Pergamon

European Journal of Cancer Vol. 32A, No. 1, pp. 47–51, 1996

Printed in Great Britain
0959-8049/96 $15.00+0.00

0959-8049(95)00398-3

Original Paper

A Phase II Study of Paclitaxel in Advanced Breast Cancer Resistant to Anthracyclines*

G. Fountzilas,[1] A. Athanassiades,[1] T. Giannakakis,[2] D. Bafaloukos,[3] K. Karakousis,[1] N. Dombros,[1] P. Kosmidis[3] and D. Skarlos[2]

[1]AHEPA Hospital, Aristotle University of Thessaloniki, Thessaloniki, Macedonia, Greece; [2]"Agii Anargyri" Cancer Hospital, Athens, Greece; and [3]"METAXA" Cancer Hospital, Piraeous, Greece

33 women with advanced breast cancer resistant to anthracyclines were treated with paclitaxel 175 mg/m² in a 3 h infusion every 3 weeks. The median age was 53 years (range 30–72) and the median performance status was 1 (range 0–2). 24 (73%) patients had visceral metastases while 22 (67%) had ≥ two involved sites. 23 (70%) patients received anthracycline or mitoxantrone in an adjuvant setting and 21 (64%) for advanced disease. There were two (6%, 95% confidence interval (CI) 1–20%) complete responses (CRs) and 12 (36%, 95% CI 20–55%) partial responses (PRs). Median dose intensity of paclitaxel delivered was 58 mg/m²/week. Median time to progression was 24 weeks (range 4–61) and median survival was 41 weeks (range 8–66). Grade 3–4 toxicities included leucopenia (9%), stomatitis (3%), alopecia (91%), neurotoxicity (9%), infection (3%) and diarrhoea (3%). In conclusion, paclitaxel at a dose of 175 mg/m² exhibits significant activity in advanced breast cancer resistant to anthracyclines.

Key words: breast cancer, anthracycline, paclitaxel
Eur J Cancer, Vol. 32A, No. 1, pp. 47–51, 1996

INTRODUCTION

IT HAS been demonstrated that patients with breast cancer previously treated with anthracyclines are usually resistant to further treatment with an anthracycline-containing regimen [1, 2]. In this case, alternative chemotherapeutic combinations are sought which could offer these patients a second chance of palliation.

Paclitaxel (Taxol, Bristol-Myers Squibb Co, Wallingford, Connecticut, U.S.A.) was extracted from the bark of the Pacific yew tree, *Taxus brevifolia* [3]. Unlike other antimitotic agents, paclitaxel appears to promote tubulin dimers formation and stabilise the microtubules against depolymerisation [4, 5]. It has been shown that the drug is active against the implanted human MX-1 mammary tumour xenograft. Furthermore, from phase II and III clinical trials in patients with advanced breast cancer who were previously exposed to chemotherapy, it has been indicated that paclitaxel was effective even in patients previously treated with anthracyclines [6–8]. Using this information, the Hellenic Cooperative Oncology Group (HeCOG) for Breast Cancer conducted a phase II study in which patients with anthracycline-resistant advanced breast cancer were treated with paclitaxel monotherapy. We report here the results of this study.

Correspondence to G. Fountzilas, 1st Dept of Internal Medicine, Oncology Section, Aristotle University, AHEPA Hospital, 1 S. Kiriakidi str., 546 36, Thessaloniki, Macedonia, Greece.
Revised and accepted 4 Apr. 1995.
*This work was presented in part at the 6th EORTC Breast Cancer Conference, Amsterdam, 6–9 September 1994.

