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Review

Docetaxel administration schedule: From fever to tears? A review of randomised studies

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Abstract

The anti-cancer agent docetaxel is approved for the treatment of patients with locally advanced or metastatic breast cancer, non-small cell lung cancer (NSCLC) and for the treatment of androgen-independent prostate cancer. At the recommended dose of 60–100 mg/m^2 given every 3 weeks, severe neutropenia is the dose-limiting toxicity and a major concern especially when treating patients at high-risk from myelotoxic complications. A less toxic schedule, involving weekly docetaxel administration was developed for patients with poor performance status, multiple comorbidities, poor haematological reserves or those who were heavily pre-treated, elderly or patients for whom palliation is the focus of treatment. Recent randomised trials allow a comparison of efficacy and toxicity between weekly and 3-weekly treatments. Efficacy appears to be similar for the two schedules regardless of the disease while weekly docetaxel is significantly less myelotoxic. However, this benefit comes at the cost of cumulative increases in hyperlacrimation, skin- and nail-toxicity and negatively affects quality of life. Currently, 3-weekly docetaxel remains the standard schedule for treatment, whereas the weekly schedule offers a possibility of treatment individualisation for those patients where the risk of myelosuppression is considered unacceptable.

Keywords: Docetaxel; Taxotere; Weekly; Efficacy; Toxicity; Metastatic breast cancer; Non-small cell lung cancer; Hormone refractory prostate cancer

1. Introduction

The anti-cancer drug docetaxel (Taxotere®) is a semi-synthetic taxane with anti-tumour activity against a broad range of human malignancies. It is approved for the treatment of patients with locally advanced or metastatic breast cancer or non-small cell lung cancer (NSCLC) and more recently for the treatment of androgen-independent metastatic prostate cancer. The docetaxel dose recommended for treating cancer patients ranges from 60 to 100 mg/m^2 given as a 1-h infusion once every 3 weeks (hereafter referred to as "3-weekly"). Severe myelosuppression is common and a concern. Neutropenia occurs in virtually all patients regardless of dose and when treated with 100 mg/m^2 docetaxel, a substantial number of patients require a dose reduction to control grade 4 neutropenia lasting 1 week or longer. Management of neutropenic infection requires patient hospitalisation and treatment with intravenous antibiotics. The other major side effect of docetaxel treatment is neuropathy that is related to cumulative dose and which can potentially limit the number of cycles that can be given. In general, non-haematological toxicities are rarely severe and mostly manageable.

In view of the myelosuppression, there are specific patient groups who are not expected to tolerate the full-dose 3-weekly regimen. In general, this applies to patients with a poor performance status, patients with multiple comorbidities, patients with poor haematological reserves whether or not due to heavy pre-treatment

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and elderly patients. Indeed, treatment recommendations for the heterogeneous group of elderly patients are inconsistent or lacking as the elderly are largely under-represented in clinical trials coupled to a general reluctance to administer chemotherapy to this group [1,2]. In addition, prolonging survival without excessive treatment-related toxicity is a major challenge in the management of patients where treatment focus is not curative. For these reasons, soon after the introduction of docetaxel in 1996, clinical trials were started investigating alternative docetaxel schedules with infusions given once every week (hereafter referred to as "weekly"). This was in spite of the fact that during the initial development of docetaxel, studies with day-1 and -8 schedule every three weeks were not pursued due to excessive toxicity [3]. The primary goal of the new set of studies was to reduce severe haematological toxicity whilst preserving dose intensity. Although, some investigators even hoped to increase dose intensity and achieve a higher cumulative dose. In the end, the recommended phase II dose for weekly docetaxel was established at 36 mg/m^2/week based on a schedule of 6 consecutive weekly administrations followed by a 2-week rest interval [4]. This dose is equivalent to a (planned) dose intensity of 27 mg/m^2/week and comparable to the dose intensity (planned) for the recommended 3-weekly doses, 75 and 100 mg/m^2 (25 and 33 mg/m^2/week, respectively) [5]. This landmark phase I trial demonstrated that the toxicity profile of weekly docetaxel was significantly altered and that dose limiting toxicities were fatigue/asthenia while overall myelosuppression was mild and severe haematological toxicity was uncommon. The new side effect profile suggested a potential for better tolerance. Since then, numerous clinical trials have further investigated the activity of weekly administrations of docetaxel both as a single agent and, given its favourable toxicity profile, in combination with other cytotoxic (myelosuppressive) drugs, new biological agents and radiotherapy.

