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Weekly paclitaxel as first-line chemotherapy for elderly patients with metastatic breast cancer. A multicentre phase II trial

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Abstract

Paclitaxel is a cytotoxic agent with proven antitumour activity in metastatic breast cancer. Weekly administration of paclitaxel has demonstrated sustained efficacy together with a more favourable toxicity profile (e.g. less myelotoxicity) than the 3-weekly administration. This study evaluates the activity and toxicity of weekly paclitaxel (Taxol®) as first-line chemotherapy in elderly patients (>70 years of age) with hormone-refractory metastatic breast cancer. Patients with metastatic breast cancer received 80 mg/m^2 paclitaxel administered weekly on days 1, 8 and 15 of a 28-day cycle. Additional cycles were given until disease progression, or unacceptable toxicity. A dose increase to 90 mg/m^2 was allowed in the absence of toxicity. 26 Patients received a total of 101 cycles (median 4, range 1–11). 22 patients completed at least two cycles (six administrations). In 23 patients who were evaluable for response, there were 10 partial responses (38%), 9 patients with stable disease (35%), while 4 patients had disease progression (15%). The median duration of response was 194 days (>6 months). Overall treatment was relatively well tolerated, but 8 patients (32%) had to prematurely discontinue treatment because of fatigue. Neuropathy >grade 1 was noted only after five or more cycles in 4 patients. Weekly paclitaxel at this dose and schedule is an effective treatment regimen in the elderly patient with metastatic breast cancer, and is feasible, but yields relevant fatigue in a subset of patients.

Keywords: Elderly; First-line chemotherapy; Metastatic breast cancer; Paclitaxel; Phase II

1. Introduction

The incidence of breast cancer increases with age. Because the population is ageing, the number of elderly women with breast cancer is expected to rise significantly in the near future. The treatment of cancer in elderly patients is increasingly recognised as an important challenge to the medical community [1]. Despite the fact that patients older than 70 years of age account for >25% of all breast cancer cases, only a small fraction of this group is generally entered into clinical studies [2,3]. Consequently, our knowledge of the use of chemotherapy in the elderly is based on very sparse data. Therefore, there is an urgent need to develop chemotherapy regimens that are well tolerated by elderly patients.

Taxanes have been used in a large number of trials investigating their activity in cancer patients. Studies with docetaxel in these patients were limited to patients younger then 75 years of age [4]. Only one trial on weekly docetaxel in elderly breast cancer patients (>65 years) has demonstrated that docetaxel at a dose of 36 mg/m^2 is feasible in this group of patients, with 36% of patients achieving an objective response [5].

Paclitaxel is an active drug in first-line therapy of metastatic breast cancer, as well as in patients with relapsed or refractory disease [6–8]. Response rates of

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21–61% in previously untreated patients have been reported in phase II and III trials evaluating paclitaxel at doses of 135–250 mg/m^2 in a 3-weekly schedule [6,8–16]. *In vitro* experiments and clinical studies have suggested that prolonged exposure to paclitaxel, through either a continuous infusion schedule or a weekly administration, can lead to enhanced cytotoxicity, while maintaining a favourable toxicity profile [17–19]. The weekly schedule of administrating paclitaxel therefore seems an attractive chemotherapeutic regimen for elderly patients. Paclitaxel has been used in elderly patients, but specific trials for this population, exploring the weekly administration schedule as first-line treatment, were lacking. We performed such a study in patients >70 years of age with hormone-refractory metastatic breast cancer to assess the activity and toxicity.

2. Patients and methods

2.1. Eligibility

Patients who were previously chemotherapy-naïve with respect to their metastatic disease and refractory to hormonal treatment were eligible for this study. Other eligibility criteria included age of at least 70 years, histologically documented and measurable (or evaluable) metastatic breast cancer; a baseline World Health Organization (WHO) performance score (PS) of ⩽2; a life expectancy of at least 3 months; bilirubin <25 μmol/l; creatinine <175 μmol/l; white blood cells (WBC) count $>1.5\times10^9$/l; platelet count $>100\times10^9$/l; haemoglobin >6.0 mmol/l; no signs of central nervous system (CNS) involvement; or neuropathy >WHO grade 1. All patients gave their written informed consent. The institutional ethical boards of the participating hospitals approved the study.