PATIENTS AND METHODS

Patients and staging

To be eligible for the present study, all patients had to have histologically confirmed metastatic breast cancer, bidimensionally measurable disease, previous exposure to an anthracycline or mitoxantrone, either in an adjuvant setting (providing that they had relapsed within 12 months of completion of chemotherapy) or for advanced disease (and subsequently progressed), an ECOG performance status of 2 or lower, adequate liver and renal function, white blood cell (WBC) count ≥ 4000/μl, platelets ≥ 100 000/μl and a life expectancy of ≥ 3 months. Prior palliative radiotherapy or hormonal therapy was allowed, but this should have been discontinued at least 4 weeks before study entry. Patients with lytic osseous metastases were only eligible if the indicator lesion was bidimensionally measurable in plain radiography or computed tomography (CT) scan. Patients were considered ineligible if they had a history of a second malignancy (except a cured non-melanoma skin cancer or *in situ* carcinoma of the cervix), or other serious intercurrent illnesses, such as active heart disease, peripheral neuropathy, severe infection or malnutrition.

All patients gave written informed consent indicating that they were aware of the investigational nature of the study. The protocol was approved by the Ethics Committees of all participating Institutions and by the National Drug Organization.

Pretreatment evaluation included a complete medical history, physical examination, complete blood counts (CBC), biochemis-

try, electrocardiogram (ECG), chest X-ray, bone scan, liver ultrasound and CT scan, as indicated. CBC was repeated weekly. An extensive cardiac monitoring and neurological evaluation, as part of another protocol, was performed in 20 patients. Cardiac toxicity in these patients was examined with an ECG prior to and at the end of the paclitaxel infusion, a MUGA (multigated radioisotopic ventriculography) scan before the initiation and after the completion of treatment, a Holter monitoring every other cycle and ultrasound every two cycles. Neurological evaluation consisted of motor and sensory conduction velocity measurements and vibration tests. Toxicities in the remaining 13 patients were assessed clinically.

Chemotherapy

Paclitaxel was supplied by Bristol-Myers Squibb, free of charge, as a concentrated sterile solution for intravenous administration in 5 ml vials, each containing 30 mg of paclitaxel in 50% polyethylated castor oil (Chemophor EL) and dehydrated alcohol. The drug was diluted in 5% dextrose injection, and was administered at a dose of 175 mg/m^2 in a 3 h infusion at the clinic. All patients were pretreated with dexamethasone 24 mg intravenously (i.v.) 12 and 6 h before paclitaxel administration, and dimethidene maleate 4 mg and cimetidine 150 mg i.v. 30 min before each treatment. Each treatment was repeated every 3 weeks. G-CSF (granulocyte-colony stimulating factor) administration was not allowed.

Dose modification

The dose of paclitaxel was reduced when granulocytopenia or thrombocytopenia was present for $\geq$ 7 days or in case of febrile neutropenia. The dosing levels which were used in modifying the dose of paclitaxel were the following: level 1 = 175 mg/m^2; level -1 = 135 mg/m^2; level -2 = 110 mg/m^2; and level -3 = 90 mg/m^2. Dose escalations were not allowed in this study. If the absolute neutrophil count (ANC) was $<$ 500/μl and/or platelet count $<$ 50 000/μl then the dose of paclitaxel was reduced by one dose level. In case of febrile neutropenia associated with or without documented infection and/or severe bleeding, the dose of paclitaxel was reduced by two dose levels. The ANC should have been $\geq$ 1500/μl and the platelet count $\geq$ 100 000/μl prior to the beginning of the next treatment cycle. If haematological recovery was not achieved after 2 weeks, then the patient was taken off the study.

In case of grade 3 mucositis, the dose of paclitaxel was reduced by one dose level. When grade 3 neurotoxicity was noticed then the dose of paclitaxel was reduced by two dose levels. In case of grade 4 neurotoxicity or symptomatic arrhythmias or AV block (except of first degree), paclitaxel administration was discontinued, and the patient was taken off the protocol. Toxicity criteria were those adopted by the World Health Organisation (WHO) [9].