This review aims to discuss the efficacy and toxicity of weekly docetaxel and compare these features to the 3-weekly regimen when used to treat patients with metastatic breast cancer, NSCLC and hormone refractory prostate cancer.

2. Efficacy of docetaxel treatment

2.1. 3-weekly docetaxel – metastatic breast cancer, NSCLC, hormone refractory prostate cancer

Treatment of patients with locally advanced or metastatic breast cancer after failure of prior chemotherapy was the first indication for which docetaxel was granted approval [6,7], followed by approval for the treatment of locally advanced or metastatic NSCLC patients after failure of prior platinum-based chemotherapy [8,9] and treatment of chemotherapy-naïve NSCLC patients in combination with cisplatin [10,11]. In addition, based upon a recent randomised phase III trial it was concluded that first-line treatment with single agent docetaxel could be a reasonable option for patients who do not tolerate cisplatin [12]. After early phase II trials demonstrated activity of single agent docetaxel in the treatment of patients with hormone refractory prostate cancer [13,14], approval was recently also granted for this indication based on a large phase III trial [15]. An overview of the efficacy of 3-weekly docetaxel in the treatment of patients with metastatic breast cancer, NSCLC and hormone refractory prostate cancer is provided in Table 1.

2.2. Weekly docetaxel – metastatic breast cancer

Several phase II clinical trials have assessed the activity of weekly docetaxel in patients with metastatic breast cancer, the majority of which had been pre-treated with chemotherapy. [16–22] (Table 2). Unfortunately only one trial was designed to directly compare safety and activity of weekly and 3-weekly treatment in a randomised phase II setting [21]. Two non-randomised trials specifically targeted the elderly and/or frail population [17,22]. The pivotal trials for the 3-weekly schedule in metastatic breast cancer patients had reported an overall response rate (ORR) of 47.8% and 30% for patients previously treated with alkylating agent-containing or anthracycline-containing chemotherapy, respectively (Table 1) [6,7]. As summarised in Table 2, the activity of weekly schedules seems to be in the same range. Although not powered to detect a difference, the randomised phase II study also suggests similar activity [21]. The limitations of phase II trial designs are expressed in the fact that ORRs and time to progression (TTP) in the indicated studies range from 25% to 41% and 4–9 months, respectively. Apart from differences in prognostic factors, part of the observed variation could be explained by selection bias. In that sense, the randomised phase II study [21] provides the most reliable information.

2.3. Weekly docetaxel – NSCLC

A number of phase II clinical trials have assessed weekly docetaxel in the treatment of patients with advanced NSCLC, both as first-line treatment, in combination with cisplatin and as single agent second-line treatment [23–28] (Table 3). Importantly, several randomised (phase II/III) trials are ongoing and definitive results are awaited [29–32].

Two recent clinical trials evaluated weekly docetaxel in combination with cisplatin [25,26]. The trial performed by Ohe and colleagues [25] specifically targeted elderly patients ($\geqslant$75 years) who however, all had a

Table 1
Efficacy of 3-weekly docetaxel in metastatic breast cancer, non-small cell lung cancer and hormone refractory prostate cancer patients

Reference	Chan [6]	Nabholtz [7]	Shepherd [9]	Fossella [8]	Fossella [10]	Georgoulias [12]	Friedland [13]	Picus [14]
N	161	203	55	125	408	152	21	35
Median age (range)	52 (32–74)[a]	51 (30–73)[b]	61 (37–73)	59	61 (30–81)	63 (41–77)	69 (55–79)	70 (49–85)
ECOG PS								
0–1			41 (74)	103 (82)		137 (90)	20 (95)	
⩾2			14 (26)	23 (18)		15 (10)	1 (5)	
Karnofsky PS (range)	90 (60–100)	90 (60–100)			⩾80[c]			⩾60[d]
Extent of disease								
Visceral metastasis	121 (75)	153 (75)					2 (10)	
Bone metastasis	89 (55)	116 (57)					20 (95)	
Measurable lesions	129 (80)[e]	151 (74)[e]						25 (71)
Stage IIIB	NA	NA	15 (27)	12 (10)	135 (33)	54 (36)		
Stage IV	NA	NA	40 (73)	113 (90)	273 (67)	98 (64)		
Median PSA ng/ml (range)	NA	NA	NA	NA	NA	NA	67 (9–2489)	96 (24–2070)
Prior treatment								
Any chemotherapy	161 (100)[f]	203 (100)	55 (100)	125 (100)	0 (0)	9 (6)[g]	11 (52)	0 (0)
Anthracycline	0 (0)	203 (100)	NA	NA	NA	NA	NA	NA
Platinum based	NA	NA	55 (100)	125 (100)	0 (0)	0 (0)	NA	NA
Dose (mg/m^2)	100	100	75	75	75[h]	100	75	75
ORR (%) (95% CI)	49 (40–56)	30 (24–36)	5.5	6.7	32 (27–36)	21 (15–29)		28
Median OS (months)	15	11.4				8.0		27
1-year survival rate (%)						43	33	
PSA response[i] (%)	NA	NA	NA	NA	NA	NA	38	46

