Weekly paclitaxel, 5-fluorouracil and folinic acid with granulocyte colony-stimulating factor support in metastatic breast cancer patients: a phase II study

Cecilia Nisticò[a], Emilio Bria[a], Biagio Agostara[b], Sandro Barni[c], Elvira Colella[a], Luciano Frontini[d], Anna Maria D'Ottavio[e], Federica Cuppone[a], Roberto Valenza[b], Isabella Sperduti[f], Fiorentino Izzo[a] and Edmondo Terzoli[a]

We conducted a phase II study to determine the activity and tolerability of weekly paclitaxel, 5-fluorouracil (5-FU) and folinic acid plus granulocyte colony-stimulating factor (G-CSF) support in anthracycline-pre-treated or -resistant metastatic breast cancer patients. The phase II study was designed following the Simon optimal-two stage method. Patients received paclitaxel 80 mg/m^2, folinic acid 10 mg/m^2 and bolus infusion of 5-FU 300 mg/m^2 every week plus G-CSF on day 3 for 24 consecutive weeks in the absence of disease progression. From May 1998 to May 2000, 51 patients entered the study. Patients received a median relative dose intensity of 97.5% (range 81–100%). No severe toxicities were observed. Seven patients (14%) experienced neutropenia grade 2. Seven patients (14%) experienced grade 2 anemia. Two patients (4%) experienced severe asthenia. Three out of 50 evaluable patients [6%, 95% confidence interval (CI) 2–12.6%] showed a complete response, whereas 23 (46%, 95% CI 32.2–59.8%) had a partial response, with an overall response rate of 52% (95% CI 38.2–65.8%). In addition, eight patients (15.7%) had stable disease. In the 13 patients untreated for metastatic disease, the overall response rate was 92.3% (CI 77.8–100), with one complete response and 11 partial responses (84.6% CI 65–100%). In the whole group, the median time to progression and overall survival were 8 (range 1–18) and 14 months (95% CI 11–17), respectively. Thus, in metastatic breast cancer patients pre-treated with anthracyclines, the weekly administration of paclitaxel, 5-FU and folinic acid with G-CSF support seems to be extremely tolerable and active. *Anti-Cancer Drugs* 17:345–351 © 2006 Lippincott Williams & Wilkins.

Anti-Cancer Drugs 2006, **17**:345–351

Keywords: 5-fluorouracil, granulocyte colony-stimulating factor, metastatic breast cancer, weekly paclitaxel

[a]Department of Medical Oncology, Regina Elena National Cancer Institute, Roma, Italy, [b]Department of Medical Oncology, Oncological Hospital M. Ascoli, Palermo, Italy, [c]U.O. Oncologia Medica, A.O. Treviglio-Caravaggio, Treviglio, Italy, [d]Ospedale San Gerardo, Monza, Italy, [e]Ospedale 'Sant'Eugenio', Roma, Italy and [f]Biostatistic Unit, Regina Elena National Cancer Institute, Roma, Italy.

Correspondence to E. Bria, Department of Medical Oncology, Regina Elena National Cancer Institute, Via Elio Chianesi 53, 00144 Roma, Italy
Tel: +39 0652 666222; fax +39 0652 666219;
e-mail: emiliobria@yahoo.it.

Received 20 November 2005 **Accepted** 13 December 2005

Introduction

Breast carcinoma is the second most frequent cause of cancer-related death for women in the US [1]. Despite the improvements achieved in the overall outcome of breast cancer patients, metastatic spread is still frequent. Indeed, up to 60% of the patients will ultimately develop distant metastases. The treatment of advanced breast cancer is still complex and, in part, controversial, as there is still no universally accepted therapy. However, conventional treatments have no curative impact on advanced disease, with a median survival of about 2 years after evidence of metastases [2]. In the advanced setting, safety of chemotherapy is an important treatment goal, due to the fact that these patients had previously received chemotherapy either for adjuvant and eventually metastatic disease.

Although anthracyclines (doxorubicin and epirubicin) still play a major role in the treatment of advanced breast cancer, new active drugs such as the taxanes (paclitaxel and docetaxel), vinorelbine and gemcitabine have become available in recent years.

