (p0) and to provide a statistical power of 80% in assessing the activity of the regimen as a 30% response rate. The upper limit for the first-stage drug rejection was three responses out of the first consecutive 19 patients, the upper limit of the second-stage rejection was 12 responses out of 55 patients consecutively enrolled. Response duration and survival were assessed using Kaplan-Meier survival curves. All analyses were performed using the SPSS/PC software program [25].

Results

The schedule adopted in the present study derived from a phase I study performed in two institutions involving a total of 18 metastatic patients with various primary malignancies (non-small-cell lung cancer, head and neck carcinoma, breast cancer, mesothelioma and prostate cancer). All these patients had progressive disease following first- or second-line chemotherapy. The initial dose of paclitaxel was 90 mg/m^2 on days 1 and 8 every 21 days. Subsequent dose escalations were in increments of 20 mg/m^2. The maximum tolerated dose was reached at 150 mg/m^2, while 130 mg/m^2 represented the recommended dose.

Table 2 Patient characteristics

No. of patients	57	
Age (years)		
Median	57	
Range	33–71	
Performance status (ECOG)		
Median	1	
Range	0–3	
Estrogen receptor status		
Positive	24	42%
Negative	23	40%
Unknown	10	18%
Menopausal status		
Premenopausal	6	11%
Postmenopausal	51	89%
Number of metastatic sites		
1	29	51%
2	20	35%
>2	7	12%
Metastatic sites		
Bone	30	53%
Liver	27	47%
Lung	17	30%
Skin and lymph nodes	15	26%
Breast	2	3%
Pleura	3	5%
Anthracycline resistance level		
Absolute resistance	25	44%
Relative resistance	14	24%
Potentially sensitive	17	30%
Not evaluable	1	2%
Previous radiotherapy	18	31%
Palliative	9	16%
Previous endocrine therapy		
Adjuvant	25	44%
Palliative	14	24%
Previous chemotherapy exposure		
One regimen	34	60%
Two regimens	16	28%
Three regimens	6	11%

The accrual of patients to this study began in March 1996 and closed in December 1997. A total of 57 consecutive patients, recruited in nine institutions entered the trial. One patient was ineligible due to the absence of measurable disease. Demographic and clinical characteristics of all patients are listed in Table 2. The median age was 57 years (range 33–71 years) and the median performance status was 1 (range 0–3). Most patients had visceral disease with prominent pulmonary and hepatic involvement.

The treatment was administered as a first-line approach for metastatic disease in 23 patients who had received prior chemotherapy in an adjuvant setting with an anthracycline-containing regimen. Relapse occurred within 12 months in nine patients (relative chemoresistance) and within 6 months in 14 patients (absolute chemoresistance). The remaining 33 patients had been previously submitted to anthracycline-containing regimens for advanced disease as follows: epirubicin in ten patients, epirubicin plus cisplatin in six, epirubicin plus

lonidamine in eight, epirubicin plus vinorelbine in three, and epirubicin plus 5-fluorouracil plus cyclophosphamide (FEC) in six. Among these patients, 5 experienced a transient response to anthracycline regimens (relative chemoresistance), 11 failed to attain a disease response upon first exposure to anthracyclines (absolute chemoresistance), and 17 attained a long-term disease response (>12 months) but further anthracycline therapy was contraindicated by previous exposure to the maximum tolerated dose. Finally, 39 patients had received hormonal therapy (25 as adjuvant therapy, 14 for metastatic disease), and 18 had received radiotherapy (9 for metastatic disease).

Response to treatment and survival

All patients included in this study were analyzed on an intention to treat basis. Three patients (5%) achieved a CR and 12 patients (21%) achieved a PR yielding a response rate of 26% (95% confidence interval (CI) 18–38%), and 30 patients (53%) had SD and 11 (19%) PD. Responses according to metastatic site are listed in Table 3. Responses were seen in all disease sites, but particularly in skin and liver. Six responses (24%, 95% CI 7–41%; one CR and five PR) were observed in the 25 patients with absolute anthracycline-resistant breast cancer, three responses (21%, 95% CI 0–42%; one CR and two PR) were observed in the 14 patients with relative anthracycline-resistant breast cancer, and six responses (35%, 95% CI 12–58%; one CR and five PR) were observed in the 17 patients bearing tumors potentially sensitive to anthracycline.

