Original article

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Weekly paclitaxel as first-line chemotherapy in elderly advanced breast cancer patients: a phase II study of the Gruppo Italiano di Oncologia Geriatrica (GIOGer)

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Background: First-line chemotherapy regimens suitable for elderly advanced breast cancer patients are still not defined.

Patients and methods: Women with stage III or IV breast cancer aged ≥70 years were enrolled in a phase II study aimed to evaluate both activity and toxicity of weekly paclitaxel. Among 46 planned patients, at least 18 responses and not more than seven unacceptable toxic events are required for a favourable conclusion. Paclitaxel 80 mg/m^2 was administered weekly for 3 weeks every 28 days.

Results: Unacceptable toxicity occurred in seven out of 46 patients evaluated for toxicity [15.2%; exact 95% confidence interval (CI) 7.6% to 28.2%] and was represented by one case of febrile neutropenia, one case of severe allergic reaction and five cases of cardiac toxicity. Among 41 patients evaluated for response, a complete response occurred in two (4.9%) patients and a partial response in 20 (48.8%), with an overall response rate of 53.7% (exact 95% CI 38.7% to 67.9%). The median progression-free survival was 9.7 months (95% CI 8.5–18.7) and median survival was 35.8 months (95% CI 19–not defined).

Conclusions: Weekly paclitaxel is highly active in elderly advanced breast cancer patients. Data on cardiovascular complications, however, indicate the need for a careful monitoring of cardiac function before and during chemotherapy.

Key words: breast cancer, cardiotoxicity, chemotherapy, elderly, phase II study, weekly paclitaxel

Introduction

Choosing chemotherapy regimens suitable for elderly patients with metastatic breast cancer can be difficult because pharmacological changes associated with ageing, as well as the functional status and the presence of comorbidities, may hamper the use of many cytotoxic drugs.

The association of anthracyclines and taxanes is considered a standard treatment [1] for metastatic breast cancer patients. However, the use of anthracycline-containing regimens in elderly patients can led to an excessively high incidence of toxicity [2]. The use of monochemotherapy with active drugs other than anthracyclines, such as paclitaxel, may be a strategy that combines both activity and tolerability in elderly patients.

Paclitaxel administered on a weekly schedule at doses of 80–100 mg/m^2 has been shown to be active and well tolerated [3, 4]. Preliminary results of a direct comparison showed superiority of weekly compared with every 3 weeks paclitaxel in terms of response rate and time to progression [5]. Our previous dose-finding study showed that weekly paclitaxel can be safely administered to elderly breast cancer patients [6].

Data suggesting high activity and low toxicity of weekly paclitaxel prompted the present study evaluating the safety and activity of weekly paclitaxel as first-line chemotherapy in women ≥70 years.

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Patients and methods

Eligibility criteria

Women with histologically or cytologically confirmed metastatic (stage IV) or locally advanced (stage IIIA, IIIB) breast cancer, aged ≥70 years, and not previously treated with chemotherapy for their metastatic or locally advanced disease were eligible. Previous adjuvant chemotherapy not containing taxanes (paclitaxel or docetaxel) and prior endocrine therapy were allowed. Other eligibility criteria were as follows: Eastern Cooperative Oncology Group performance status of 0–2; absence of brain metastases; adequate bone marrow (absolute granulocyte count ≥1500 μl, platelets ≥100 000 μl), renal (serum creatinine less than or equal to the upper normal limit) and liver [in the absence of liver metastases: total bilirubin and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) less than or equal to the upper normal limit; in the presence of liver metastases: total bilirubin ≤1.5× the upper normal limit and AST and ALT ≤2.5× the upper normal limit] functions, and presence of measurable or non-measurable tumour lesions. Patients with non-measurable disease were enrolled but they were *a priori* considered evaluable only for toxicity, time to progression and overall survival and not for activity (response rate). Patients with serious medical conditions potentially compromising study participation were excluded. Pre-study evaluation included a complete history and physical examination, complete blood cell count with differential, platelet count, serum chemistries, ECG, multigated acquisition (MUGA) or echocardiography, and tumour measurement. All patients gave their written informed consent before study entry.

