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ORIGINAL ARTICLE

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A phase II study of weekly docetaxel in patients with anthracycline pretreated metastatic breast cancer

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Abstract *Background*: Docetaxel has significant activity in metastatic breast cancer and weekly schedules are associated with less myelosuppression than 3-weekly schedules. We evaluated the toxicity and the activity of weekly docetaxel in anthracycline-pretreated patients. *Patients and methods*: A total of 42 patients were studied. Treatment consisted of docetaxel 35 mg/m^2 weekly as a 30-min infusion for 6 weeks followed by a 2-week rest, with dexamethasone 8 mg i.v. pre-medication and 4 mg orally 12-hourly for 48 h following treatment. *Results*: The median age of the patients was 53 years (range 34–74). Twenty-six (62%) patients had received prior chemotherapy for advanced disease. Patients received a median 10 weeks of treatment (range 1–24). 11 had a partial response (ORR 26%; 95% CI 13–39%), five of whom had relapsed <12 months since the end of previous anthracycline-based chemotherapy. In addition six patients (14%) had stable disease for >16 weeks. Myelosuppression was rare with only 2 patients (5%) experiencing grade 3 neutropenia (no grade 4 neutropenia). Non-haematological grade III toxicities were as follows: fatigue 17%, neuropathy 0%, hyperlacrimation 5%, stomatitis 7%, diarrhoea 14%, and cutaneous toxicity 19%. Skin toxicity consisted of limb/palmar–plantar erythematous reactions, or fixed-plaque erythrodysaesthesia. *Conclusions*: Weekly docetaxel has moderate activity in women with anthracycline pre-treated breast cancer. Although the level of myelosuppression is lower than 3-weekly regimens, this weekly regimen cannot be recommended due to the significant non-haematological toxicities associated with the treatment.

Keywords Metastatic breast cancer · Docetaxel · Weekly chemotherapy

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Introduction

Docetaxel (Taxotere®) is an active drug for the treatment of patients with metastatic breast cancer. A phase III study confirmed that docetaxel had significantly higher efficacy than mitomycin and vinblastine (overall response rate 30 vs. 12%) in patients who had previously received anthracyclines [31]. A recent phase III trial comparing 3-weekly docetaxel with 3-weekly paclitaxel in women failing anthracyclines reported that docetaxel was superior in terms of response rate (32 vs. 25%), median time to progression (5.7 vs. 3.6 months) and overall survival (15.4 vs. 12.7 months) [21]. Docetaxel is conventionally administered as a 3-weekly infusion, and at the standard dose of 100 mg/m^2 every 3 weeks the incidence of grade 3/4 neutropenia approaches 90% and is the dose-limiting toxicity. Other common toxicities include hypersensitivity reactions, asthenia, cutaneous/nail toxicity and fluid retention.

There are a number of potential advantages to weekly administration of chemotherapy. Weekly scheduling may potentially increase dose density to prevent emergence and re-growth of drug-resistant cell clones by more frequent exposure to cytotoxic agents. The therapeutic index may also be improved with the reduction of grade 3–4 myelosuppression by giving lower doses more frequently. In addition some data have suggested that the taxanes (particularly paclitaxel) may have anti-angiogenic properties [4, 23], and two studies have suggested that this effect could be greater with docetaxel than with paclitaxel

[16, 45]. An anti-angiogenic mechanism of action could be better exploited using a low-dose weekly schedule rather than conventional 3-weekly dosing, although formal pharmacological evidence for this in clinical studies is lacking. In addition, docetaxel may have a direct effect on apoptosis by promoting the phosphorylation and inactivation of the cell survival factor BCL-2, thus abrogating the anti-apoptotic action of this protein [20].

The preliminary results of CALGB 9840 study which included 585 women with metastatic breast cancer showed that weekly paclitaxel was superior to 3-weekly paclitaxel with significantly higher response rates (40 vs. 28%) and longer time to progression (9 vs. 5 months). Overall survival was similar in both arms. Myelosuppression was reduced although there was increased neurotoxicity [37]. This study was originally conceived with the aim of maintaining efficacy while reducing the severity and incidence of myelosuppression by administering a lower dose weekly. The role of weekly docetaxel in metastatic breast cancer has not been investigated in large randomised studies to date.