N: number of patients; ECOG PS: Eastern cooperative group performance status; If no value specified then not available; NA: not applicable; ORR: overall response rate; 95% CI: 95% confidence interval; OS: overall survival; PSA: prostate specific antigen. If no value specified then not available. Values between brackets are percentage of total number of patients, unless otherwise specified.

[a] 13% aged >65 years.
[b] 11% aged >65 years.
[c] 96% of patients PS ⩾80.
[d] PS ⩾60 inclusion criterion, majority of N PS 80.
[e] ⩾1 measurable lesion.
[f] Alkylating agent-containing therapy.
[g] Adjuvant therapy, otherwise chemotherapy-naïve.
[h] Followed by cisplatin 75 mg/m^2.
[i] PSA response defined as ⩾50% decline from baseline PSA confirmed by second value.

good performance status (0–1). These two studies yielded activity in the same range as for 3-weekly docetaxel followed by cisplatin 75 mg/m^2 [10] (Table 1). The results of randomised studies are again eagerly awaited. The importance of such phase III evaluations is further stressed by the fact that seemingly achieved activity is less than expected in chemotherapy-naïve elderly patients or (young) patients who were poor candidates for first-line combination therapy [23] (Table 3).

Lilenbaum and colleagues [24] evaluated second-line treatment with single agent docetaxel in a small ($N = 30$) group of patients, where 1 in 3 had a poor performance status (⩾2). Importantly, it should be noted that all patients with a poor performance status progressed underlining, the 2003 treatment guidelines which recommend that second-line treatment with docetaxel should be confined to patients with adequate performance status [11] as well as the possible influence of selection bias on outcome parameters. Most recently, two small randomised clinical trials comparing weekly and 3-weekly second-line treatment have been completed [27,28]. Gridelli and colleagues [27] focussed on quality of life (QoL) issues and found no overall statistically significant differences in the assessed items. Disappointingly, both studies showed low response rates regardless of schedule and even opposite differences in 1-year survival rate (Table 3), again suggesting that larger trials will be needed to completely eradicate selection bias.

2.4. Weekly docetaxel – hormone refractory prostate cancer

Phase II clinical trials had demonstrated that weekly or 3-weekly docetaxel had single agent activity in hormone refractory prostate cancer patients [13,14,33–36] (Tables 1 and 4). For this reason, a large phase III study was performed comparing weekly docetaxel-prednisone to 3-weekly docetaxel-prednisone and to mitoxantrone-prednisone [15]. In assessing the outcome one has to take into account that prostate cancer patients are frequently elderly and frail and that treatment is often