Geriatric assessment

At baseline a multidimensional geriatric assessment was performed as described previously [7, 8]. Comorbidities were scored as absent/present using a predefined list of 33 possible diseases; the Charlson score [9] was then built by summing data regarding myocardial infarction, congestive heart failure, peripheral vascular disease, cerebral vascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, mild liver disease and diabetes. The other pathological conditions hypothesised in the Charlson score were not taken into account because they were precluded by the exclusion criteria for the study. Geriatric scales, namely those exploring activities of daily living (ADL) [10] and instrumental ADL (IADL) [11] were also used. Response codes range from 0 (full ability) to 8 (full disability) for the IADL scale and from 0 to 6 for the ADL scale.

Study design and sample size

The study was designed as a multicentre, two-stage, phase II study with activity and toxicity as primary end points [12]. The primary objective was to evaluate the activity (response rate) and toxicity (within the first four cycles) of weekly paclitaxel. The following parameters were considered for calculation of sample size: 30% as the lower acceptable response rate, 50% as the auspicated response rate, 25% as the higher acceptable rate of patients with unacceptable toxicity, 5% as the auspicated rate of patients with unacceptable toxicity, 10% of risk of false-negative result, 10% of risk of false-positive result for activity and 10% of risk of false-positive result for toxicity.

With these requirements, the planned sample size was 22 patients for the first stage and 46 at the end of the study, when at least 18 responses and not more than seven unacceptable toxic events within the first four cycles of chemotherapy were required for a favourable conclusion. The first stage was considered to be successfully passed if at least eight responses and not more than four unacceptable toxic events were observed. The protocol was approved by the Protocol Review and the ethics committees of the National Cancer Research Institute of Genoa, Italy.

Treatment regimen

Paclitaxel 80 mg/m^2 was administered intravenously over 1 h weekly for 3 weeks every 28 days. Premedications, given 30 to 60 min before chemotherapy, consisted of diphenhydramine 40 mg administered intramuscularly, dexamethasone 12 mg administered intravenously and ranitidine 150 mg administered intravenously. Treatment continued for a minimum of four and a maximum of six cycles. Treatment was delayed for 1 week for grade ≥2 neutropenia and/or grade ≥1 thrombocytopenia. No dose reduction was planned by protocol. Treatment was interrupted if disease progression or unacceptable toxicity occurred. The use of granulocyte colony-stimulating factor was allowed in the presence of an absolute granulocyte count <1000/mm^3.

Assessment of response

According to RECIST (Response Evaluation Criteria in Solid Tumors) guidelines, tumour lesions were categorised as measurable if they could be accurately measured in at least one dimension as ≥20 mm with conventional techniques or as ≥10 mm with spiral computed tomography. All other tumour lesions, including small lesions and truly non-measurable lesions, were categorised as non-measurable lesions [13]. Tumour measurements for response assessment were obtained every two cycles. Response evaluation was performed according to RECIST guidelines.

Assessment of toxicity

Complete blood cell count, platelet count and toxicity assessment were performed weekly, with performance status, serum chemistry and ECG assessed before each cycle. Echocardiography or MUGA with the evaluation of left ventricular ejection fraction was performed at baseline and every two cycles. Toxicity was evaluated according to the National Cancer Institute Common Toxicity Criteria, version 2.0.

Unacceptable toxicity, requiring interruption of the treatment at the planned dose of 80 mg/m^2, was defined by the occurrence within the first four cycles of chemotherapy, of at least one of the following events: grade ≥3 thrombocytopenia (platelets ≤50 000 μl); grade 3 or 4 anemia (hemoglobin <8 g/dl); grade 4 vomiting or mucositis, or diarrhoea or constipation; organ toxicity of grade ≥2, excluding alopecia and neurotoxicity; toxicity of any grade that worsened general conditions thus hampering tumour assessment after two cycles.