There have been three phase I studies of weekly docetaxel which reported a maximum tolerated dose (MTD) of 42–45 mg/m^2/week, with dose limiting toxicities being fatigue and skin toxicity. In two studies [18, 26], docetaxel was given as a 1 h infusion on a weekly basis. A third study reported similar efficacy and toxicity profiles utilising a shorter 15–30 min infusion [24]. Although one study had reported grade 4 leucopenia at the MTD [26], grade 4 neutropenia was generally not seen, and these early trials seemed to confirm that a weekly schedule could substantially reduce the haematological toxicity seen with conventional 3-weekly docetaxel.

Docetaxel has since been evaluated in a number of phase II studies in advanced breast cancer at doses of 25–40 mg/m^2 weekly infused over 30–60 min. A recent review of these studies revealed responses of 30–40% in different populations of pretreated patients, with a low incidence of severe haematologic toxicities [9]. The weekly regimen was felt to be potentially useful for certain groups of patients, such as those with reduced bone marrow reserve [3]. We report our experience from our multicentre phase II trial which specifically targeted patients pre-treated with anthracyclines. It was designed to evaluate the response rates and toxicity profile of weekly docetaxel at a dose of 35 mg/m^2/week on a 6/8 week schedule, but using a shorter 30-min infusion schedule based on the promising data from the phase I study mentioned above [24]. A shorter infusion time may also be more convenient for patients.

Patients and methods

Patient selection

Patients were recruited from four participating centres in the UK. To be eligible for the study, patients were required to have histologically confirmed breast cancer with locally advanced or progressive metastatic disease, and have been previously treated with anthracycline based chemotherapy either in the adjuvant setting or for advanced disease. They were also required to have measurable disease, and to have a WHO performance status 0–2. Other requirements were satisfactory haematologic, renal and hepatic function. Patients were excluded if they had a history of other malignant conditions (except non-melanotic skin cancer or adequately treated carcinoma in situ of the cervix), had untreated cerebral metastases, or had received any investigational drug within 30 days of study entry. All patients signed written informed consent, and the study was approved by the local ethics committees of all participating hospitals.

Treatment and monitoring

Pre-treatment evaluation consisted of full history and physical examination including assessment of WHO performance status. All patients had an electrocardiogram, baseline full blood count, and measurement of urea and electrolytes, liver function tests and serum calcium. Tumour was assessed at baseline using appropriate radiological and clinical measurements not more than 4 weeks prior to study entry. Patients received docetaxel 35 mg/m^2 by a 30 min intravenous infusion weekly for 6 weeks followed by a 2 week break (q 6/8 week schedule, which constituted one cycle). Patients received premedication with dexamethasone 8 mg intravenously immediately prior to treatment followed by oral dexamethasone 4 mg every 12 h for 48 h. While on study patients had weekly full blood counts and assessment of toxicity using the NCI common toxicity criteria. Serum biochemistry was performed at the beginning of each 8-week cycle. Full dose docetaxel was administered if the absolute neutrophil count was $>1.5\times10^9$/l. If the absolute neutrophil count was less than 1.5×10^9/l, treatment was delayed until the count had recovered. The protocol allowed dose reduction to 30 mg/m^2 following an episode of grade 3 or 4 neutropenia with infection. Grade 2 neuropathy required dose reduction to 25 mg/m^2 for subsequent cycles. Treatment was discontinued if grade 3 neuropathy occurred. The dose of docetaxel could be reduced by 25% in the event of any other grade 3 or 4 non-haematological toxicity. In the event that any grade 3 or 4 non-haematological toxicity failed to resolve, patients were withdrawn from the study.

Treatment evaluation

All patients who completed the first cycle of docetaxel, or who developed evidence of progression during the first cycle were considered evaluable for response. Formal clinical and radiological assessments of response occurred after 2 cycles (16 weeks), or earlier if there was a clinical suspicion of disease progression. Responses were assessed using standard WHO criteria [30]. It was anticipated that patients would receive up to a maximum

of 4 cycles (32 weeks) of therapy, although treatment could be discontinued for either progressive disease, unacceptable toxicity, or patient request.

Statistical considerations

The primary endpoint was clinical response rate. The study was designed using a Simon 2-stage protocol [39], designed to have an 80% chance of being positive with a true response rate of 40%, and a 20% chance of being positive with a true response rate of 20%. Four responses were required in the first cohort of 13 patients to proceed to the second stage of the study. Overall 13 responses were required from a planned recruitment figure of 42 patients to conclude that the treatment merited further evaluation. Secondary endpoints included time to disease progression, overall survival, and toxicity profile. The time to disease progression and overall survival were measured from the first day of treatment, and actuarial survival curves were generated using the Kaplan–Meier method.