Definition of response

Tumour measurements were required at each cycle if they could be obtained by physical examination or chest X-ray. Otherwise, tumour response was assessed by CT scan or ultrasound every two cycles. Complete response (CR) was defined as a complete disappearance of all clinical symptoms and signs of disease for a minimum of 4 weeks. Partial response (PR) was defined as a reduction by 50% or more in the sum of the products of the largest perpendicular diameters of the measurable lesions and of the measurable parameter of the evaluable lesions, in the absence of any new or progressive tumour lesions. Stable disease (SD) was defined as an objective response not satisfying the criteria of a PR or an increase of 25% or less in the tumour measurements in the absence of any new lesion. Progressive disease was an increase by more than 25% in the above measurements, or the appearance of a new lesion.

The CT scans of all responding patients were reviewed by one of the authors (A.A.). In case of a CR, a minimum of four additional cycles of treatment were administered. Those patients who achieved a PR or SD were treated with a maximum of 10 cycles or until progression. Finally, patients who progressed during treatment were taken off the study.

Duration of response was defined from the date PR or CR criteria were first met until the first documentation of clinical progression. The time to disease progression (TTP) and survival were calculated from initiation of chemotherapy with paclitaxel using the Kaplan–Meier method [10].

Statistical analysis

The present study was a non-randomised phase II study. The initially planned number of participating patients was 30. This sample size allowed us to estimate the expected response rate of 40% with a standard error of 8.3%.

RESULTS

From February 1993 until June 1994, 33 patients entered this study. Patient characteristics are shown in Table 1. The median age was 53 years and the median ECOG performance status was 1. 18 of these patients had received adjuvant chemotherapy containing doxorubicin (3 patients); or epirubicin (7 patients) or mitoxantrone (8 patients). None of these had a relapse during this treatment. Epirubicin was given as treatment for metastatic disease in 21 patients, none of whom had progressive disease during treatment. Median number of previous regimens was one (range 1–3), while the median number of cytotoxic drugs delivered was three (range 1–9). The vast majority (73%) of the patients presented with visceral metastases. Also, 22 (67%) patients had at least two sites of metastatic disease.

Response to treatment and survival

All patients included in this study were analysed on "the intention to treat" basis. Overall, 14 patients (42%, 95% confidence interval (CI) 25–61%) responded, two (6%, 95% CI 1–20%) with a CR and 12 (36%, 95% CI 20–55%) with a PR. The two CRs were observed after the second and seventh cycle respectively, and lasted for 6+ and 22 weeks. Response by initial site of disease is shown in Table 2. The relationship between the type of previous chemotherapy and tumour response is shown in Table 3. Up until 1 December 1994, after a median follow-up of 7 months (range 1.7–16.5) for all patients, 22 patients had died. Median time to progression was 24 weeks (range 4–61) and median survival 41 weeks (range 8–66) (Figure 1).

Compliance to treatment and toxicity

A total of 234 cycles were delivered, 224 (96%) of which were at full dose. In 10 patients, treatment was interrupted before the sixth cycle of paclitaxel due to progression of the disease (9 patients) and voluntary withdrawal (1 patient) because of severe fatigue. Finally, 12 patients (36%) received 10 cycles according to the protocol (Table 4). The median dose intensity of paclitaxel actually delivered was 58 mg/m^2/week, amounting to 99.8% of the initially planned dose (Table 4). Toxicity data were available for all cycles and from all patients, with the exception of weekly CBC in 6 patients. Haematological nadir counts between cycles for 27 patients are shown in Table 5. Grade 3–4 granulocytopenia was noticed in 7 and febrile neutropenia in 3 patients. Other

Table 1. Patient characteristics

Number of patients	33
Age	
Median	53
Range	30–72
Performance status	
0	2
1	21
2	10
ER status	
Positive	14
Negative	8
Unknown	11
Menopausal status	
Premenopausal	12
Postmenopausal	16
Perimenopausal	5
Previous chemotherapy	
a. Adjuvant	23
Anthracycline or mitoxantrone	18
No anthracycline	5
b. Treatment for metastatic disease	22
Anthracycline	21
No anthracycline	1
Previous hormonotherapy	
Adjuvant	14
Palliative	10
Previous radiotherapy	
Adjuvant	16
Palliative	6
Number of metastatic sites	
1	11
2	9
>2	13
Metastatic sites	
Lymph nodes	16
Bones	16
Skin	5
Lung	18
Liver	16
Breast	5
Ascites	2
Pleural effusion	2
Pericardial effusion	1
Visceral metastases	24