Table 2
Efficacy of weekly docetaxel in patients with metastatic breast cancer

Reference	Burstein [16]	Hainsworth [17]	Stemmler [18]	Aihara [19]	Mey [20]	Tabernero [21]		D'Hondt [22]
N	29	41	35	37	20	41	42	47
Median age (range)	57 (35–75)	74 (50–88)	53 (42–66)	53 (31–74)	57 (28–80)	56 (25–75)	55 (33–72)	63 (43–82)
Age ⩾70 years		27 (66)			1 (5)			11 (23)
ECOG PS								
0–1	28 (97)	32 (78)	Median[a]	36 (97)	16 (80)	39 (95)	40 (95)	17 (36)
⩾2	1 (3)	9 (22)		1 (3)	4 (20)	2 (5)	1 (2)	30 (64)
Visceral metastasis								
Liver	19 (66)		20 (57)	7 (19)	13 (65)	17 (42)	20 (48)	30 (64)
Lung	14 (48)		23 (66)	11 (30)	5 (25)	13 (32)	17 (41)	19 (40)
Overall		30 (73)			16 (80)			34 (72)
Prior treatment								
Any chemotherapy	19 (66)	20 (49)	35 (100)	34 (92)	20 (100)	40 (98)	41 (98)	37 (79)
Anthracycline	9 (31)	7 (17)	32 (91)	17 (46)	18 (90)	30 (73)	28 (67)	35 (74)
No chemotherapy	10 (35)	21 (51)	0 (0)	3 (8)	0 (0)	1 (2)	1 (2)	10 (21)
Dose (mg/m^2); schedule[b]	40; 6/2	36; 6/2	35; 6/2[c]	40; 3/1	40; 6/2	40; 6/2	100; 3-weekly	36; 6/1[d]
Dose intensity (mg/m^2/wk)	30	27	26	30	30	30	33.3	31
Relative median dose Intensity (range)	1.0			0.95 (0.73–1.0)		0.95 (0.54–1.07)	0.96 (0.68–1.00)	0.78
Median cumulative dose (mg/m^2) (range)	720 (80–1440)			560 (120–1080)	380	620 (80–2400)	614 (100–1200)	278
ORR (%) (95%CI)	41 (24–61)	36	34 (18–51)	38 (22–53)	25	34 (21–51)	33 (20–50)	30
Median TTP (range or 95%CI)		5 (3–21)	2.6 (1.5–⩾ 5.5)	5	8.8	5.7 (*4–7.5*)	5.3 (*4.3–6.2*)	3.5 (0–25)
1-year survival rate (%)		61			40			29
Median OS, months (95%CI)				12		29 (24–34)	20 (15–25)	7

TTP: time to progression; If no value specified then not available; Values between brackets are percentage of total number of patients unless otherwise specified.
[a] Range 0–2.
[b] Number of consecutive weekly treatments/number of rest weeks.
[c] First cycle only, following cycles 3/2.
[d] First cycle only, following cycles 2–3/1.

Table 3
Efficacy of weekly docetaxel in patients with locally advanced or metastatic non-small cell lung cancer

Reference	Hainsworth [23]	Lilenbaum [24]	Ohe [25]	Tsunoda [26]	Gridelli [27]	Gervais [28]		
N	39	30	33	38	110	110	62	63
Median age (range)	71 (55–82)	68 (47–84)	77 (75–86)	62 (34–73)	62 (26–74)	63 (28–75)	59 (37–72)	58 (26–74)
Age ⩾65 years	20 (51)[a]							
Age ⩾75 years			33 (100)[b]					
ECOG PS								
0–1	23 (59)	21 (70)	33 (100)	37 (97)	93 (85)	92 (84)	49 (79)	50 (79)
⩾2	16 (41)	9 (30)	0 (0)	1 (3)	17 (15)	18 (16)	13 (21)	13 (21)
Stage								
IIIB	12 (31)		12 (36)	16 (42)	21 (19)	10 (9)	21 (34)	21 (33)
IV	27 (69)		17 (52)	22 (58)	89 (81)	100 (91)	41 (66)	42 (67)
Prior treatment								
Radiotherapy	4 (10)		4 (12)	0 (0)				
Chemotherapy	0 (0)[c]	30 (100)	0 (0)	0 (0)	110 (100)	110 (100)	62 (100)	63 (100)
-platinum-based	–	13 (43)	–	–	94 (85)	92 (84)	62 (100)	63 (100)
-non-platinum based	–	12 (40)	–	–	16 (15)	18 (16)		
None	35 (90)	0 (100)	24 (73)	38 (100)	0 (0)	0 (0)	0 (0)	0 (0)
Dose (mg/m^2); schedule	36; 6/2	36; 6/2	20[c]; 3/1	25[d]; 3/1	75; 3-weekly	33.3; 6/2	75; 3-weekly	40; 6/2
Dose intensity (mg/m^2/wk)	27	27	15	18.8	25	25	25	30
ORR (%) (95% CI)	18	10 (1.6–29)	52 (31–67)	31.6 (17–46.4)	2.7	5.5[e]	4.8	3.2
Median OS, months (95%CI)	5	8.0 (5.6–13.9)	15.8	11.8 (9.4–15)	7.3 (5.3–9)	6.3 (4.5–8.5)	5.8	5.5
1-year survival rate (%) (95% CI)	27	31 (17–58)	64	46.5 (30–63.8)	21	31	18	6

If no value specified then not available.
Values between brackets are percentage of total number of patients, unless otherwise specified.
[a] Aged >70 years.
[b] Inclusion criterion age ⩾75 years.
[c] Combined with cisplatin 25 mg/m^2 on days 1, 8 and 15.
[d] Combined with cisplatin 80 mg/m^2 on day 1.
[e] $P = .50$.