Paclitaxel administered at a dose of 135–250 mg/m^2 has been reported to provide an overall response rate ranging from 20 to 65% as in phase II than phase III studies in both naive or pre-treated patients [3]. In the conventional 3-weekly schedule, neutropenia and neurological are considered to be the major dose-limiting toxicities when paclitaxel is administered in 24 or 3 h [4–6]. Furthermore, the activity of paclitaxel has been demonstrated to be independent of response to prior anthracyclines [6].

The clinical effect of the weekly dose-densification approach has been reported in several phase II trials, in which paclitaxel at the dose of 80–100 mg/m^2 provided a response rate of 50–68% with minimal hematological toxicity [7]. Furthermore, weekly paclitaxel has shown

0959-4973

activity in patients progressed after 3-weekly paclitaxel, suggesting an intriguingly different mechanism of action [8]. Weekly paclitaxel has recently demonstrated higher activity that the 3-weekly schedule in both metastatic and locally advanced disease [9,10].

5-Fluorouracil (5-FU) has been demonstrated to be active in breast cancer, and its combination with anthracyclines and cyclophosphamide is one of the more widely used chemotherapy approaches in either adjuvant and metastatic disease [11]. Furthermore, the biomodulation of the 5-FU mechanism of action with folinic acid to increase activity has also been tested in advanced breast cancer [12].

This phase II trial was therefore conducted to study the activity and toxicity of the combination of weekly paclitaxel, 5-FU and folinic acid plus granulocyte-colony stimulating factor (G-CSF) support.

Patients and methods

Inclusion criteria

Eligibility criteria to enter this phase II study included: histological proof of primary breast cancer with at least one bidimensionally measurable or evaluable metastatic lesion, life expectancy ≥ 3 months, age 18–75 years and performance status (Eastern Cooperative Oncology Group) ≤ 2. Other requirements were: adequate bone marrow function (absolute neutrophil count (ANC) $\geq 2.0 \times 10^3$/dl, platelet count $\geq 100 \times 10^3$/dl and hemoglobin ≥ 9 g/l), adequate liver function [bilirubin concentration $\leq 1.5 \times$ upper normal limit (ULN), and aspartate aminotransferase and alanine aminotransferase $\leq 1.5 \times$ ULN), adequate renal function (creatinine concentration ≤ 1.5 mg/dl and BUN < 50 mg/dl) and cardiac function. All patients had to have received no more than one prior anthracycline-containing regimen in the metastatic setting, or had to be progressed while receiving either adjuvant or metastatic anthracycline-containing chemotherapy or within 12 months after adjuvant anthracycline-containing chemotherapy. Treatment had to start at least 4 weeks after the end of any previous treatment. Biphosphonate administration for bone metastases was not allowed. All patients had to provide informed consent.

Exclusion criteria

Patients with symptomatic brain metastases, carcinomatous lymphangitis, neoplastic and/or pleural effusion as the only site of disease were considered not eligible. Other exclusion criteria included inadequate bone marrow reserve and renal or cardiac insufficiency.

Treatment plan

Patients were pre-medicated with dexamethasone 8 mg and 5-HT_3 antagonist intravenously, followed by 1-h intravenous infusion of paclitaxel 80 mg/m^2, folinic acid 10 mg/m^2 and bolus infusion of 5-FU 300 mg/m^2 in the outpatient setting. G-CSF (300 μg subcutaneously) was scheduled to be administered 72 h after chemotherapy administration in a 1-day single dose.

Weekly chemotherapy was administered without planned treatment interruptions for a maximum of 24 weeks in the absence of progressive disease. After 12 weeks of therapy, patients were re-evaluated for response. Response evaluation was assessed according to WHO criteria [13]. Staff at each single center had to review and confirm the response evaluation. Radiological evaluation included chest radiograph, head, chest and abdomen computed tomography scan, radionuclide bone scan, and bone magnetic resonance imaging; responses needed to be confirmed after 4 weeks. All patients who received at least one chemotherapy infusion were included in the toxicity evaluation. Complete blood counts as well as blood chemistry tests were evaluated prior to each treatment. Patients were assessed every week for toxicity according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0. The protocol was approved by local ethical committees. Signed informed consent was required.