Pre-treatment evaluations included a medical history, complete physical examination, a complete blood count with differential, and the following serum chemistry tests: electrolytes, creatinine, glucose, alkaline phosphatase, aspartate-aminotransferase (AST), alanine-aminotransferase (ALT), lactate-dehydrogenase (LDH), and total and direct bilirubin. The cardiological function was evaluated by an electrocardiogram (ECG), and by a multiple gated acquisition (MUGA) scan when indicated. All sites of disease were documented by computerised tomography (CT), X-ray, or bone scan, depending on the site of disease activity.

2.2. Treatment

Paclitaxel (Taxol®, Bristol-Myers Squibb, Woerden, The Netherlands) was infused intravenously (i.v.) over 1 h, at a dose of 80 mg/m^2, and given on days 1, 8 and 15 of a 28 day cycle. Standard i.v. premedication to prevent hypersensitivity reactions (HSR) consisted of dexamethasone 8 mg, clemastine 2 mg and ranitidine 50 mg administered approximately 30 min before the paclitaxel infusion [20]. During treatment, blood cell count and toxicity assessment were performed weekly. Toxicity was evaluated using the National Cancer Institute Common Toxicity Criteria (NCI CTC) version 2.0 (URL: https://webapps.ctep.nci.nih.gov/ctcv2/plsql/ctc000w$.startup). The dose of paclitaxel was modified depending on the haematological and non-haematological effects observed. The treatment was postponed in case of a neutrophil count $<0.5\times10^9$/l, and/or platelet count $<50\times10^9$/l, febrile neutropenia (temperature >38 °C and neutrophil count $<1.0\times10^9$/l), any grade >1 non-haematological toxicity, except nausea and vomiting or alopecia. When treatment had to be postponed for a second week, the patient went off the study. In case the administration had to be postponed for 1 week, the dosage of paclitaxel was reduced by 10 mg/m^2 in the next course. In case more than two dose reductions were necessary, the patients went off the study. In patients who tolerated the weekly regimens for three consecutive administrations without delay, a dose escalation to 90 mg/m^2 per administration was allowed at the discretion of the treating physician.

2.3. Response evaluation and follow-up

Response evaluation criteria in solid tumours (RECIST) criteria were used to define measurable and evaluable disease and response [21]. Response was evaluated after every two cycles of treatment (i.e. every 8 weeks), and every 2 months thereafter for the first year and every 3 months for the following years, for all responding and stable patients until progression. Paclitaxel treatment was stopped in the case of progressive disease, stable disease (SD) after 16 weeks (four cycles), at the patient's preference at any time, or following unacceptable toxicity.

2.4. Statistical analysis

The primary endpoint in this study was the overall response rate of weekly administered paclitaxel.

The sample size was calculated based on the assumption that a 40% objective response rate would be detected. The accrual consisted of two stages. If there were no complete or partial responses in the first 6 enrolled patients, the study would be terminated. In the case of one or more responses in these 6 patients, 19 additional patients would be enrolled (for a total of 25 patients), so that the standard error of the response rate would be less than or equal to 0.10. This scheme ensured that if the drug is active in at least 40% of the patients, the chance of erroneously rejecting the drug after the first 6

patients is less than 5%. The advantage of such a two-stage scheme is that it allows early rejection of an ineffective drug.

Time to disease progression (TTP) was estimated from the beginning of paclitaxel therapy, while duration of response (DR) was determined from the date the response [complete response (CR) or partial response (PR)] was initially reported. Patients who discontinued treatment for any reason or died from probable disease-related causes were considered, at that time, as having disease progression.

The Kaplan–Meier analysis method was used to calculate the duration of response, and TTP curves.

3. Results

3.1. Patients' characteristics

The demographics of the 26 enrolled patients is depicted in Table 1. All but 5 patients presented with a PS of 0–1. The time from first diagnosis of breast cancer to study entry was more than 12 months in 19 patients (73%), 6–12 months in 1 patient (4%), and less than 6 months in 6 patients (23%). All patients were chemonaïve for their metastatic disease.