Table 4
Efficacy of weekly docetaxel in patients with hormone refractory prostate cancer

Reference	Beer [33]	Berry [34]	Beer [37]		Gravis [35]	Ferrero [36]	Tannock [15]	
N	25	60	34	52	30	64	335	334
Median age (range)	72 (55–81)	72 (41–86)	< 70	⩾70	67 (52–83)	73 (49–88)	68 (42–92)	69 (36–92)
Age ⩾65 years		48 (80)				48 (75)		
Age ⩾75 years							67 (20)	70 (21)
ECOG PS								
0–1	13 (52)	50 (83)	25 (74)	38 (73)		57 (89)		
⩾2	12 (48)	10 (17)	9 (26)	14 (27)		7 (11)		
Karnofsky PS (range)					80 (70–90)		⩾60[a]	⩾60[a]
Median PSA ng/ml (range)	201 (1–1432)	92 (0–2737)	83 (1–1502)	159 (0–2737)	73 (1–895)	82 (2–857)	114	108
Extent of disease								
Bone metastasis	24 (96)	57 (95)	31 (91)	50 (96)	19 (63)	58 (91)	302 (90)	304 (91)
Visceral metastasis	1 (4)	9 (15)	4 (12)	3 (6)	5 (17)	12 (19)	74 (22)	80 (24)
Measurable lesions	5 (20)	6 (10)	16[b]	9 (30)	6 (9)	134 (40)	130 (39)	
Prior treatment								
Radiotherapy	14 (56)	42 (70)	30 (88)	31 (60)	20 (67)	8 (13)	174 (52)	147 (44)
Chemotherapy	0 (0)	16 (27)	8 (24)	9 (17)	15 (50)	16 (25)	64 (19)[c]	60 (18)[c]
Dose (mg/m^2); schedule	36; 6/2	36; 6/2	36; 6/2	36; 6/2	35; 6/2	40; 6/2	75; 3-weekly	30; 5/1
Dose intensity (mg/m^2/wk)	27	27	27	27	26.3	30	25	25
PSA response (%) (95% CI)	46 (25–67)	41	40 (23–57)[d]	47 (33–61)	48	64 (51–76)	45 (40–51)	48 (42–54)
ORR % (95% CI)	40	33	33 (0–66)[d]	29 (0–65)	0	17	12 (7–19)	8 (4–14)
Median overall survival, months (range or 95% CI)	9.8 (4.5–>22.3)	9.4 (1.6–18.2)	11.3[d] (*9–13.5*)	8.3 (*3.3–13.5*)	20 (4–41)	16.2	18.9 (*17.0–21.2*)	17.4 (*15.7–19.0*)
1-year survival rate (%)		38				58.4		

If no value is specified then this was not available.
Values between brackets are percentage of total number of patients unless otherwise specified.
[a] PS ⩾60 inclusion criterion, ⩽13% of patients PS ⩽70%.
[b] number of measurable lesions in both age groups.
[c] Only estramustine allowed.
[d] No statistically significant differences between age groups.

intended to be palliative. In the randomised phase III study there was no significant difference between weekly and 3-weekly efficacy and the percentage of patients who had an improvement in QoL was also similar in both docetaxel groups. Although based on phase II studies [34,36], age does not seem to affect treatment outcome (Table 4). In addition, a retrospective analysis of the pooled individual patient data from two trials [33,34] also showed no difference between older and younger patients with respect to efficacy endpoints [37]. Most importantly in this respect, survival benefit in the randomised phase III study was similar for patients younger than 65 years *vs.* those 65 years or older [15].

3. Docetaxel toxicity

The toxicity profile of docetaxel when given once every 3 weeks is well known. The dose is limited by dose-dependent, mostly short lasting neutropenia, relatively frequently complicated by fever. Other side effects include nausea, vomiting, stomatitis and diarrhoea. Docetaxel induces a peculiar type of skin and nail toxicity, peripheral oedema as well as frequent hypersensitivity reactions. All of these latter side effects can be largely circumvented or diminished by adding a short prophylactic corticosteroid schedule [6–10,12–15]. Finally the drug induces neuropathy related to cumulative dose rather than the cycle dose.