Table 2. Tumour response by site

	Number of responses			
Site	CR	PR	SD	PD
Lymph nodes	4	4	6	2
Skin	2		2	1
Bones			14	2
Liver	1	4	8	3
Lung		4	12	2
Breast		2	3	

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Table 3. Tumour response according to type of previous chemotherapy

	Response			
Previous chemotherapy	CR	PR	SD	PD
Adjuvant chemotherapy only	1	5	2	3
Chemotherapy for advanced disease only	0	3	6	1
Chemotherapy in an adjuvant setting and also for advanced disease	1	4	4	3

For abbreviations see legend to Table 2.

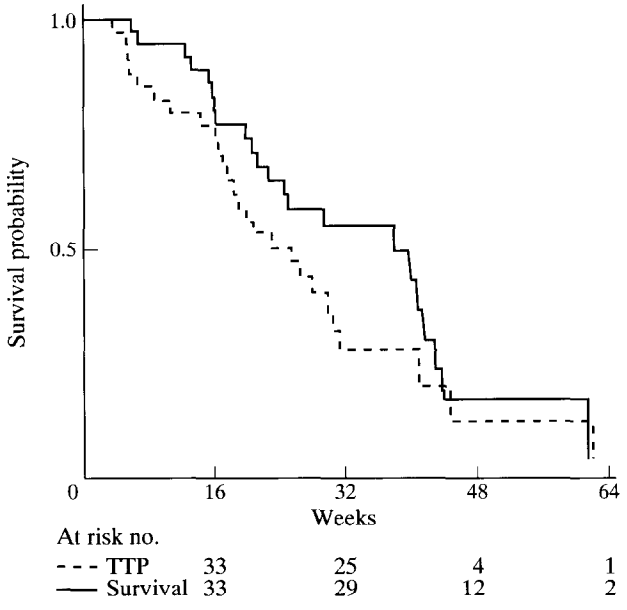

Figure 1. Time to progression (----) and survival (——) of all patients.

Table 4. Treatment characteristics

Number of cycles per patient	*c*	*n*
	1	0
	2	2
	3	5
	4	2
	5	1
	≥6	23
Interval between cycles (days)		
Median	21	
Range	20–31.5	
Dose intensity (mg/m²/week)		
Mean	57	
Median	58	
Range	39–60	
Relative	0.99	
Mean % of protocol dose	99.97	
Median % of protocol dose	99.81	

c, number of treatment cycles; *n*, number of patients. Total number of cycles = 234.

Table 5. Haematological nadirs

Number of cycles	Number of patients	Haemoglobin	WBC	Neutrophils	Platelets
1	27	11.9 (8.7–14.0)	3.7 (1.8–6.8)	1.7 (0.2–4.9)	206 (110–479)
2	27	11.4 (8.6–13.5)	3.7 (2.0–6.1)	1.6 (0.3–4.9)	220 (111–377)
3	26	11.3 (8.3–15.5)	3.6 (1.5–15.6)	1.9 (0.4–8.4)	235 (108–524)
4	24	11.7 (9.5–13.9)	4.1 (1.8–12.2)	2.4 (0.1–11.5)	219 (129–623)
5	22	11.5 (9.2–13.5)	3.2 (1.7–6.3)	1.5 (0.1–11.4)	207 (124–406)
6	19	11.3 (8.0–15.5)	3.6 (1.4–12.4)	1.2 (0.1–14.9)	241 (124–406)
7	15	12.0 (9.8–13.5)	3.4 (1.7–12.3)	1.4 (0.4–9.5)	198 (110–464)
8	14	11.8 (9.2–15.2)	3.8 (2.0–11.3)	2.3 (0.2–9.0)	222 (127–502)
9	11	11.1 (8.8–13.5)	3.4 (2.0–9.7)	0.9 (0.1–4.7)	213 (102–316)
10	8	11.4 (9.5–13.6)	5.8 (2.2–13.8)	3.3 (0.6–5.8)	216 (157–303)