Statistical methods

For response rate and unacceptable toxicity rate, exact 95% confidence intervals (CIs) were calculated. Time to progression was defined as the time elapsed from beginning of treatment to the date of documented disease progression, the date of death without progression or the date of the last visit for patients who had not yet progressed at the end of the study. Survival was defined as the time elapsed from beginning of treatment to the date of death or the date of the last visit for patients alive at the end of the study. Two patients who were lost immediately after registration and never starting chemotherapy were censored at time zero. Unplanned subgroup analyses were performed to generate hypotheses regarding the possibility that baseline geriatric assessment could help to predict toxicity or efficacy of treatment. Associations between Charlson index, ADL and IADL scores (all transformed in dichotomic variables), response rate and unacceptable toxicity rate were studied by contingency tables analysed by Fisher's exact test. Progression-free survival curves within the same subgroups were compared using the log-rank test. All analyses were performed using S-PLUS 6.0 Professional Release 1 (Insightful Corporation, Seattle, WA, USA).

Results

From May 2000 to June 2001, 23 patients were enrolled; one was not eligible because of prior chemotherapy for metastatic disease. Among 22 eligible patients there were 13 objective responses and four episodes of unacceptable toxicity. Thus the enrolment was continued. By March 2003, 48 eligible patients had been enrolled by seven participating centres. The main baseline characteristics are listed in Table 1. Presence of comorbidities at baseline was assessed in 41 patients, and hypertension, arthrosis-arthritis, osteoporosis, arrhythmias and peripheral vascular disease were the most common comorbidities (Table 2). Based on comorbidity data, 26 patients (63.4%) had none of the diseases used for the calculation of the Charlson scale (Charlson index 0). Baseline ADL and IADL data were available for 38 and 36 patients, respectively; at least one ADL dependency was reported in 10 (26.3%) patients and IADL dependency in at least one item was reported in 25 (73.2%) patients.

Table 1. Patient characteristics

Characteristic	
Overall number	48
Age (years)	
Median	74
Range	70–87
ECOG performance status [*n* (%)]	
0	25 (52.1)
1	19 (39.6)
2	4 (8.3)
Stage [*n* (%)]	
IIIA/IIIB	9 (18.7)
IV	39 (81.3)
Previous therapy for early breast cancer [*n* (%)]	
None (stage IIIA/IIIB)	9 (18.7)
None (presenting as stage IV)	8 (16.7)
Neoadjuvant chemotherapy	4 (8.3)
Surgery	31 (64.6)
Radiotherapy	13 (27.1)
Adjuvant chemotherapy	20 (41.7)
Adjuvant endocrine therapy	18 (37.5)
Prior therapy for metastasis [*n* (%)]	
None	35 (72.9)
Radiotherapy alone	1 (2.1)
Endocrine therapy	12 (25.0)
No. of target lesions [*n* (%)]	
0 (not evaluable for response)	7 (14.6)
1	27 (56.3)
2	9 (18.7)
>2	5 (10.4)
Overall no. of metastatic sites [*n* (%)]	
1	10 (20.8)
2	17 (35.4)
>2	21 (43.8)

ECOG, Eastern Cooperative Oncology Group.

Table 2. Main comorbidities

Type of comorbidity	*n* (%)
Cardiovascular diseases	
Hypertension	26 (63.4)
Previous myocardial infarction	2 (4.9)
Ischemic disease	2 (4.9)
Arrhythmia	7 (17.1)
Peripheral vascular disease	6 (14.6)
Lung diseases	
Chronic obstructive pulmonary disease	1 (2.4)
Other lung disease	1 (2.4)
Digestive diseases	
Peptic ulcer	1 (2.4)
Gastritis	5 (12.2)
Cholelithiasis	4 (9.8)
Chronic epatopathy	1 (2.4)
Other digestive diseases	1 (2.4)
Kidney/urinary diseases	
Renal calculi	3 (7.3)
Urinary incontinence	3 (7.3)
Osteoarticular diseases	
Arthrosis/arthritis	15 (36.6)
Osteoporosis	12 (29.3)
Other osteoarticular diseases	4 (9.8)
Depression	5 (12.2)
Skin diseases	2 (4.9)
Endocrine/dismetabolic diseases	
Diabetes	3 (7.3)
Other endocrine/dismetabolic diseases	2 (4.9)
Other	1 (2.4)