Dose modifications

No dose reductions were planned for toxicity. In the presence of hematological toxicity grade > 2, treatment was stopped until White Blood Count (WBC) recovered to 2.5×10^3/dl and ANC to 1.5×10^3/dl. In the presence of non-hematological toxicity > 2, treatment was suspended until recovery to ≤ 1. When a grade ≥ 3 toxicity was noted before each drug infusion, the therapy was delayed no more than 2 weeks, otherwise the patient had to be excluded from the study.

Statistics

The objectives of this phase II study were to evaluate the anti-tumor activity and toxicity profile of weekly paclitaxel, 5-FU and folinic acid plus G-CSF support in patients affected by advanced/metastatic breast cancer pre-treated with anthracyclines. Sample size was computed according to the Simon two-step method design [14]. It was assumed that the treatment would be of no further interest if the true tumor response rate was less than 30% (P_0). The alternative hypothesis (P_1) assumed that a true response rate of 50% or more would be of considerable interest. The study was planned to be conducted in two stages; the first stage consisted of 15 patients. If less than five responses had been seen then the trial would have been terminated, otherwise accrual was to continue to a total of 46 patients with a 5% rejection error and a power of 80%. Overall survival and time to progression were measured from start of treatment and analyzed by the Kaplan–Meier [15] method. Cox's proportional hazard model was used to

assess the impact of known prognostic factors. The cut-off *P* values to enter in or to be removed from the model were set to 0.10 and 0.15. Statistical analyses were performed using SPSS version 11 packages for Windows.

Results

Patient characteristics

From May 1998 to May 2000, 51 patients from four national institutions were recruited in this phase II study. Thus, the requirements to complete the two planned design steps were satisfied. Detailed patient characteristics are listed in Table 1. All patients provided written informed consent.

Fifty patients were evaluable for toxicity and response. One patient was lost at follow-up after the first administration of chemotherapy. Median disease-free survival for the entire group was 35 months. Overall, 864 courses were delivered in the outpatient setting; the median number of treatment weeks was 22 (range 4–24), with 19 patients (37.2%) completing the planned treatment and 25 patients (50%) receiving more than 20 weeks of chemotherapy. No further treatment was given after week 24. Median delivered dose intensity was high: paclitaxel 78 mg/m^2/week (range 70–80) and 5-FU 292 mg/m^2/week (range 262–300) (relative dose intensity 97.5% for both drugs).

Table 1 **Patient characteristics**

	No. of patients (total 51)	%
Median age (range)	62 (37–75)	
Performance status (WHO)		
0–1	46	90.2
2	5	9.8
Menopausal status		
pre	7	13.7
post	44	86.3
Estrogen receptor status		
positive	26	51
negative	14	27.5
unknown	11	22.5
HER-2		
positive	7	13.7
negative	26	51
unknown	18	35.3
Dominant metastatic sites		
bone	35	68.6
liver	5	9.8
lung	3	6
other	8	15.6
No. of metastatic sites		
1	18	35.3
2	21	41.2
>2	12	23.5
Hormonal treatment		
adjuvant	21	41.2
advanced	23	45.1
adjuvant chemotherapy	29	56.8
anthracyclines	20	39.2
CMF	9	17.6
Previous chemotherapy lines for metastatic disease		
0	13	25.5
1	26	51
≥ 2	12	23.5
Chemotherapy in advanced	38	74.5
anthracyclines	34	66.6
vinorelbine	20	39.2
CMF	5	9.8
docetaxel	3	5.9

Toxicity

Treatment was generally well tolerated (Table 2) and no dose reductions were required. No grade 3 or 4 WHO hematological or non-hematological toxicity was recorded. Twenty-seven patients (54%) developed grade 3 alopecia. Twenty-four (47%) patients developed mild nail toxicity. Neutropenia, nausea/vomiting and neurological toxicity were the main grade 2 toxicities, occurring in seven (14%), five (10%) and three (6%) patients, respectively. None of the patients experienced conjunctivitis or ocular disorders requiring treatment. There were no serious adverse events requiring hospitalization and no treatment-related deaths.