Data available for 27/33 patients. The median value is shown for haemoglobin, WBC, neutrophils and platelets; and the range is shown in parentheses.

toxicities are indicated in Table 6, where the worst grade for each form of toxicity is recorded. Neurotoxicity was frequent and appeared to be cumulative because serious neurotoxicity became apparent after the fourth cycle in most patients. Oedema was not observed in any of the patients.

DISCUSSION

We performed a phase II study with paclitaxel monotherapy in order to evaluate its activity in patients with advanced breast cancer, who were considered resistant to anthracyclines.

Although there is a possibility for clinical cross-resistance between paclitaxel and anthracyclines, early phase II studies have suggested that paclitaxel may be active in patients with breast cancer resistant to anthracyclines. In such a study, conducted by the M.D. Anderson Cancer Center group, in a subset of 6 patients resistant to doxorubicin, there were two PRs which lasted 2.5 and 6.1 months, respectively [6]. In addition, *in vitro* studies [11, 12] have suggested that there are at least two mechanisms responsible for acquired resistance to the taxanes. The first mechanism is related to microtubule assembly and the other to the multidrug resistance (*MDR*) gene. It is well established that the *MDR* phenotype confers varying degrees of cross-resistance to several classes of natural products including the vinca alkaloids, anthracyclines, taxanes and etoposide [13]. However, the existence of more than one mechanism may, at least, partially explain the lack of complete clinical cross-resistance between paclitaxel and anthracyclines, as was observed in the following two studies.

Table 6. Patient incidence (%) of various toxicities

	Grade*				
	0	1	2	3	4
Anaemia	55	24	21	0	0
Leucopenia	40	24	27	9	0
Stomatitis	88	9	0	3	0
Nausea/vomiting	73	15	12	0	0
Diarrhoea	70	27	0	3	0
Infection	85	6	6	3	0
Neurotoxicity	6	61	24	6	3
Skin	85	6	9	0	0
Arthralgias/myalgias	25	45	24	6	0
Alopecia	6	0	3	91	0
Cardiac	97	3	0	0	0

*WHO criteria.

In a phase II study, investigators at The Memorial Sloan Kettering Cancer Center reported that the incidence of objective responses to paclitaxel in patients with advanced breast cancer was similar between those who responded (30%) and those who failed on doxorubicin (32%) [14]. In a European–Canadian randomised phase III study, patients with advanced breast cancer who had received prior chemotherapy were treated either with 175 mg/m^2 or 135 mg/m^2 of paclitaxel in a 3 h infusion. Approximately 70% of the registered patients had been exposed to an anthracycline. The results of the interim analysis indicated that prior exposure to anthracyclines did not affect the response rate and also, in the higher dose arm, the response rate in patients sensitive to anthracyclines was the same as the one in resistant patients [15]. The results of these two trials support the use of paclitaxel as salvage treatment in patients with breast cancer deemed resistant to anthracyclines.

Nevertheless, the aforementioned studies [6, 14, 15] have a serious methodological problem which does not allow us to draw definite conclusions about the activity of paclitaxel in breast cancer resistant to anthracyclines. According to the design of these three studies, patients were registered irrespective of the class of drugs they had previously given. Therefore, patients who were deemed resistant to anthracyclines comprised only a proportion of the entire study population, and results were evaluated retrospectively following subset analysis.