3.2. Treatment characteristics

A total of 101 treatment cycles was administered to 26 patients. Since two responses were noted in the first 6 patients, a total of 25 patients had to be included according to the protocol. All patients were evaluable for toxicity. One patient was replaced due to the development of a severe HSR immediately at the start of the first paclitaxel infusion. One other patient developed erythema after paclitaxel infusion, but she was evaluable for toxicity evaluation after this single course. One patient received only two cycles due to vomiting (grade 3) and refused further treatment. In 6 out of the 23 remaining patients (26%), the dose was escalated to 90 mg/m^2. In 2 patients, the dose was lowered to 70 mg/m^2. The median delivered dose intensity was 240 mg/m^2/4-week-cycle (range 210–270). The median number of cycles delivered was 4 (range 1–11). 22 patients completed at least 2 cycles, 15 patients completed four or more cycles. Treatment delay was uncommon and was most often related to patients' requests, rather than toxicity. 9 patients (35%) continued treatment after four cycles.

3.3. Toxicity

Toxicity data were evaluated in the 25 patients receiving at least one full cycle. Toxicity data are outlined in Table 2. Overall, paclitaxel therapy was relatively well tolerated and manageable on an outpatient basis (Table 2). Myelosuppression was mild and relatively infrequent. Fatigue constituted an important problem and occurred in 67% of patients. In 8 patients (32%), fatigue was the reason for treatment discontinuation. Fatigue could not be related to anaemia. In many of these elderly patients, the distinction between cancer-related and treatment-related fatigue was difficult to determine. Neuropathy occurred in 39% of patients and resulted in discontinuation of treatment in three patients. Neuropathy grades 2 and 3 were only seen after five or more courses in 4 out of 9 patients. Nausea was observed in 11 patients, but not during all their paclitaxel administrations. Alopecia grade 1 developed in 4 patients; grade 2 in 15 patients. Other toxicities consisted of oedema and nail changes in less than 10% of patients, and were all easy to manage (CTC grades 1 and 2). 2 patients were withdrawn from the study due to HSR. One patient developed a grade 3 toxicity (neutropenia and generalised erythroderma) after the

Table 1
Patient and tumour characteristics

	n (%)
n	26 (100)
Age in years	
Median (range)	77 (71–84)
Performance status	
0	4 (15)
1	17 (65)
2	5 (19)
ER/PR	
Positive	10 (38)
Negative	10 (38)
Unknown	6 (23)
Previous adjuvant	
Chemotherapy	1 (4)
HT	6 (23)
Previous hormonal treatment for metastatic disease	
0	7 (27)
1 line	2 (8)
2 lines	9 (35)
$\geqslant 3$	8 (31)
No of metastatic sites	
1 organ	2 (8)
2 organs	11 (42)
$\geqslant 3$ organs	13 (50)
Site of metastasis	
Locoregional only	1 (4)
Distant	
Bone	19 (73)
Lung	6 (23)
Liver	10 (38)
Lymph node	11 (42)
Distant only	18 (69)
Locoregional + distant	7 (27)

HT, hormonal therapy; ER, oestrogen receptor; PR, progesterone receptor.

first administration; the other patient suffered a severe allergic reaction with hypotension after the infusion of a small amount of paclitaxel and was not evaluable for further toxicity.

3.4. Tumour response and survival

In 23 out of 26 patients (88%) enrolled, the response could be assessed. A total of 3 patients were not evaluable for response due to early treatment discontinuation because of severe HSR in 2 patients, and vomiting grade 3 in 1 patient. 2 patients withdrew informed consent because of side-effects after two treatment courses. 10 patients achieved PR (38%- intent-to-treat-analysis), complete responses were not seen. In addition, SD was observed in 9 patients.

Time-to-progression (TTP) analysis (Fig. 1) was performed on 1 May 2003, at which time 15 patients had died, including the 3 non-evaluable patients. 2 patients were still in remission. The median time-to-progression was 6.5 months. Median follow-up time for surviving patients was 557 days (range 196–1141 days).

Table 2
Worst grade toxicity per patient observed (% of patients)[a]

NCI toxicity grade	1	2	3	4
Toxicity				
Neutropenia	50	23	12	–
Anaemia	15	27	12	–
Thrombocytopenia	–	–	–	–
Infection	–	4	–	–
Febrile neutropenia	–	4	–	–
HSR	–	4	4	–
Fatigue	27	38	4	–
Alopecia	15	73	NA	NA
Neuropathy	23	12	4	–
Myalgia	8	–	–	–
Nausea	4	12	–	–
Vomiting	–	4	4	–
Nail disorders	8	4	–	–
Stomatitis	23	8	–	–

HSR, hypersensitivity reactions; NCI, National Cancer Institute; NA, not available.