At the time of writing (November 1999) 45 treated patients had died. The median time to progression in responding patients was 10.3 months, and median survival was 15.4 months.

Treatment and toxicity

A total of 295 chemotherapy courses were administered, with a median of 6 courses for each patient (range 2–6). A 1-week treatment delay occurred in only ten patients (16 cycles), due to leukopenia, eight of whom required G-CSF administration for a total of 13 cycles. The median delivered dose intensity of paclitaxel was 86.6 mg/m^2 per week (range 65–86.6 mg/m^2 per week), amounting to 100% of the initially planned dose (range 75–100%).

No serious hypersensitivity reactions were observed and no patient developed arrhythmias while receiving chemotherapy. The major toxicities, recorded at the start of each cycle, are shown in Table 4. Hematological toxicity was mild. Grade 2–3 leukopenia and grade 2–3 anemia occurred in 6% and 17% of patients, respectively. Only one patient experienced grade 1 thrombocytopenia. The leukocyte/neutrophil nadir (on the 15th day) was available in 25 patients for a total of 114 cycles: grade 3–4 leukopenia was observed in five patients (20%) and grade 3–4 neutropenia was observed in 14 patients (56%). Febrile neutropenia which did not require hospitalization was observed in only one patient.

Neurotoxicity was the most common nonhematological toxicity, being grade 2–3 in 15 patients (26%). All the six patients pretreated with cisplatin-containing regimens developed grade 2–3 neurotoxicity. Three out of four patients experiencing grade 3 neurotoxicity withdrew from paclitaxel administration during the fourth, fifth and sixth cycle, respectively, due to this side effect, while the remaining patient received a reduced paclitaxel dose of 50% from the fourth to the sixth cycle. Nausea and vomiting, diarrhea, and stomatitis were infrequent and mild. All patients experienced grade 3 alopecia. One patient developed a transient asymptomatic reduction in left ventricular ejection fraction.

Discussion

Since the initial studies of paclitaxel, there has been interest in defining the optimal schedule for delivering the drug. Trials of various doses, infusion durations and frequency intervals, including the weekly schedule, have been reported but have not yet resolved the issue. Randomized trials using higher doses administered on a 3-week schedule have not demonstrated significantly greater response rates in metastatic patients although higher doses have been associated with improved time to progression and a greater degree of toxicity [24, 37].

Table 3 Response rate according to the site of disease (*CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease)

Site	CR	PR	SD	PD
Liver	1 (4%)	7 (26%)	13 (48%)	6 (22%)
Bone	0	4 (13%)	21 (70%)	5 (17%)
Lung	0	2 (12%)	11 (65%)	4 (23%)
Pleura	1 (33%)	0	2 (67%)	0
Breast	0	0	1 (50%)	1 (50%)
Lymph nodes	1 (14%)	1 (14%)	2 (29%)	3 (43%)
Skin	1 (13%)	2 (25%)	2 (25%)	3 (37%)

Table 4 Major paclitaxel toxicity. For each patient, the greatest toxicity is recorded. Data refer to toxicity recorded on days 1 and 8 of treatment

	Grade			
	1	2	3	4
Leukocytes	33 (58%)	2 (3%)	2 (3%)	0
Anemia	21 (37%)	7 (12%)	3 (5%)	0
Platelets	1 (2%)	0	0	0
Nausea and vomiting	17 (30%)	12 (21%)	4 (7%)	0
Diarrhea	3 (5%)	3 (5%)	1 (2%)	0
Stomatitis	13 (23%)	6 (10%)	0	0
Neurosensory	11 (19%)	11 (19%)	4 (7%)	0
Myalgias	12 (21%)	5 (9%)	8 (14%)	0

Administration of paclitaxel on a sustained weekly schedule has been shown to be very active in the treatment of advanced breast cancer [9, 31]. These findings are consistent with the notion that paclitaxel activity is schedule-related and not dose-related [28].