Treatment compliance

Two patients never started chemotherapy, one who was lost immediately after enrolment and one who developed heart failure after registration and before the first planned day of treatment; these two patients are not accounted for in compliance description. Among the 46 patients actually treated, the median number of administered cycles was six (range one to six); 24 (52.2%) patients received six cycles and 35 (76.1%) received four or more cycles. Treatment was interrupted for reasons other than protocol completion in 15 patients (32.6%), namely for progression (eight cases) and toxicity (seven cases including two toxic deaths). Median delivered dose-intensity was 56 mg/m^2/week, which is 93% of that planned; 34 patients (73.9%) received at least 80% of the planned dose-intensity.

Table 3. Details of unacceptable toxicity

Type of toxicity (time)	Number of cases
Cardiovascular grade 5	
Congestive heart failure (26 days after day 1, cycle 2)	1
Pulmonary embolism (2 days after day 15, cycle 3)	1
Cardiovascular grade 4 + thrombocytopenia grade 3	
Acute myocardial infarction (7 days after day 1, cycle 2)	1
Cardiovascular grade 2	
Resting ejection fraction reduced by 27% (after cycle 2)	1
Resting ejection fraction reduced by 24% (after cycle 4)	1
Febrile neutropenia	
Associated with lung infiltrates, dyspnea, disoriented to time and place (7 days after day 8, cycle 3)	1
Allergic reaction grade 4 (day 1, cycle 1)	1

Toxicity

All 46 patients who received at least one administration of chemotherapy were evaluated for toxicity. Unacceptable toxicity (Table 3) within the first four cycles occurred in seven patients (15.2%; exact 95% CI 7.6% to 28.2%) and was represented by one case of febrile neutropenia associated with lung infiltrates, one case of severe allergic reaction and five cases of cardiac toxicity, including two patients who died, one with pulmonary embolism 2 days after chemotherapy (third cycle) and one with congestive heart failure 26 days after administration of the second cycle.

Worst grade toxicities observed across the whole treatment period are reported in Table 4. Two additional cases of severe cardiotoxicity (one case of grade 2 and one of grade 3) occurred after the fifth cycle. Clinically relevant hematological toxicity was uncommon, with two cases of febrile neutropenia (including the one considered as unacceptable according to study design), one of grade 4 neutropenia, one of grade 3 thrombocytopenia and one of grade 3 anemia. This grade 3 anemia was present at baseline and was not considered as unacceptable toxicity. Grade ≥2 sensorial neuropathy occurred in 33% of patients. One patient, with concomitant cholelithiasis, had an increase in gamma-glutamyl transpeptidase value that was classified as grade 3 liver toxicity.

Activity

Seven patients, including the patient who was lost immediately, were not eligible for response assessment because of a lack of target lesions at baseline. As reported in Table 5, out of the remaining 41 patients, three were not actually evaluated for response and were considered as non-responders. A complete response occurred in two (4.9%) patients and a partial response in 20 (48.8%), with an overall response rate of 53.7% (exact 95% CI 38.7% to 67.9%); 11 patients (26.8%) had disease stabilisation. Among the nine patients with locally advanced breast cancer there were eight partial responses (response rate 88.9%; exact 95% CI 56.5% to 99.4%) and one stable disease. Among 32 patients with stage IV disease, there were two complete and 12 partial responses, for a response rate of 43.8% (exact 95% CI 28.2% to 60.7%).