The toxicity profile of weekly docetaxel is significantly altered compared to 3-weekly treatment. Overall, acute toxicities are uncommon. However, chronic toxicities that develop and increase with successive weekly dosing (*i.e.*, related to cumulative dose) are more prominent. Although the randomised trials comparing weekly and 3-weekly docetaxel treatment were performed in three different patient categories, taken together they provide a relevant overview of the toxicities related to both schedules (Table 5).

Haematological toxicity: As expected, weekly docetaxel is associated with mild haematological toxicity; severe neutropenia ranged from 2% to 16% for weekly docetaxel and febrile neutropenia was either absent or low (⩽5%) (Table 5). Only one non-randomised trial reported a higher incidence (22%) of severe neutropenia which was attributed to baseline abnormalities in haematology parameters [22]. In the randomised trials, incidences of grade 3–4 neutropenia for 3-weekly treatment ranged from 19% to 48%, which is relatively low compared to previously reported values even though

Table 5
Toxicity (%) in randomised trials comparing weekly and 3-weekly docetaxel

Reference – Cancer	Tabernero [21] – Breast		Gridelli [27] – Lung		Gervais [28] – Lung		Tannock [15] – Prostate	
N	42	41	110	110	62	63	335	334
Median age (range)	55 (33–72)	56 (25–75)	62 (26–74)	63 (28–75)	59 (37–72)	58 (26–74)	68 (42–92)	69 (36–92)
ECOG PS								
0–1	40 (95)	39 (95)	93 (85)	92 (84)	49 (79)	50 (79)	Karnfosky PS	⩾60
⩾2	1 (2)	2 (5)	17 (15)	18 (16)	13 (21)	13 (21)		
Dose (mg/m^2); schedule	100; 3-weekly	40; weekly	75; 3-weekly	33.3; weekly	75; 3-weekly	40; weekly	75; 3-weekly	30; weekly
Haematological gr 3–4								
Neutropenia	37	7	19	2	48	16	32	2
Anaemia	⩽5	⩽5	3	0	10	13	5	5
Thrombocytopenia	⩽5	⩽5	1	1			1	0
Febrile neutropenia	20	5	5	0	7	0	3	0
Non-haematological gr 3–4								
Fatigue/asthenia	12	15	7	6	5	11	5	5
Nausea and vomiting	15	12	0	0	3	5		
Diarrhoea	7	2	3	3	2	3		
Stomatitis	17	7	1	0				
Skin	10	7	1	0				
Fluid retention	7	2						
Infection	2	7	0	4				
Neuro-motor/-sensor	17	2	1	4				
Non-haematological gr 1–2								
Fatigue/asthenia	81	68	49	49			48	44
Nausea and vomiting			27	35			42	41
Diarrhoea			18	23			32	34
Fluid retention	33	33					19	12
Neuro-motor/-sensor			23	21			30	24
Alopecia, grade 2	87	78	20	7			65	50
Hyperlacrimation	39	53					10	21
Nail changes	56	56					30	37
Dose reductions	42	15			1	1	12	9
Treatment stopped[a]	37	46	21	11	5	13	11	16

If no value is specified then this was not available.
[a] For reasons of toxicity.

all patients had received some form of prior chemotherapy. Severe anaemia and thrombocytopenia are uncommon regardless of schedule. In two non-randomised trials, higher incidences of severe anaemia (13–17%) were also reported, possibly explained by the fact that more than one third of all patients had a poor baseline performance status [23,24].

Non-haematological toxicity: Severe fatigue and asthenia were the most common complaints after weekly treatment. These side effects usually occured at the end of the consecutive treatment weeks (6 weeks) and were partly reversible during the 2-week rest interval. In general, incidences ranged between 5% and 20%, which is actually not higher than observed after 3-weekly treatment. Higher incidences (33%) were only incidentally observed (in patients with a poor performance status) [24]. Indeed, studies from Gridelli and Tannock [15,27] observed no difference in the incidence of fatigue/asthenia between the two schedules. In contrast, Tabernero and Gervais [21,28] have both reported that fatigue/asthenia were more common with the weekly regimen. Recommendations for management of severe fatigue include a dose reduction or shorter schedule for instance, 2 or 3 consecutive weekly infusions followed by a 1-week rest interval. However, it is advisable to exercise caution as is it unknown how these schedule changes will affect activity.