Activity and survival

Staff at each single center reviewed and confirmed the response evaluation. In the evaluable population analysis, objective responses were observed in 26 out of 50 patients [52%, 95% confidence interval (CI) 38.2–65.8%], three of which were complete (6%, 95% CI 2–12.6%) and 23 partial (46%, 95% CI 32.2–59.8%). Eight patients had stable disease (15.7%) and 15 had progressive disease (29.4%). The median duration of the response was 11 months (range 10–12). In patients untreated for metastatic disease, objective responses were observed in 12 out of 13 patients (92.3%, 95% CI 77.8–100%); one was complete (7.7 %, 95% CI 0–22.2%) and 11 partial (84.6%, 95% CI 65–100%). One patient underwent progressive disease (7.7%). Between the 22 patients previously exposed to vinorelbine and/or docetaxel, nine achieved an overall response rate of 40.9% (Table 3).

Median time to progression for the entire group of patients was 8 months (range 1–18). The median survival was 14 months (95% CI 11–17). The 1- and 2-year survival rates were 56 and 18%, respectively. Time to progression was significantly longer in patients who received the treatment as first line (11 months, range 4–18) than in patients that had undergone second-line treatment (4.5 months, range 1–18) ($P = 0.03$). No significant difference was found in median overall survival between first-line patients (17 months, 95% CI 11–23) and second-line patients (14 months, 95% CI 11–17).

At the multivariate analysis, performance status 0–1, exclusive bone localization and response achievement were independent variables related to longer time to progression (Table 4), while a disease-free interval of more than 24 months, only one metastatic site and

Table 2 NCI-CTC toxicity in 50 patients and 864 courses

	Grade							
	1		2		3		4	
	Patients/courses	%	Patients/courses	%	Patients/courses	%	Patients/courses	%
Hematological								
neutropenia	2/4	4/0.5	7/14	14/1.5	–	–	–	–
anemia	10/100	20/11.5	7/24	14/3	–	–	–	–
thrombocytopenia	4/7	8/0.8	1/1	2/0.1	–	–	–	–
Non-hematological								
nausea/vomiting	14/47	28/5.5	5/13	10/1.5	–	–	–	–
diarrhea	3/17	6/2	5/8	10/1	–	–	–	–
constipation	5/21	10/2.3	1/2	2/0.2	–	–	–	–
mucositis	4/4	8/0.4	1/1	2/0.2	–	–	–	–
neurological	16/97	32/11.5	3/23	6/2.5	–	–	–	–
cardiological	–	–	–	–	–	–	–	–
cutaneous	8/21	16/2.5	3/10	6/1	–	–	–	–
	Mild		Moderate		Severe			
	Patients/courses	%	Patients/courses	%	Patients/courses	%		
Asthenia	14/73	28/8.5	9/19	18/2	2/6	4/0.5		

Table 3 Response evaluation (WHO Criteria): *n* [% (95% CI)]

	Evaluable population (50 patients)	First line (13 patients)
Overall response rate	26 [52 (38.2–65.8)]	12 [92.3 (77.8–100)]
Complete response	3 [6 (2–12.6)]	1 [7.7 (0–22.2)]
Partial response	23 [46 (32.2–59.8)]	11 [84.6 (65–100)]
Stable disease	8 (15.7)	–
Progression	15 (29.4)	1 (7.7)

response achievement were independent factors related to better overall survival (Tables 4 and 5).

Discussion

Weekly administration of anti-blastics represents one of the emerging issues in the optimization of chemotherapy delivery, together with the dose-dense theory. From a theoretical perspective, the exposure to more sustained anti-neoplastic administration should inhibit tumor re-growth between each cycle and decrease the onset on chemotherapy-resistant cancer clones [16].

Paclitaxel has become the most studied drug for weekly administration, as preclinical and clinical evidence has shown charming scenarios [17]; while the 'laboratory bench' had suggested pro-apoptotic and neoangiogenetic pathways involved in the weekly paclitaxel mechanism of action [18–20], the 'patient's bed' demonstrated higher activity and efficacy for such a schedule when compared to 3-weekly administration in both advanced and neoadjuvant treatment settings [9,10]. On a sustained weekly basis, paclitaxel is able to increase the dose intensity as in the dose-dense approach, but the exploited cytotoxicity did not seem to be related only to this, rather to the increased 'rhythmic' administration, which involves pathways different from the 3-weekly schedule. This theory is actually demonstrated in the direct comparison with a 3-weekly regimen with the same dose intensity [10].