Table 4. Worst toxicity reported in 46 evaluable patients

Type	NCI CTC grade (% of patients[a])					
	0	1	2	3	4	5
Allergy	40 (87.0)	5 (10.9)	–	–	1 (2.2)	
Anemia	24 (52.2)	18 (39.1)	3 (6.6)	1 (2.2)	–	–
Neutropenia	36 (78.3)	2 (4.3)	4 (8.7)	3 (6.6)	1 (2.2)	
Febrile neutropenia	44 (95.7)			2 (4.3)	–	–
Thrombocytopenia	44 (95.7)	1 (2.2)	–	1 (2.2)	–	–
Cardiovascular	34 (73.9)	5 (10.9)	3 (6.6)	1 (2.2)	1 (2.2)	2 (4.3)
Fatigue	9 (19.6)	15 (32.6)	20 (43.5)	2 (4.3)	–	–
Alopecia	6 (13.0)	24 (52.2)	16 (34.8)			
Constipation	30 (65.2)	13 (28.3)	2 (4.3)	1 (2.2)	–	–
Diarrhoea	34 (73.9)	10 (21.7)	2 (4.3)	–	–	–
Nausea	27 (58.7)	7 (15.2)	10 (21.7)	2 (4.3)	–	–
Vomiting	32 (69.6)	8 (17.4)	6 (13.0)	–	–	–
Liver	45 (97.8)	–	–	1 (2.2)	–	–
Neuropathy motor	44 (95.7)	2 (4.3)	–	–	–	–
Neuropathy sensor	24 (52.2)	7 (15.2)	14 (30.4)	1 (2.2)	–	–

[a]Because of rounding, percentages do not sum up to 100.
NCI CTC, National Cancer Institute Common Toxicity Criteria.

Time to progression and overall survival

At the time of this analysis (March 2003), out of 39 patients with stage IV disease, 28 (71.8%) had suffered progression

Table 5. Objective response according to RECIST

	n (%)	Exact 95% CI
All eligible patients ($n = 41$)		
Responding	22 (53.7)	38.7–67.9
Complete response	2 (4.9)	
Partial response	20 (48.8)	
Non-responding	19 (46.3)	
Stable disease	11 (26.8)	
Progressive disease	5 (12.2)	
Not evaluated[a]	3 (7.3)	
Patients with stage IV disease ($n = 32$)		
Responding	14 (43.8)	28.2–60.7
Non-responding	18 (56.2)	
Patients with stage III disease ($n = 9$)		
Responding	8 (88.9)	56.5–99.4
Non-responding	1 (11.1)	

[a]Two cases never started chemotherapy (one lost and one for decline of cardiac function after enrolment); one case not restaged at proper time for response assessment.
RECIST, Response Evaluation Criteria in Solid Tumors; CI, confidence interval.

and 15 had died. Median progression-free survival was 9.7 months (95% CI 8.5–18.7) and median survival was 35.8 months (95% CI 19–not defined). Among nine patients with locally advanced breast cancer, one patient died of pulmonary embolism during treatment and another progressed 6 months from the beginning of treatment and died 1 month later; seven patients are disease-free after a median follow-up of 14 months.

Predictive value of geriatric scales

Unplanned subgroup analyses were performed to generate hypotheses regarding the possibility that geriatric assessment can help to predict toxicity and activity of treatment. The Charlson and the IADL scales were never predictive of either toxicity or activity. On the contrary, the presence of at least one inability among those itemised in the ADL scale was significantly associated with both a lower probability of response (P=0.009, Fisher's exact test) and a shorter progression-free survival (P=0.04, log-rank test), but not with unacceptable toxicity rates.

Discussion

A major question faced by oncologists treating older patients with chemotherapy is the selection of regimens with a favourable balance between toxicity and activity, particularly in the palliative setting. Prediction of toxicity and activity in the elderly is very difficult. Compared with younger patients, the elderly are generally at increased risk of developing chemotherapy-induced toxicity, such as cardiotoxicity [14, 15], myelodepression [16, 17] and mucositis [18, 19]. Therefore, the toxicity profile of the majority of cytotoxic drugs may be different and sometimes unpredictable in elderly patients.