Results

Patients and treatment received

Between January 2000 and January 2001, 42 patients were enrolled into the study (Table 1). All patients had previously received anthracycline either in the adjuvant or metastatic setting. Twenty-three (55%) patients had previously received one line of chemotherapy for metastatic breast cancer while 3 (7%) had previously received two lines of palliative chemotherapy. None had received taxanes previously. Patients received a median of 10 weeks of treatment (range 1–24). Thirty-four patients (81%) completed the first cycle of treatment. Of the eight patients who did not complete the first cycle, four discontinued treatment due to rapid disease progression and were considered non-responders. Of the other four patients, one patient had an acute hypersensitivity reaction following the first infusion of docetaxel. Three stopped at their own request; one due to severe lethargy and difficulty in attending hospital weekly, and two because of severe cutaneous toxicity manifested by erythrodysaesthia on their hands and face after 4 and 5 weeks of treatment, respectively. Although these four patients were not truly evaluable for response, they were considered as treatment failures and included in the intent-to-treat analysis.

Table 1 Patient characteristics

Characteristic	No. of patients (%)
Median age (range)	53.5 years (34–74)
WHO performance status	
0	6 (14%)
1	31 (74%)
2	3 (7%)
Not recorded	2 (5%)
Sites of disease	
Visceral (liver, lung)	24 (57%)
Soft tissue (breast, nodes, skin)	16 (38%)
Bone	2 (5%)
No previous lines of chemotherapy	
Adjuvant	
0	17 (41%)
1	24 (57%)
2	1 (2%)
Metastatic	
0	16 (38%)
1	23 (55%)
2	3 (7%)

Clinical efficacy

On an intent-to-treat (ITT) analysis, there were 11 partial responses (PR) out of the total of 42 patients, giving an objective response rate of 26.2% (95% CI 13–39%) (Table 2). A further 11 patients (26.2%) had stable disease as their best response, of whom 6 patients (14.3%) had stable disease for greater than 16 weeks (i.e. at least 2 completed cycles). Of the 11 patients who had an objective PR, 5 had an interval of less than 12 months since prior anthracycline therapy. Kaplan–Meier curves for time to progression (TTP) and overall survival (OS) are shown in Fig. 1, with overall a median TTP of 3.9 months and a median OS of 9.2 months.

Dose reductions/delays

Twenty-nine (85%) of the 34 patients who completed the first cycle of docetaxel received all the intended weekly doses. Of 204 planned doses in the first cycle, only 6 (3%) were given with a 25% dose reduction and 5 (2%) were omitted. In addition 11 cycles (5%) were delayed by a median of 7 days (range 3–14). However out of 27 patients who embarked on a second treatment cycle, only 17 completed the cycle. Of the ten patients who

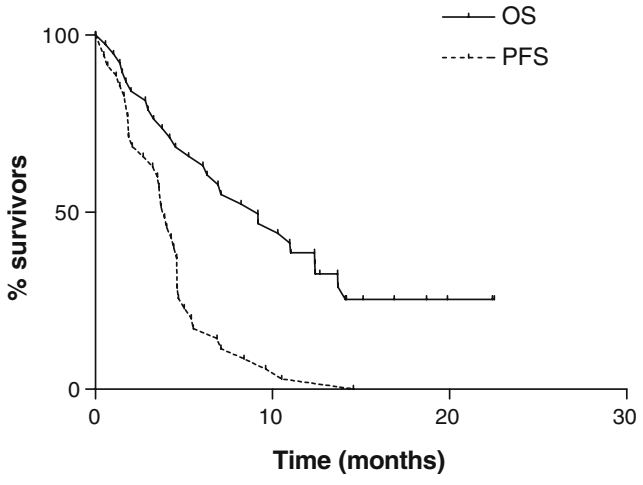

Fig. 1 Survival curves

Table 2 Overall response rate in 42 patients (ITT analysis)

Best response	No. of patients (%)
CR	0
PR	11 (26%)
SD at 8 week	5 (12%)
SD at 16 week	6 (14%)
PD	16 (38%)
Not evaluable	4 (10%)