The property to be easily and safely administered on a sustained weekly basis, and also provide an increased dose intensity at the same time, seems peculiar to paclitaxel and is not shared by all drugs; indeed, we previously demonstrated that the sustained administration of weekly docetaxel did not provide a significant dose intensity increase and, moreover, the expected toxicities appeared at a threshold level [21].

The chemotherapy intensification provided by both the dose-dense and weekly schedules becomes possible with the concurrent use of hematopoietic growth factors such as G-CSF [22]. The maintenance of the continuous sustained frequency obtained with G-CSF support is crucial for the activity of weekly paclitaxel, rather than to avoid hematological toxicity which is supposed to be mild in such a regimen [9,23]. A previous report demonstrated that a less-intensive G-CSF administration modulated on growth factor half-life, chemotherapeutics pharmacokinetics and bone marrow function, is equally active as a classical schedule in breast cancer in avoiding toxicity and dose-intensity maintenance [24]. In the same direction, we previously demonstrated that a 2-day G-CSF administration is able to reduce neutropenia and to maintain dose intensity in a sustained weekly schedule as well; a 1 unit delay per month translates into a 25% dose intensity reduction [25].

Recent phase I studies suggested 80–100 mg/m^2/week as the recommended dose for sustained weekly paclitaxel administration [26]. In the large phase II trial conducted by Perez *et al.*, 27 patients achieved an objective

Table 4 Univariate and multivariate analysis for time to progression

Variables	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	*P*	Hazard ratio	95% CI	*P*
DFS (<24 versus >24 months)	1.26	0.65–2.47	0.50	–	–	–
Sites number (>1 versus 1)	1.79	0.96–3.30	0.06	–	–	NS
PS (2 versus 0–1)	3.81	1.42–10.2	0.008	2.61	0.95–7.16	0.06
Previous treatment			0.14	–		
vinorelbine/docetaxel versus no previous treatment	1.37	0.69–2.74	0.37	–	–	–
other chemotherapy versus no previous treatment	2.19	1.00–4.76	0.048	–	–	NS
Pre-treated patients (>second versus first line)	1.60	0.84–3.03	0.15	–	–	–
Dominant metastatic site (visceral + other versus bone)	1.38	0.74–2.56	0.31	–	–	–
Exclusive metastatic site (visceral + other versus bone)	2.23	1.10–4.54	0.027	2.34	1.13–4.85	0.02
Response (non-overall response rate versus overall response rate)	3.11	1.70–5.68	<0.0001	3.28	0.76–6.11	<0.0001

Non-overall response rate: non-responder patients; overall response rate: responder patients.

Table 5 Univariate and multivariate analysis for overall survival

Variables	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	*P*	Hazard ratio	95% CI	*P*
DFS (<24 versus >24 months)	1.78	0.90–3.53	0.097	2.82	1.32–6.0	0.007
Sites number (>1 versus 1)	3.0	1.5–6.0	0.0002	3.85	1.76–8.44	0.001
PS (2 versus 0–1)	1.6	0.64–4.13	0.31	–	–	–
Previous treatment			0.22	–	–	
vinorelbine/docetaxel versus no previous treatment	1.22	0.60–2.48	0.58	–	–	–
other chemotherapy versus no previous treatment	1.93	0.89–4.20	0.098	–	–	NS
Pre-treated patients (>second versus first line)	1.42	0.73–2.75	0.23	–	–	–
Dominant metastatic site (visceral + other versus bone)	1.18	0.64–2.18	0.59	–	–	–
Exclusive metastatic site (visceral + other versus bone)	2.55	1.24–5.27	0.01	–	–	NS
Response (non-overall response rate versus overall response rate)	2.28	1.22–4.22	0.009	2.60	1.30–5.19	0.007

Non-overall response rate: non-responder patients; overall response rate: responder patients.

response and 46 had stable disease [8]. The combination of 5-FU and leucovorin resulted in an objective response rate of 28–42% in metastatic breast cancer. Loprinzi *et al.* [27] reported responses in patients who progressed after previous 5-FU therapy. Preclinical studies showed synergic activity of paclitaxel and 5-FU due to different mechanisms of action, which also provide no additive or overlapping toxicity [28,29]. From these perspectives, the adjunction of 5-FU/leucovorin to paclitaxel could be considered as an interesting option to improve activity in metastatic breast cancer.