Weekly docetaxel is associated with an unexpected increase in the incidence of excessive tearing (incidences up to 52% have been reported) [16]. Hyperlacrimation, due to canalicular/nasolacrimal duct stenosis and possibly a result of docetaxel secretion in tears [38] was initially classified as an unexpected and merely bothersome side effect. However, currently it is recognised to be a complaint which, although mild (rarely classified ⩾ grade 3), can be particularly persistent, leading to significant problems with reading, driving, and other daily activities requiring adequate visual function. Indeed, this recently underestimated side effect has a substantial negative impact on a patient's quality of life. Esmaeli and colleagues [39] specifically reported on the severity and management of excessive tearing in patients who received weekly ($N = 71$) or 3-weekly docetaxel ($N = 72$). After a median cumulative dose of 1080 mg (range 168–2116), corresponding to a median of 24 weeks (range 11–48) after initiation of weekly treatment,

a surgical intervention (temporary silicone intubation, dacryocystorhinostomy (DCR) with placement of a temporary silicone tube or a permanent Pyrex tube) was required in more than 40% of patients' eyes, and successfully relieved symptoms. Indeed, in 21 patients with complaints in both eyes who received no surgical treatment, either due to patient refusal or because of other co-morbidity, complaints were still persistent 6 months after docetaxel discontinuation. Only 28% of the patients had mild complaints and they were treated with topical steroids. In contrast, in the majority of patients given 3-weekly docetaxel, complaints were adequately managed with topical treatment and only 3 patients required surgical intervention. Recommendations for the management of this common side effect include a baseline ophthalmologic examination followed by regular monitoring so that early diagnosis is possible and appropriate treatment can be initiated [39,40]. Silicone intubation has been recommended as the safest approach in symptomatic patients if weekly treatment is to be continued [39].

In addition, cumulative nail toxicity can lead to severe discomfort, limitation of function and treatment discontinuation after repetitive dosing [18,22]. Although the incidence of low grade nail toxicity was not different for weekly or 3-weekly docetaxel in metastatic breast cancer patients, nail changes substantially affected the QoL in the weekly treatment arm and were the major reason for withdrawal followed by excessive tearing, asthenia and infection [21]. Similarly, in the protstate cancer phase III trial [15], major reasons for treatment withdrawal also included fatigue and nail changes. It should be noted that, in acknowledgment of the severe impact on patients' QoL, the recent version of the Common Toxicity Criteria of the National Cancer Institute, (CTC-NCI-version 3.0) includes grade 3 nail changes (interfering with daily life, severe adverse event) whereas version 2.0 only included rating up to grade 2 (partial/complete loss of nail(s), pain in nail beds). Most trials published to date, and certainly most of the larger randomised trials where accrual started several years ago, have used version 2.0 CTC-NCI for toxicity rating. It is likely that the reported severity of nail disorders is underestimated due to lack of more specific rating.

In general, in the randomised trials, dose reductions were less often required after weekly treatment. Yet in 3 out of 4 randomised trials, treatment discontinuations were more common after weekly treatment (Table 5). It is conceivable that persistent cumulative toxicities eventually lead to treatment discontinuation.

3.1. Prophylaxis schedules

Prophylaxis of cumulative fluid retention and hypersensitivity reactions is recommended when patients are treated with docetaxel. The most commonly used premedication schedule for 3-weekly treatment is dexamethasone 8 mg administered twice daily orally for 3 days, starting 1 day prior to treatment (40–48 mg/3 weeks; dose intensity 13–16 mg/week). Although steroid pre-medication remains mandatory [41], at this point, there is no universally recommended prophylactic regimen for weekly docetaxel. In most cases, an abbreviated course of 3 oral administrations of dexamethasone 8 mg given every 12 h starting 12 h prior to docetaxel infusion is chosen (24 mg/week; dose intensity 18 mg/week). This schedule adequately controls fluid retention and hypersensitivity reactions. It has been advised to monitor patients more closely for signs of toxicity after repetitive corticosteroid dosing. However, the incidence of corticosteroid-related complications (*e.g.*, hyperglycaemia, peptic/duodenal ulcers) is low [34]. Indeed, dexamethasone dose intensity with weekly docetaxel is only marginally higher. Incidentally used schedules include (methyl)-prednisone containing regimens or a single dose of 8 mg dexamethasone 1 h prior to infusion [15,18,19,22,28,36].