CR complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease

Table 3 Toxicity; number (%) patients with worst grade

	Grade 1	Grade 2	Grade 3	Grade 4
Neutropenia	4 (10%)	4 (10%)	2 (5%)	0
Thrombocytopenia	5 (12%)	0	0	0
Infection	1 (2%)	10 (24%)	4 (10%)	0
Alopecia	12 (29%)	21 (50%)	–	–
Fatigue	4 (10%)	11 (26%)	7 (17%)	1 (2%)
Neuropathy	8 (19%)	3 (7%)	0	0
Cutaneous	4 (10%)	8 (19%)	8 (19%)	0
Hyperlacrimation	3 (7%)	12 (29%)	2 (5%)	0
Diarrhoea	5 (12%)	6 (14%)	6 (14%)	0
Stomatitis	5 (12%)	10 (24%)	3 (7%)	0

stopped treatment early in the second cycle, this was because of disease progression in six cases and toxicity in four. In the second treatment cycle dose reductions and omissions were slightly more common, occurring in 9 (6%) and 8 (5%) out of 152 planned doses, respectively. Twelve doses (8%) were delayed in the second cycle, again for a median of 7 days. Overall the incidence of dose reductions in the first two cycles was low (15/356 treatments), and in subsequent treatments the frequency of dose reductions remained low.

Toxicity

The most common toxicity was fatigue, which was seen at grade 2 or more in 19 patients (45%) (Table 3). Haematological toxicity was rare, and only 2 patients (5%) developed grade 3 neutropenia, one of which was complicated by fever requiring hospital admission and antibiotics. In particular there were no cases of grade 4 neutropenia, and no cases of grade 2–4 thrombocytopenia. Cutaneous toxicity occurred in a total of 20 patients, manifested at worst as grade 3 in 8 patients (19%) with painful erythematous palmar–plantar rash, sometimes associated with desquamation. Fixed plaques of erythrodysaesthesia at other sites (forearms, legs and face) were also seen. Hyperlacrimation occurred in 17 patients (40%); it was considered severe in 2 patients (5%). Other serious toxicities were uncommon (Table 3).

Discussion

These data demonstrate the activity of weekly docetaxel in anthracycline pre-treated metastatic breast cancer, but the eleven responses observed fell short of the number of responses initially projected to conclude that the regimen merited further evaluation. Moreover, our response rate of 26% is slightly lower than the published Phase III data with the 3-weekly schedule in anthracycline pre-treated patients [21, 31]. Similar to most other published phase II studies of weekly docetaxel where the incidence of grade 3–4 neutropenia ranged between 2 and 22% (Table 4), we observed a very low incidence of myelosuppresion and its associated complications (5% grade 3 neutropenia, no grade 4 neutropenia, and only 1 patient with neutropenic fever). A subsequent randomised study in 83 patients with advanced breast cancer has compared weekly docetaxel at 40 mg/m^2 weekly for 6/8 weeks with conventional 3-weekly docetaxel at 100 mg/m^2 [43]. The authors reported similar efficacy in both arms (34 and 33% respectively, objective response rate), but that the haematological toxicity profile was substantially better with weekly docetaxel, resulting in significantly fewer patients requiring dose reductions (15 vs. 42%). Very recently, preliminary results from a large Intergroup adjuvant chemotherapy study which included a comparison of weekly versus 3-weekly docetaxel have shown similar findings with no difference in efficacy, but decreased haematological toxicity [40]. Thus administration of docetaxel in a weekly schedule does appear to substantially improve the haematological toxicity profile when compared with 3-weekly docetaxel given at 100 mg/m^2, whilst at the same time maintaining therapeutic efficacy.

Although serious haematological toxicities were uncommon in our study, there was a high incidence of ophthalmic and cutaneous toxicity as well as fatigue. In our study the incidence of grade 2 or 3 cutaneous toxicity was 16/42 (38%), and 14/42 (34%) for grade 2 or 3 hyperlacrimation. Cutaneous toxicity was most commonly manifested as palmar–plantar erythema, often associated with desquamation. In addition we observed five cases of fixed plaques of erythrodysaesthesia, a condition that has been previously reported with docetaxel therapy [7]. Cutaneous toxicity was often associated with hyperlacrimation in the same patient, and in two patients was severe enough to merit delay or discontinuation of therapy. Docetaxel is known to be present in the tears following intravenous therapy and may cause chemical conjunctivitis, although hyperlacrimation (epiphora) may also relate to canalicular stenosis [10]. This toxicity would appear to be more common with weekly docetaxel, and in a previous study 9/14 patients treated with the combination of weekly docetaxel and trastuzumab who developed epiphora were found to have canalicular stenosis [11, 13]. In these patients surgical treatment was effective in relieving symptoms, although artifical tears and/or steroid-based eye drops may relieve conjunctival inflammation [1]. The incidence of grade 2–3 epiphora in our studies was considerably high at 34%. A retrospective review of patients with epiphora from docetaxel at MD Anderson Cancer Center found that a higher proportion of patients receiving weekly docetaxel required