We report here the significant antitumor activity of paclitaxel administered in a new schedule (130 mg/m^2 on days 1 and 8 every 21 days) in 57 anthracycline-pretreated breast cancer patients, 39 (68.4%) of whom were resistant. Responses were observed in disease located in all organ systems, but particularly in the liver, a well-known negative prognostic variable [38]. The 26% overall response rate (95% CI 18–38%) obtained in the present study is similar to that obtained in other studies (23% to 37%) involving pretreated patients in whom paclitaxel was administered at doses of 175–250 mg/m^2 every 21 days [1, 10, 13, 16, 20, 29, 36].

The median duration of response (10.3 months) in the present study, however, is noteworthy and seems in contrast with previous findings showing that responses to paclitaxel are short-lived [1, 10, 12, 13, 16, 20, 29, 36]. Wide variation in outcome among different phase II studies is a well-known phenomenon and is mainly due to patient selection. Nevertheless, the relatively long duration of response in the present study suggests that further testing of this schedule is warranted. Of particular interest is the observation of antitumor activity of paclitaxel in patients with de novo resistance to anthracycline as well as in those who had an acquired anthracycline resistance. These findings corroborate previous results [13, 29] suggesting that failure to respond to anthracycline therapy may not be a contraindication to paclitaxel therapy.

High response rates (up to 53%) to paclitaxel administered on a weekly basis at doses ranging from 50 to 175 mg/m^2 have been found in some recent phase II trials [2, 4, 9, 31, 32]. These results are very interesting but need confirmation since only very few patients in total have been treated up to now. In any case, these results are not comparable with those of the present study, as the majority of patients included were anthracycline-naive or potentially sensitive to anthracyclines.

On the whole, our schedule was well tolerated. As expected the predominant toxicities were hematological and neurological. The neutropenic nadir was deep (grade 3–4 granulocytopenia in about 56% of patients) but brief and was accompanied by fever in only one patient. Grade 2–3 neurological toxicity occurred in 26% of patients, leading to treatment withdrawal in three patients. Previous treatment with cisplatin greatly contributed to the onset of this adverse event. As cisplatin is not routinely used as first-line treatment in breast cancer, our results are not comparable with those of other paclitaxel studies. Indeed, if cisplatin-pretreated patients were excluded, this adverse event occurred in only 15% of patients. The frequency of neurotoxicity in the present study is equivalent on average to that found in studies involving an every-3-week schedule of administration [10, 12, 13, 29, 37] but seems to be lower than that observed in some studies involving a weekly schedule, particularly when doses more than 100 mg/m^2 were employed [4].

The median dose intensity delivered of 86 mg/m^2 every week is similar to that achieved in some weekly regimens, such as 80 mg/m^2 [3] and 90 mg/m^2 [17], but less than in others, for example 100 mg/m^2 [31]. A greater dose intensity of up to 175 mg/m^2 every week [4, 32] has been attempted but is not recommended due to the high frequency of severe (grade 3–4) neuropathy [31]. In the absence of randomized comparisons, it is difficult to state whether the difference in response rate obtained in the above-mentioned studies (29% [3], 39% [17] and 53% [31]) is attributable to the different doses employed or to patient selection. It is noteworthy that 150 mg/m^2 paclitaxel administered in a biweekly schedule which corresponds to a weekly dose intensity of 75 mg/m^2 has been recently reported to be very active (61% response rate as first-line therapy) [9]. Data published in the literature may suggest therefore that a weekly dose intensity of 80 mg/m^2 is probably as active as 100 mg/m^2 and 1 or 2 weeks of rest between one administration and the next seems to be feasible without influencing drug activity. Randomized comparisons of activity and safety profiles between different paclitaxel dose-dense schedules are needed.

In previously treated metastatic breast cancer patients, concerns arise as to the resiliency of the bone marrow to further exposure to myelosuppressive agents. The grade 3–4 myelotoxicity frequently observed after 15 days, in our experience, suggests that a week of rest between one cycle and another might be necessary in order to allow pretreated patients to tolerate the drug.

To conclude, this phase II study supports and extends the results of other studies showing that paclitaxel is non-cross-resistant with anthracyclines. The schedule adopted was well tolerated and represents a valid option to be tested alone or in association with other drugs in randomized studies for patients with primary resistance to anthracyclines, or with progression of disease after discontinuation of anthracycline-based chemotherapy.

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