[a]26 patients were evaluable for toxicity, of whom 1 patient received only a few mgs of paclitaxel.

4. Discussion

Weekly paclitaxel is clearly active as first-line treatment in patients with metastatic breast cancer, and has several suggested advantages over 3-week schedules, in terms of both toxicity and probably efficacy [16,22–24]. In the current study, we assessed toxicity and efficacy of weekly paclitaxel as first-line treatment in patients older than 70 years with metastatic breast cancer. This is a clearly an underrepresented age group in trials for chemotherapeutic treatment of metastatic breast cancer, which is probably due to the high incidence of co-morbidity, and the reluctance of physicians to treat elderly patients with chemotherapy. Nevertheless, in this phase II study a sufficient number of patients was included, although the accrual was relatively slow.

Weekly paclitaxel at this dose and schedule yielded a response rate of 38%. This response rate seems relatively high compared with the response rate of 20% reported by Perez and colleagues in Ref. [25], but might

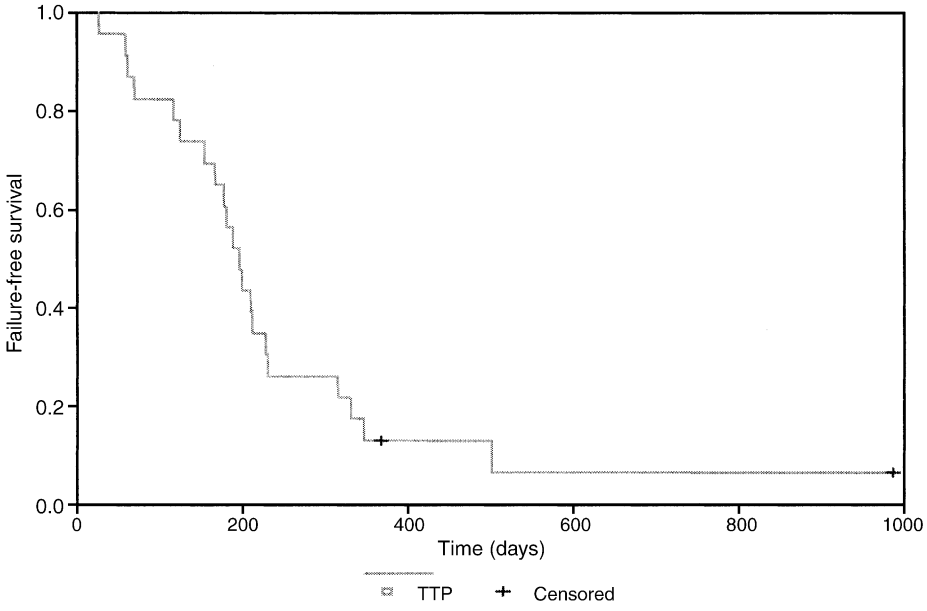

Fig. 1. Kaplan–Meier analysis of time to progression (TTP) of patients treated with weekly paclitaxel. Median time to progression = 194 days. Data were censored at 1 May 2003; at this time, 2 patients were still free of progression.

be explained by the differences in pretreatment. All of our patients except one were chemo-naïve, while 82% of patients in the study of Perez received prior chemotherapy. Response rates of 21 to 49% have been reported from other multicentre trials of single agent paclitaxel administered at different doses and with different infusion schedules every 3 weeks to patients with metastatic breast cancer [6,8–16]. Thus, our response results are within the range observed in other trials with paclitaxel. In addition, weekly treatment with both docetaxel [5] and vinorelbine [26] in elderly patients revealed similar response levels.

The regimen appears relatively feasible, but the observation of fatigue in 67% of patients is of concern. In other studies with weekly administrations of paclitaxel in elderly patients, a similar incidence of asthenia was reported [25,27]. This side-effect following weekly docetaxel treatment in the elderly appears to be even more severe when compared with paclitaxel treatment, since Hainsworth and colleagues reported grade 3 fatigue in 20% of patients, and grades 1 and 2 in 73% of patients [5]. Given the relatively short median treatment period of 16 weeks, the incidence of neuropathy in this weekly paclitaxel regimen is another reason for concern, although neuropathy $>$grade 1 was only noted after five or more cycles. By contrast, docetaxel causes hardly any neuropathy in the weekly regimen [5].