Table 4 Summary of other phase II studies with weekly docetaxel in advanced breast cancer

Author Ref.	No. of patients	Docetaxel dose/schedule and infusion duration	Steroid pre-medication regimen	% patients prior anthra-cycline	G3/4 neutro-penia (%)	G2/3 epiphora (%)	G2/3 skin and nail (%)	ORR (%)
30 min i.v. infusions								
Ford et al.	42	35 mg/m^2, q 6/8 week	8 mg i.v. pre, 4 mg po bid 2/7	100	5	34%	38%	26
Leoffier [25]	41	40 mg/m^2, q 6/8 week	8 mg i.v. pre only	61	10	2%	34% (G1/2)	48
Mey [29]	20	40 mg/m^2, q 3/4 week	8 mg po bid day -1, 16 mg i.v. pre	90	10	–	25%	25
Maisano [27]	30	35 mg/m^2, q 6/8 week	8 mg i.v. pre only	50	10	13%	7% (G3skin) 17% (G2nail)	33
Ramos [35]	35	36–40 mg/m^2, q 6/8 week	8 mg po bid day −1, 0	100	17	14% G3	6% (G3skin) 29% (G3nail)	34
Taberno [43]	41	40 mg/m^2, q 6/8 week	8 mg po day −1, 0	73.2	7.3	7.3% (treatment withdrawal)	14.6% (treatment withdrawal 9.7%)	34
	42	100 mg/m^2, q 3 week	8 mg bd day -1, 0	66.7	36.6	0%	9.7%	33
Stemmler [42]	54	35 mg/m^2, q 6/8 week	8 mg i.v. pre only	48	3.7	5.6%	7.5%	48
Maisano [28] (elderly)	21	35 mg/m^2, q 6/7 week, then 3/4 week	8 mg i.v. pre only	–	4.8	28.6%		
60 min i.v. infusions								
Hainsworth [19]	41	36 mg/m^2, q 6/8 week	8 mg po bid day -1, 0	17	4	–	0% (G3)	36
Burstein [5]	29	40 mg/m^2, q 6/8 week	8 mg po bid day -1, 0	31	14	7%G2	0% (G2/3skin) 7% (G2nail)	41
Aihara [2]	37	40 mg/m^2, q 3/4 week	8 mg i.v. pre only	46	19	5%G2	3% (G2skin) 14% (G2nail)	38
Kuroi [22]	57	25 mg/m^2, q 3/4 week	8 mg i.v. pre only	61	2	2%G2	2% (G2skin) 14% (G2nail)	30
Nistico [33]	28	35 mg/m^2/week	8 mg 12 h pre, i.v. day 0	53.6	4	0%	7%	36
D'hondt [8] (frail, elderly)	47	36 mg/m^2, q 6/7 week, then 2–3/3–4 week	32 mg po methylprednisolone 12 and 3 h pre	–	22	0%G3	2% (G3nail)	30

surgical treatment (30 out of 71) compared to patients receiving docetaxel every 2–3 weeks (3 out of 77) [12]. It has been suggested that the incidence of epiphora in weekly docetaxel schedules may be related to cumulative doses of docetaxel beyond 300–400 mg/m^2 [22].

To compare our incidence of cutaneous and ophthalmic toxicities with other phase II studies of weekly docetaxel schedules, we reviewed all the published phase II studies. These studies used a variety of docetaxel doses and schedules, infusion times, and corticosteroid pre-medication schedules. Likewise there were differences in the patient populations, particularly in relation to the number of patients that had received previous anthracyclines. Table 4 summaries the weekly docetaxel schedules, prior anthracycline exposure, and key toxicity/efficacy findings from all these studies including our study. Some of these studies also used a 30-min rather than 60-min infusion for weekly docetaxel [25, 27–29, 35, 42, 43], and reported significant rates of both cutaneous toxicity and epiphora. While the incidence may appear higher than that reported in some other studies that used a 60-min infusion [2, 5, 8, 19, 22, 33], differences in reporting scales for various non-haematological toxicities arising from skin, nail and eyes make such comparisons difficult [41]. In the randomised trial of Taberno et al. [43], although the incidence of grade 3/4 skin changes was only 7.3 versus 9.8% (weekly vs. 3-weekly), the overall incidence of nail toxicity (onycholysis) and tearing with the weekly docetaxel schedule was high (56 and 53%, respectively). Indeed in this randomised trial there was a higher incidence of treatment withdrawal due to non-haematological toxicity reported for patients treated with weekly versus 3-weekly schedules (12.2 vs. 2.4% for onycholysis, 7.3 vs. 0% for tearing). A probable explanation is that prolonged cumulative exposure of docetaxel in the skin, nails and tear ducts achieved through weekly schedules may account for the different non-haematological toxicity profile observed. Both peak concentration and total cumulative drug dose have previously been implicated in the causation of hand–foot syndrome [32].