This phase II trial focused exclusively on elderly patients and its design took into account both toxicity and activity as criteria for recommendation about the treatment with weekly paclitaxel. We planned to consider weekly paclitaxel clinically interesting and useful for future metastatic breast cancer trials in the elderly if no more than 25% and possibly only 5% of patients experienced unacceptable toxicity, and if not less than 30% and possibly 50% of patients obtained an objective response. The actual figures we observed in the study were 15% unacceptable toxicity and 54% objective response; therefore, on the basis of our premise weekly paclitaxel can be considered a useful regimen for elderly advanced breast cancer patients. Notably, there was a relevant rate of unacceptable cardiovascular toxicity (five patients) ranging from grade 2 to 5. Two patients had a decrease in resting ejection fraction, one patient had acute myocardial infarction and two patients had fatal cardiovascular toxicity consisting of congestive heart failure (one patient) and pulmonary embolism (one patient). Two additional patients developed severe cardiotoxicity (one grade 2 and one grade 3) after the fifth cycle. In addition, grade 1 cardiotoxicity (i.e. asymptomatic decline of resting ejection fraction ≥10% but ≤20% of baseline value) was observed in five patients (11%). Overall, cardiotoxicity of any grade developed in 12 patients (26%). Specifically, grade 5, 4, 3, 2 and 1 cardiotoxicity occurred in two (4%), one (2%), one (2%), three (7%) and five (11%) patients, respectively. No cases of cardiotoxicity were observed in previous studies with weekly paclitaxel administered in metastatic breast cancer patients [3, 4]. The different profile of cardiotoxicity observed in our study may have various explanations. The majority of the events (eight out of 12; 67%) were grade 1 (five cases) and grade 2 (three cases) cardiotoxicity, i.e. laboratory decline of resting ejection fraction without clinical symptoms. These events were recorded because a routine MUGA or echocardiographic evaluation was performed in our study every two cycles. In the previous studies such a routine monitoring of cardiac function was not carried out, so such a toxicity could not be recorded. The 9% incidence of clinically overt cardiotoxic events observed in our study and not previously described may be related to the higher risk of cardiotoxicity of our patients as compared with patients treated in other studies. A major risk of developing cardiotoxicity is older age: the median age of our patients was 74 years (range 70–87) compared with a mean age of 60 years (range 31–88) reported in the study by Perez et al. [4] and a median age of 57 years (range 35–74) in the study by Seidman et al. [3]. Moreover other cardiotoxicity risk factors, such as hypertension, were present in up to 63% of our patients. Such differences in patients' characteristics, mainly related to the enrolment in our study of true elderly patients, may explain the difference in cardiotoxicity and strongly indicate that results in terms of toxicity from studies performed in young patients cannot automatically be transferred to elderly patients.

The mortality rate (4%) during chemotherapy observed in our study is similar to that reported in the study by Chen et al. [20], where 5% of 59 elderly patients died after starting chemotherapy. Cardiovascular complications, in particular, were also the main cause of death in clinical trials on elderly patients not receiving chemotherapy. Castiglione et al. [21] reported 2% of cardiovascular mortality in breast cancer elderly patients undergoing adjuvant endocrine therapy with tamoxifen and prednisone for 1 year.

We observed a response rate of 54% in the overall population (stage III plus stage IV) and of 44% in stage IV patients. This percentage is similar to that recently reported with weekly paclitaxel in a phase III study not focused on elderly patients, i.e. 40% [5]. On the other hand, the activity observed in our study is higher than that obtained in other studies in which elderly metastatic breast cancer patients were treated with monochemotherapy with drugs such as docetaxel (response rate 25%) [22], doxifluoridine (27%) [23], mitoxantrone (25%) [24], vinorelbine (38%) [25] and capecitabine (36%) [26]. Moreover, a clinically very interesting long progression-free survival (9.7 months) and overall survival (36 months) were observed in this setting of metastatic breast cancer patients.

Our data indicate that weekly paclitaxel is a highly active treatment in elderly patients with advanced breast cancer. Data on cardiovascular complications, however, indicate

the need for careful monitoring of cardiac function before and during chemotherapy.

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