In agreement with other studies with weekly paclitaxel, only a few patients (12%) developed serious haematological side-effects of neutropenia of more than grade 2. This is in line with the haematological side-effects reported in the weekly docetaxel regimen [5]. In the weekly regimen with vinorelbine, haematological side-effects were the dose-limiting toxicity [26].

The pharmacokinetic study reported by Smorenburg and colleagues performed in this group of patients revealed that the clearance of both unbound and total paclitaxel are significantly lower in elderly women with metastatic breast cancer, compared with younger females (124 ± 35.0 versus 237 ± 43.0 l/h/m^2 ($P=0.002$), and 13.9 ± 2.31 versus 17.4 ± 4.52 l/h/m^2 ($P=0.004$), respectively) [28]. In the entire population, a significant negative correlation was observed between age and unbound paclitaxel clearance. Therefore, we anticipated observing increased toxicity in this elderly population, compared with younger patients. Obviously, a formal comparison cannot be made. However, the number of treatment discontinuations based on fatigue, and to a lesser extent based on neuropathy, is of concern. It suggests a decreased tolerance in this elderly population. Whether this is related to the decrease in drug clearance remains to be elucidated. In addition, the same pharmacokinetic study revealed a significant and rather unusual increase in Cremophor EL (CrEL) clearance. Since neuropathy [29,30] and HSR [20,30] are partly related to this vehicle, a lower incidence of these side-effects could be expected. However, this was not the case.

In conclusion, the weekly administration of paclitaxel is an effective first-line regimen for elderly patients with metastatic breast cancer, but yields relevant toxicity. Fatigue is the main toxicity, and, overall, is the main reason for treatment discontinuation. Weekly paclitaxel can be considered for elderly patients with metastatic breast cancer, although treatment will not be tolerated in the longer run in an important sub-set of patients.

References

1. Aapro MS. Progress in the treatment of breast cancer in the elderly. *Ann Oncol* 2002, **13**(Suppl. 4), 207–210.
2. Trimble EL, Carter CL, Cain D, Freidlin B, Ungerleider RS, Friedman MA. Representation of older patients in cancer treatment trials. *Cancer* 1994, **74**, 2208–2214.
3. Hutchins LF, Unger JM, Crowley JJ, Coltman Jr CA, Albain KS. Underrepresentation of patients 65 years of age or older in cancer—treatment trials. *N Engl J Med* 1999, **341**, 2061–2067.
4. Burstein HJ, Manola J, Younger J, *et al*. Docetaxel administered on a weekly basis for metastatic breast cancer. *J Clin Oncol* 2000, **18**, 1212–1219.
5. Hainsworth JD, Burris III HA, Yardley DA, *et al*. Weekly docetaxel in the treatment of elderly patients with advanced breast cancer: a Minnie Pearl Cancer Research Network phase II trial. *J Clin Oncol* 2001, **19**, 3500–3505.
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. Hortobagyi GN, Holmes FA. Single-agent paclitaxel for the treatment of breast cancer: an overview. *Semin Oncol* 1996, **23**, 4–9.
8. Nabholtz JM, Gelmon K, Bontenbal M, *et al*. Multicenter, randomized comparative study of two doses of paclitaxel in patients with metastatic breast cancer. *J Clin Oncol* 1996, **14**, 1858–1867.
9. Abrams JS, Vena DA, Baltz J, *et al*. Paclitaxel activity in heavily pretreated breast cancer: a National Cancer Institute Treatment Referral Center trial. *J Clin Oncol* 1995, **13**, 2056–2065.
10. Gianni L, Capri G, Munzone E, Straneo M. Paclitaxel (Taxol) efficacy in patients with advanced breast cancer resistant to anthracyclines. *Semin Oncol* 1994, **21**, 29–33.
11. Gianni L, Munzone E, Capri G, *et al*. Paclitaxel in metastatic breast cancer: a trial of two doses by a 3-hour infusion in patients with disease recurrence after prior therapy with anthracyclines. *J Natl Cancer Inst* 1995, **87**, 1169–1175.
12. Paridaens R, Biganzoli L, Bruning P, *et al*. Paclitaxel versus doxorubicin as first-line single-agent chemotherapy for metastatic breast cancer: a European Organization for Research and Treatment of Cancer Randomized Study with cross-over. *J Clin Oncol* 2000, **18**, 724–733.
13. Reichman BS, Seidman AD, Crown JP, *et al*. Paclitaxel and recombinant human granulocyte colony-stimulating factor as initial chemotherapy for metastatic breast cancer. *J Clin Oncol* 1993, **11**, 1943–1951.
14. Seidman AD, Reichman BS, Crown JP, *et al*. Taxol plus recombinant human granulocyte-colony stimulating factor as initial and as salvage chemotherapy for metastatic breast cancer: a preliminary report. *J Natl Cancer Inst Monogr*, 1993, 171–175.
15. Smith RE, Brown AM, Mamounas EP, *et al*. Randomized trial of 3-hour versus 24-hour infusion of high-dose paclitaxel in patients with metastatic or locally advanced breast cancer:

National Surgical Adjuvant Breast and Bowel Project Protocol B-26. *J Clin Oncol* 1999, **17**, 3403–3411.
16. Perez EA, 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.
17. Seidman AD, Hochhauser D, Gollub M, *et al*. Ninety-six-hour paclitaxel infusion after progression during short taxane exposure: a phase II pharmacokinetic and pharmacodynamic study in metastatic breast cancer. *J Clin Oncol* 1996, **14**, 1877–1884.
18. Fennelly D, Aghajanian C, Shapiro F, *et al*. Phase I and pharmacologic study of paclitaxel administered weekly in patients with relapsed ovarian cancer. *J Clin Oncol* 1997, **15**, 187–192.
19. Akerley W, Sikov WM, Cummings F, Safran H, Strenger R, Marchant D. Weekly high-dose paclitaxel in metastatic and locally advanced breast cancer: a preliminary report. *Semin Oncol* 1997, **24**, S17.
20. Wiernik PH, Schwartz EL, Strauman JJ, Dutcher JP, Lipton RB, Paietta E. Phase I clinical and pharmacokinetic study of taxol. *Cancer Res* 1987, **47**, 2486–2493.
21. Therasse P, Arbuck SG, Eisenhauer EA, *et al*. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000, **92**, 205–216.
22. Green MC, Buzdar AU, Smith T, Singletary SE, Carter C, Rosales MF. Weekly paclitaxel followed by FAC in the neoadjuvant setting provides improved pathologic complete remission (PCR) rates compared to standard paclitaxel followed by FAC therapy—preliminary results of an ongoing prospective randomized trial. *Proc Am Soc Clin Oncol* 2001, **18** (abstr. 129), 33.
23. Zimatore M, Danova M, Vassallo E, *et al*. Weekly taxanes in metastatic breast cancer (review). *Oncol Rep* 2002, **9**, 1047–1052.
24. Seidman AD, Hudis CA, McCaffrey J, *et al*. Dose-dense therapy with paclitaxel via weekly 1-hour infusion: preliminary experience in the treatment of metastatic breast cancer. *Semin Oncol* 1997, **24**, S17, 72–76.
25. Perez EA, Vogel CL, Irwin DH, Kirshner JJ, Patel R. Weekly paclitaxel in women age 65 and above with metastatic breast cancer. *Breast Cancer Res Treat* 2002, **73**, 85–88.
26. Vogel C, O'Rourke M, Winer E, *et al*. Vinorelbine as first-line chemotherapy for advanced breast cancer in women 60 years of age or older. *Ann Oncol* 1999, **10**, 397–402.
27. Fidias P, Supko JG, Martins R, *et al*. A phase II study of weekly paclitaxel in elderly patients with advanced non-small cell lung cancer. *Clin Cancer Res* 2001, **7**, 3942–3949.
28. Smorenburg CH, ten Tije AJ, Verweij J, *et al*. Altered clearance of unbound paclitaxel in elderly patients with metastatic breast cancer. *Eur J Cancer* 2003, **39**, 196–202.
29. Rowinsky EK, Burke PJ, Karp JE, Tucker RW, Ettinger DS, Donehower RC. Phase I and pharmacodynamic study of taxol in refractory acute leukemias. *Cancer Res* 1989, **49**, 4640–4647.
30. ten Tije A, Verweij J, Loos W, Sparreboom A. Pharmacological effects of formulation vehicles: implications for cancer chemotherapy. *Clin Pharmacokinet* 2003, **42**, 665–685.