Weekly paclitaxel and 5-FU have been investigated in a phase I study [30]; with fixed protracted infusion 5-FU and escalating paclitaxel, the recommended dose for subsequent phase II trials was 90 mg/m^2/week.

In our study, the combination of weekly paclitaxel and 5-FU plus leucovorin has clearly shown interesting activity in advanced breast cancer. Of the 50 patients evaluable for response, 26 of them achieved an objective response (Table 3). These data appear impressive considering the relevant rate of patients pre-treated for advanced disease. Only one patient in the first-line setting did not respond to treatment and experienced progression. Considering the relatively high delivered dose intensity (97.5%), toxicity was remarkably low; none of the patients experienced severe hematologic toxicity due to G-CSF prophylactic administration. The growth factor schedule was chosen according to our previous experience: we demonstrated that the higher neutropenic combination of weekly epirubicin and vinorelbine required a 2-day G-CSF administration to maintain dose intensity [25]. In this case, due to the lower rate of expected neutropenia, a 1-day single dose was preferred.

Weekly paclitaxel administration did not produce severe clinical neurotoxicity; diarrhea was extremely mild and did not cause treatment discontinuation. No cardiac events were registered; as expected, alopecia was a severe toxicity (Table 2).

Other experiences have been published with paclitaxel/5-FU/leucovorin: the Essen group and the Vanderbilt Clinic

conducted two phase II trials in which paclitaxel was delivered every 3 weeks plus 5-FU 24-h continuous infusion and bolus, respectively. Klassen *et al.* [31] obtained an overall response rate of 59%, but, as they concluded, grade 2/3 neutropenia was common in most of the patients; Nicholson *et al.* [32] reached an overall response rate of 52% in their series, with grade 3/4 leucopenia in 17% of the cycles. Twenty-four-hour continuous infusion of both paclitaxel and 5-FU every 3 weeks was used by Madajewich *et al.* [33] in four breast cancer patients; two complete responses and one partial response were observed. Neutropenia was the dose-limiting toxicity. In a recent multicenter phase II trial, 155 patients received first-line paclitaxel 80 mg/m^2/week plus 5-FU 425 mg/m^2/week and folinic acid 20 mg/m^2/week, every week or '3 weeks on/1 week off' [34]. G-CSF was not prophylactically administered; 5.8, 3.2 and 2% of patients had grade 4 neutropenia, nausea/vomiting and diarrhea, respectively.

Considering the selection bias of a phase II study, the achieved objective response rate, particularly in the first-line approach, and the extremely safe handling profile of this combination strongly suggest weekly paclitaxel and 5-FU plus leucovorin as a feasible and active schedule in advanced breast cancer. Indeed, weekly administration of these drugs plus G-CSF support produced maintenance of dose intensity and absence of significant toxicity.

As recent phase III trials have demonstrated that taxane-based combination regimen produce longer survival than monochemotherapy after anthracyclines, and that weekly paclitaxel seems better than 3-weekly in terms of activity and efficacy, the weekly administration of paclitaxel and 5-FU deserves further investigation in a phase III fashion [35,36]. In this scenario, 5-FU continuous infusion or, better, capecitabine could easily take the place of 5-FU bolus in order to increase activity and decrease toxicity [36].

References

1 Jemal A, Thomas A, Murray T, Thun M. Cancer Statistics. *CA Cancer J Clin* 2002; **52**:23–47.

2 Beahrs OH, Henson DE, Hutter RVP, Myers MH (editors). *Manual for staging of cancer.* Philadelphia: JB Lippincott; 1998.

3 Perez EA. Paclitaxel in breast cancer. *Oncologist* 1998; **3**:373–389.

4 Gianni L, Munzone E, Capri G, Villani F, Spreafico C, Tarenzi E, *et al.* Paclitaxel in metastatic breast cancer: a trial of two doses by 3-hour infusion in patients with disease recurrence after prior therapy with anthracyclines. *J Natl Cancer Inst* 1995; **87**:1169–1175.