Another possible explanation for the higher rate of non-haematological toxicity observed in our study was the higher proportion of patients who had received prior anthracycline therapy than some of the other published phase II studies [2, 5, 19, 22, 33] (100% compared to 46, 31, 17, 61 and 53.6%, respectively). Although it seems unlikely that the extent of pre-treatment would increase the amount or degree of non-haematological toxicity seen, anthracyclines may also cause palmar–plantar erythrodysaesthesia, and it is possible that these drugs have a sensitising effect leading to increased susceptibility to subsequent docetaxel induced hand–foot syndrome.

Fatigue was another significant problem encountered by patients in our study. Nineteen patients (45%) reported grade 2 or greater fatigue, with 7 patients (17%) and 1 patient (2%) experiencing grade 3 and 4 fatigue, respectively. This can significantly impair the function and quality of life in patients for whom palliation is the goal of treatment. Although the randomised phase 2 study be Taberno et al. [43] found similar rates of grade 3–4 fatigue in the weekly and 3-weekly docetaxel arms (14.6 and 12.2%, respectively), the incidence of fatigue reported with weekly paclitaxel appears lower. No grade 3 or 4 asthenia/malaise was experienced in a study on weekly paclitaxel by Seidman et al. [38], with only 3% grade 2 asthenia or malaise. A larger multicentre study on weekly paclitaxel published by Perez et al. [34] reported 18% grade 2 asthenia and 4% grade 3 asthenia. These data would suggest that weekly paclitaxel is associated with much less fatigue that weekly docetaxel, as confirmed by the recent first report from the large adjuvant study (ECOG1199) where the incidence of grade 3/4 fatigue was 3% with weekly paclitaxel, but 11% with weekly doctexal [40].

Do the benefits of a weekly docetaxel regimen with reduced myelotoxicity outweigh the potential risks of increased fatigue, ophthalmic, skin and nail toxicity? The weekly regimen is also associated with increased healthcare costs and resources as well as patient inconvenience compared to the standard 3-weekly regimen. Superior efficacy and improved survival have not been reported with the weekly regimen as large randomised studies have not been performed in metastatic breast cancer. Quality of life is also an important aspect that needs to be fully evaluated. Apart from breast cancer, docetaxel is increasingly used in the treatment of lung cancer and prostate cancer. Four randomised clinical trials comparing weekly and 3-weekly second-line treatment in lung cancer have been completed. Low response rates were reported in both arms with no significant survival differences [6, 15, 17, 36]. A recent study on 1,006 men with metastatic hormone-refractory prostate cancer found that 3-weekly, but not weekly docetaxel with prednisolone reduced the hazard ratio of death significantly compared with mitoxantrone and prednisolone. The median survival was 18.9 months in the 3-weekly docetaxel arm, 17.4 months in the weekly docetaxel arm and 16.5 months in the mitoxantrone arm [44]. Whether these findings can be extrapolated to the setting of metastatic breast cancer requires a large randomised study comparing weekly with 3-weekly docetaxel in breast cancer. While superior response rates and TTP have been reported for weekly paclitaxel [37], the two compounds are quite different. Paclitaxel is known to be more schedule-dependent with non-linear pharmacokinetics [46], so there may be an advantage with weekly rather than 3-weekly administration.

In conclusion, this study confirms that weekly docetaxel has only moderate activity in anthracycline pretreated patients, with a very low rate of myelosuppression, but at the cost of significant non-haematological toxicities in the form of fatigue, cutaneous and ophthalmic toxicities. Such toxicties make the concept of accelerating docetaxel difficult to achieve, as confirmed by recent studies in the adjuvant setting for both weekly [40] or bi-weekly schedules [14]. As such, 3-weekly docetaxel should remain the standard treatment schedule, especially in metastatic disease where palliation is an important goal.

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