In contrast, our study was designed to evaluate paclitaxel specifically in this group of patients. The response rate of 42% achieved in the present study is similar to that reported by other investigators (Table 7). Unfortunately, these other studies share several limitations which call for careful interpretation of their results. Firstly, most [14–16] appeared only in an abstract form and include limited number of patients. Secondly, between institutions, there are wide variations in study design, dosage of paclitaxel and schedule. Thirdly, the definition of "resistance" to anthracyclines varies considerably among trials resulting from large differences in patient population.

In a similar study to ours, published recently, investigators from the National Cancer Institute (NCI) Medicine Branch treated 33 patients with advanced breast cancer resistant to anthracyclines or mitoxantrone using paclitaxel. The dosage used was lower than that used in this study (140 versus 175 mg/m^2) but the duration of infusion was considerably longer (96

Table 7. Selected data from studies evaluating the activity of paclitaxel in anthracyline-resistant breast cancer patients

Principal investigators [Ref.]	Evaluable patients	Response (%) (CR + PR)	Dose (mg/m²)/duration of infusion (h)
Holmes *et al.* [6]	6	33	200–250/24
Seidman *et al.* [14]	37	30	200–250/24
Wilson *et al.* [18]	33	48	140/96
Nabholtz *et al.* [15]	26	29	175/3
Munzone *et al.* [16]	15	46	175/3
Vermorken *et al.* [17]	17	18	250/3
Present study	33	42	175/3

versus 3 h), thus requiring hospitalisation. The PR rate was 48% which is similar to the one reported in the present study (42%): median time to progression (27 weeks) and survival (43 weeks) were almost identical to ours ((24 and 41 weeks, respectively) [18].

Paclitaxel toxicity in our study was generally manageable. The major and most common side-effect was granulocytopenia. Febrile neutropenia was present in 15% of the cases. The only cumulative toxicity was peripheral neuropathy, although it did not result in interruption of treatment. The site of paclitaxel-induced peripheral neurotoxicity has been postulated to be either the nerve cell or the axon [19]. Sensory symptoms, such as numbness and paresthesias in a glove-and-stocking distribution, usually develop 24–72 h after paclitaxel administration [20] as was the case in this study. Another point to be emphasised is the lack of serious cardiotoxicity among our patients. Even with extensive cardiac monitoring performed in 21/33 of our patients, we were not able to identify any moderate or severe toxicity. Review of the relative literature shows that the most common cardiac complication is a transient asymptomatic bradycardia, which has been noted in up to 29% of patients [21]. Angina pectoris, myocardial infarction and atrial arrhythmias have been rarely observed in patients receiving paclitaxel alone or in combination with cisplatin [22]. To date, there is no convincing evidence that paclitaxel enhances the cardiotoxic effects of anthracyclines.

The rarity of severe complications accompanying the administration of paclitaxel represents a contribution to the quality of life of these patients, considering the palliative nature of this treatment and the fact that most of them face several medical and psychological problems.

In conclusion, in patients with breast cancer resistant to anthracyclines, paclitaxel at a dose of 175 mg/m² in a 3 h infusion exhibits significant activity with mild or moderate toxicity. Future trials should focus on the definition of the optimal dosage, duration of infusion and combinations of paclitaxel with other agents. Our group has recently initiated a phase II study in advanced breast cancer, in which a higher dose of paclitaxel (200 mg/m²) will be combined with carboplatin, given at an AUC (area under the curve) of 7 and G-CSF support.