5 Seidman AD, Tiersten A, Hudis C, Gollub M, Barrett S, Yao TJ, *et al.* Phase II trial of paclitaxel by 3-hour infusion as initial and salvage chemotherapy for metastatic breast cancer. *J Clin Oncol* 1995; **13**:2575–2581.

6 Seidman AD, Reichman BS, Crown JP, Yao TJ, Currie V, Hakes TB, *et al.* Paclitaxel as second and subsequent therapy for metastatic breast cancer: activity independent of prior anthracycline response. *J Clin Oncol* 1995; **13**:1152–1159.

7 Seidman AD, Hudis CA, Albanel J, Tong W, Tepler I, Currie V, *et al.* Dose-dense therapy with 1-hour paclitaxel infusion in the treatment of metastatic breast cancer. *J Clin Oncol* 1998; **16**:3353–3361.

8 Perez E, Vogel CL, Irwin DH, Kirshner JJ, Patel R. Multicenter phase II trial of weekly paclitaxel in women with metastatic breast cancer. *J Clin Oncol* 2001; **19**:4216–4223.

9 Seidman AD, Berry D, Cirrincione C, Harris L, Dressler L, Muss H, *et al.* CALGB 9840: phase III study of weekly paclitaxel via 1-hour infusion versus standard 3-hour infusion every third week in the treatment of metastatic breast cancer (MBC), with trastuzumab (T) for HER2 positive MBC and randomized for T in HER2 normal MBC [abstract]. *Proc Am Soc Clin Oncol* 2004; **22**(**14S**).

10 Green MC, Buzdar AU, Smith T, Ibrahim NK, Valero V, Rosales MF, *et al.* Weekly paclitaxel improves pathologic complete remission in operable breast cancer when compared with once-every-3-weeks paclitaxel. *J Clin Oncol* 2005; **23**:5983–5992.

11 Fossati R, Confalonieri C, Torri V, Ghislandi E, Penna A, Pistotti V, *et al.* Cytotoxic and hormonal treatment for metastatic breast cancer: a systematic review of published randomized trials involving 31,510 women. *J Clin Oncol* 1998; **1**:3439–3460.

12 Swain SM, Lippman ME, Egan EF, Drake JC, Steinberg SM, Allegra CJ. Fluorouracil and high-dose leucovorin in previously treated patients with metastatic breast cancer. *J Clin Oncol* 1989; **7**:439–444.

13 Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer* 1981; **47**:207–214.

14 Simon S. Optimal two-stage design for phase II clinical trials. *Controlled Clin Trials* 1989; **10**:1–10.

15 Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Ass* 1958; **53**:475–481.

16 Norton L. Conceptual and practical implications of breast tissue geometry: toward a more effective, less toxic therapy. *Oncologist* 2005; **10**:370–381.

17 Seidman A. 'Will weekly work?' seems to be so…. *J Clin Oncol* 2005; **23**:5873–5874.

18 Taghian AG, Abi-Raad R, Assaad SI, Casty A, Ancukiewicz M, Yeh E, *et al.* Paclitaxel decreases the interstitial fluid pressure and improves oxygenation in breast cancers in patients treated with neoadjuvant chemotherapy: clinical implications. *J Clin Oncol* 2005; **23**:1951–1961.

19 Pasquier E, Honore S, Pourroy B, Jordan MA, Lehmann M, Briand C, *et al.* Anti-angiogenic concentrations of paclitaxel induce an increase in microtubule dynamics in endothelial cells but not in cancer cells. *Cancer Res* 2005; **65**:2433–2440.

20 Marchetti P, Urien S, Antonini Cappellini G, Ronzino G, Ficorella C. Weekly administration of paclitaxel: theoretical and clinical basis. *Crit Rev Oncol Hematol* 2002; **44**:S3–S13.

21 Nisticò C, Cognetti F, Frontini L, Barni S, Ferretti G, Bria E, *et al.* Weekly docetaxel in pretreated metastatic breast cancer patients: a phase I–II study. *Oncology* 2005; **68**:356–363.