4. Conclusion

Since the landmark phase I trial [4], numerous clinical trials have evaluated weekly docetaxel treatment. However, due to considerably different patient populations enrolled in the various trials and the limited numbers, comparisons of weekly *vs.* 3-weekly efficacy have been difficult. Hence, recommendations when or when not to consider weekly treatment were lacking. Recently, final results of the first comparative trials have become available. These randomised trials demonstrate, for the three approved indications, that the efficacy of weekly docetaxel is comparable to 3-weekly treatment, with the addition that activity in NSCLC is disappointingly low for both schedules. The toxicity profile of weekly docetaxel does however distinguish this schedule from the standard 3-weekly regimen. Acute toxicities, in particular myelosuppression, are as expected mild and never dose-limiting. However, cumulative side effects were much more prominent and require increased awareness and early recognition for adequate management. The most common and dose-limiting toxicity was fatigue/asthenia. Other chronic toxicities included alopecia, excessive tearing and nail disorders. Despite the fact that the latter two side effects are usually of low grade they were persistent and had a substantial negative impact on a patient's QoL, which has previously been largely underestimated. As of yet, there has not been any health economics assessment of the differences between the two schedules.

Given the similar efficacy observed for the two schedules and the above remarks on toxicity, it is reasonable

to conclude that, at this point, 3-weekly docetaxel should still be considered the standard and most convenient schedule, and that treatment with weekly docetaxel should only be considered as an alternative for specific patient populations who are unlikely to tolerate the standard 3-weekly treatment. For patients with a poor performance status, multiple comorbidities, a history of extensive pre-treatment and severe toxicity, decreased haematological reserves and elderly patients at high risk for myelotoxic complications, weekly docetaxel offers an additional treatment option. The place of elderly patients in this list deserves a more detailed discussion. Elderly patients form a heterogeneous group and therefore the interpretation of clinical trials results and subsequent implementation of treatment recommendations is especially difficult. Chronologic age itself is not a contra-indication for full-dose chemotherapy. However aging, a highly individual process, is frequently associated with a high prevalence of comorbidity, poor performance status and with a decline in functional reserves of organ systems, especially bone marrow. A patient's physiologic age, determined through a comprehensive geriatric assessment has therefore been suggested to better predict the increased risk of chemotherapy induced (haematological) toxicity. In general, largely due to poor haematological reserves, elderly patients are considered to be more susceptible to drug-induced myelosuppression yet, if otherwise fit, not at an increased risk for other toxicities [42–45]. In our opinion, a decision to administer weekly or 3-weekly docetaxel to an elderly person should take into account all these aspects and result in a treatment tailored to the individual's tolerance. As increased exposure to docetaxel is a strong predictor of haematological toxicity regardless of schedule [46,47], altered pharmacokinetics have also been suggested to play a role. However, there are no differences in docetaxel pharmacokinetics between elderly and non-elderly patients [45,48] or for that matter, between the 3-weekly and weekly schedule [49]. Interestingly in these trials, the majority of baseline patient characteristics did not differ between the age groups, however elderly patients had statistically significant, albeit only slightly lower serum α_1-acid glycoprotein (AAG) levels ($P = 0.018$ and $P = 0.04$). Docetaxel is extensively bound to AAG and this protein is one of the main determinants of the fraction of unbound, pharmacologically active drug. Docetaxel-induced haematological toxicity is significantly better correlated with systemic exposure to unbound drug than with exposure to total drug [50]. Although unbound docetaxel pharmacokinetics have not been extensively investigated in elderly patients, it is possible that besides the increased susceptibility for myelosuppression due to a functional decline in haematological reserves, decreased AAG levels result in a higher exposure to the unbound fraction of docetaxel and contribute to increased myelosuppression.

Several aspects of weekly docetaxel administration still remain to be further elucidated. The optimal duration of subsequent administrations, the timing of rest episodes and the optimal number of courses have not yet been established. Furthermore, it is unknown how frail patients selected for weekly treatment perceive more frequent visits to the hospital and the burden of travelling. The negative impact on QoL as reported is a particular concern in this respect. Finally, as indicated, there is as yet no comparative cost-effectiveness analysis including direct and indirect costs. For 3-weekly treatment, the indirect costs associated with the management of adverse effects can significantly increase (up to 20%) the total cost of docetaxel treatment [51].

For the time being, 3-weekly docetaxel remains the first schedule to be considered. However, there is no single schedule for any drug that offers an optimal balance between efficacy and toxicity in all patients. Instead dose, schedule and overall toxicity should be considered against an individual's characteristics including performance status, comorbidity, haematological reserves and prior treatment. As an individualised treatment, the weekly schedule of docetaxel appears to be an acceptable alternative.

Conflict of interest statement

None declared.

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