1. Buzdar AV, Legha S, Hortobagyi G, *et al.* Management of breast cancer patients failing adjuvant chemotherapy with adriamycin containing regimens. *Cancer* 1981, **47**, 2798–2802.
2. Kosmidis P, Kondylis D, Lissaios B. Salvage chemotherapy for breast cancer patients treated with adjuvant adriamycin-containing regimen. *Oncology* 1990, **47**, 1–3.
3. Wall ME, Wani MC. Antineoplastic agents from plants. *Ann Rev Pharmacol Toxicol* 1977, **17**, 117–132.
4. Schiff PB, Fant J, Horowitz SB. Promotion of microtubule assembly *in vitro* by taxol. *Nature* 1979, **277**, 665–667.
5. Kumar N. Taxol-induced polymerization of purified tubulin. Mechanism of action. *J Biol Chem* 1981, **256**, 10435–10441.
6. Holmes FA, Walters RS, Theriault RL, *et al.* Phase II trial of taxol, an active drug in the treatment of metastatic breast cancer. *J Natl Cancer Inst* 1991, **83**, 1797–1805.
7. Reichman BS, Seidman AD, Crown JPA, *et al.* Paclitaxel and recombinant human granulocyte colony-stimulating factor as initial chemotherapy for metastatic breast cancer. *J Clin Oncol* 1993, **11**, 1943–1951.
8. Seidman AD. Single agent use of TAXOL (paclitaxel) in breast cancer. *Ann Oncol* 1994, 5 (suppl 6), S17–S22.
9. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer* 1981, **47**, 207–214.
10. Kaplan EL, Meier P. Non-parametric estimation from incomplete observations. *J Am Stat Assoc* 1985, **53**, 229–232.
11. Cabral FR. Isolation of Chinese hamster ovarian cell mutants requiring the continuous presence of taxol for cell division. *J Cell Biol* 1983, **97**, 22–29.
12. Horwitz SB, Cohen D, Rao S, *et al.* Taxol: mechanisms of action and resistance. *J Natl Inst Monog* 1993, **15**, 63–67.
13. Moscow JA, Cowan KH. Multidrug resistance. *J Natl Cancer Inst* 1988, **80**, 14–20.
14. Seidman AD, Crown JPA, Reichman BS, *et al.* Lack of clinical cross-resistance of Taxol with anthracycline in the treatment of metastatic breast cancer. *Proc Am Soc Clin Oncol* 1993, **12**, 63 (abstract 53).
15. Nabholtz JM, Gelmon K, Bontenbal M, *et al.* Randomized trial of two doses of taxol in metastatic breast cancer: an interim analysis (Abstr). *Proc Am Soc Clin Oncol* 1993, **12**, 60.
16. Munzone E, Capri G, Demicheli R, *et al.* Activity of Taxol by 3 h infusion in breast cancer patients with clinical resistance to anthracyclines. *Eur J Cancer* 1993, **29A** (suppl 6), S79 (abstract 413).
17. Vermorken JB, Huizing MZT, Liefting AJM, *et al.* High-dose taxol with G-CSF in patients with advanced breast cancer refractory to anthracycline therapy. *Eur J Cancer* 1993, **29A** (suppl 6), S83 (abstract 435).
18. Wilson WH, Berg SL, Bryant G, *et al.* Paclitaxel in doxorubicin-refractory or mitoxantrone-refractory breast cancer: a phase I/II trial of 96-hour infusion. *J Clin Oncol* 1994, **12**, 1621–1629.
19. Rowinsky EK, Chaudhry V, Forastiere AA, *et al.* A phase II and pharmacologic study of taxol and cisplatin with granulocyte colony-stimulating factor. Neuromuscular toxicity is dose-limiting. *J Clin Oncol* 1993, **11**, 2010–2020.
20. Lipton RB, Apfel SC, Dutcher JP, *et al.* Taxol produces a predominantly sensory neuropathy. *Neurology* 1989, **39**, 368–373.
21. McGuire WP, Rowinsky EK, Rosenhein NB, *et al.* Taxol. A unique antineoplastic agent with significant activity in advanced ovarian epithelial neoplasms. *Ann Intern Med* 1989, **111**, 273–279.
22. Rowinsky EK, McGuire WP, Guarnieri T, *et al.* Cardiac disturbances during the administration of taxol. *J Clin Oncol* 1991, **9**, 1692–1703.

Acknowledgement—The authors thank Mrs Christina Bammia for programming the data.