22 Piccart-Gebhart MJ. Mathematics and oncology: a match for life? *J Clin Oncol* 2003; **21**:1425–1428.

23 Konishi K, Tani Y, Minami S, Tamura M, Kameda H, Ogita M, *et al.* Pharmacokinetic comparison between weekly paclitaxel treatment and by 3 weeks treatment in patients with metastatic breast cancer. *Proc Am Soc Clin Oncol* 2001; **21**: 2001.

24 Papaldo P, Lopez P, Marolla P, Cortesi E, Antimi M, Terzoli E, *et al.* Impact of five prophylactic filgrastim schedules on hematologic toxicity in early breast cancer patients treated with epirubicin and cyclophosphamide. *J Clin Oncol* 2005; **23**:6908–6918.

25 Nistico C, Garufi C, Barni S, Frontini L, Galla DA, Giannarelli D, *et al.* Phase II study of epirubicin and vinorelbine with granulocyte colony-stimulating factor: a high-activity, dose-dense weekly regimen for advanced breast cancer. *Ann Oncol* 1999; **10**:937–942.

26 Seidman AD. Single-agent paclitaxel in the treatment of breast cancer: phase I and II development. *Semin Oncol* 1999; **26**(**Suppl 8**):14–20.

27 Loprinzi CL. 5-Fluorouracil with leucovorin in breast cancer. *Cancer* 1991; **63**:1045–1047.

28 Kano Y, Akutsu M, Tsunoda S, Ando J, Matsui J, Suzuki K, *et al.* Schedule-dependent interaction between paclitaxel and 5-fluorouracil in human cell lines *in vitro*. *Br J Cancer* 1996; **74**:704–710.

29 Grem JL, Nguyen D, Monahan BP, Kao V, Geoffroy FJ. Sequence-dependent antagonism between fluorouracil and paclitaxel in human breast cancer cells. *Biochem Pharmacol* 1999; **58**:477–486.

30 Cortesi E, Grifalchi F, Ramponi S, Padovani A, Mancuso A, Paoluzzi L, *et al.* Weekly paclitaxel and 5-fluorouracil in pretreated patients with metastatic breast cancer: a phase I study. *Anticancer Res* 2003; **23**(**2C**):1961–1966.

31 Klaassen U, Wilke H, Harstrick A, Philippou Pari C, Strumberg D, Neumann K, *et al.* Paclitaxel in combination with weekly 24-hour infusional 5-fluorouracil plus leucovorin in the second-line treatment of metastatic breast cancer: results of a phase II study. *Ann Oncol* 1998; **9**:45–50.

32 Nicholson B, Paul D, Shyr Y, Garrett M, Hande KR, Johnson DH. Paclitaxel/5-fluorouracil/leucovorin in metastatic breast cancer: a Vanderbilt Cancer Center phase II trial. *Semin Oncol* 1997; **24**(**Suppl 11**):20–23.

33 Madajewicz S, LiPera W, Pendyala L, Hentschel P, Avvento L, Chowhan N, *et al.* Phase I study of 96 hours continuous intravenous infusion of Taxol followed by 24 hours CI of 5-Fluorouracil and folinic acid [abstract]. *Proc Am Soc Clin Oncol* 1995; **14**:487.

34 Loesch DM, Asmar L, Canfield VA, Parker GA, Hynes HE, Ellis PG, *et al.* A phase II trial of weekly paclitaxel, 5-fluorouracil, and leucovorin as first-line treatment for metastatic breast cancer. *Breast Cancer Res Treat* 2003; **77**:115–123.

35 Albain KS, Nag S, Calderillo-Ruiz G, Jordaan JP, Llombart A, Pluzanska A, *et al.* Global phase III study of gemcitabine plus paclitaxel (GT) vs. paclitaxel (T) as frontline therapy for metastatic breast cancer (MBC): first report of overall survival [abstract]. *Proc Am Clin Oncol* 2004; **23**.

36 O'Shaughnessy J, Miles D, Vukelja S, Moiseyenko V, Ayoub JP, Cervantes G, *et al.* Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: phase III trial results. *J Clin Oncol* 2002; **20**:2812–2823.