

Weekly docetaxel in the treatment of metastatic breast cancer

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Abstract: Breast cancer is the most frequent tumor among women worldwide and is the second cause of cancer-related mortality in the US. Metastatic breast cancer (MBC) accounts for less than 10% of newly diagnosed breast cancer patients and about 30% of early breast cancer patients will develop recurrent, advanced, or metastatic disease. It remains an incurable illness and the primary goal of its management is palliative. Several agents are active for the first-line treatment of MBC. The taxanes, paclitaxel and docetaxel, represent the standard of care for the treatment of these patients. Among the various schedules, docetaxel can be administered weekly, achieving similar efficacy results with lower toxicity compared with conventional schedules. Weekly docetaxel (25–40 mg/m²) has been widely tested in several phase I and II studies both as a single agent and in multichemotherapy regimens, reaching overall response rates ranging from 26% and 86% or 20% and 73% with docetaxel alone or in combination, respectively, depending on doses, associations, and line of treatment. Overall, published data support the administration of weekly docetaxel for the treatment of MBC patients even if data from phase III randomized trials are still lacking.

Keywords: docetaxel, weekly, metastatic breast cancer, chemotherapy

Introduction

Breast cancer is the most frequent tumor among women worldwide and represents the second cause of cancer-related mortality in the US (SEER 2008).

Metastatic breast cancer (MBC) is uncommon as initial presentation, accounting for less than 10% of newly diagnosed breast cancer patients (SEER 2008). Despite optimization of treatment for early breast cancer, about 30% of women will develop recurrent, advanced, or metastatic disease. By 2003, 5-year relative survival exceeded 90% and 80% respectively for localized and regional breast cancer, while it did not reach 30% for MBC (Brenner et al 2007; Hayat et al 2007). The majority of breast cancer-related deaths are a result of complications from recurrent or metastatic disease.

MBC remains an incurable illness. The primary goal of its management is palliative and aims to improve quality of life, prolong disease-free survival (DFS) and possibly overall survival (OS). The main treatment modalities include endocrine therapy, cytotoxic chemotherapy and biological agents. The best option should be established considering multiple prognostic and predictive factors such as hormonal receptor status, HER-2 overexpression, growth rate, presence of visceral metastases, history of prior therapy and response.

Chemotherapy clearly provides tumor shrinkage and substantial clinical benefit in advanced breast cancer (Stockler et al 2000), so that it is accepted as standard treatment for hormone-resistant and rapidly progressive disease. On the other hand, no randomized trials comparing chemotherapy with supportive care only are available and such kinds of studies are unlikely to be considered ethical in the future.

Several agents are active for the first-line treatment of MBC, anthracyclines and taxanes being the most effective (Table 1).

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Table 1 Most active drugs in first-line treatment of metastatic breast cancer and range of activity

	Objective response rate (%)
Adriamycin ¹	40–50
Epirubicin ¹	52–68
Paclitaxel ²	29–63
Docetaxel ³	47–65
Vinorelbine ⁴	18–52
Gemcitabine ⁴	25–46
Capecitabine ^{5–7}	20–30
Carboplatin ⁸	20–35

¹Findlay et al 1998; ²Paridaens et al 2000; ³Chan et al 1999; ⁴Hortobagyi 1998; ⁵Blum et al 1999; ⁶Blum et al 2001; ⁷Fumoleau et al 2004; ⁸Perez 2004.

Abbreviation: ORR, complete + partial response.

Anthracyclines provide an overall response rate (ORR) ranging from 35% to 50% as first-line single agents (Findlay et al 1998). Nowadays they are extensively used in the adjuvant setting so that many patients with recurrent disease may have already had a significant anthracycline exposure. Therefore taxane-based regimens are frequently considered for this subset of MBC patients.

Platinum compounds, alkylating agents, antimetabolites, and vinca-alkaloids might be also considered alone or in combination for the first-line treatment of MBC patients based on their single-agent activity (ORRs ranging from 18% to 52%) (Colozza et al 2007).

Several novel biological agents have recently started to be tested in such a setting of treatment: to date, only trastuzumab and bevacizumab, monoclonal antibodies against Her2/neu receptor and the vascular endothelial growth factor, respectively, have obtained regulatory agency approval, both in the US and in Europe. Trastuzumab is the standard therapy for HER-2 overexpressing tumors, both for early and advanced breast cancer patients, with response rates ranging from 50% to 70% with combination treatment (Slamon et al 2001; Burstein et al 2003; Marty et al 2005) and from 20% to 30% with monotherapy in the metastatic setting (Piccart-Gebhart et al 2005; Romond et al 2005). Bevacizumab has recently been approved for the first-line treatment of MBC patients, since its addition to paclitaxel led to a significant prolongation of progression-free survival (median, 11.8 versus 5.9 months; hazard ratio [HR] for progression, 0.60; $p < 0.001$) and an increase in the objective response rate (36.9% versus 21.2%, $p < 0.001$) when the association was compared with single-agent paclitaxel (Miller et al 2007).

The results of the AVADO trial, comparing the efficacy of the association of bevacizumab (7.5 or 15 mg/kg) and

docetaxel (100 mg/m²) with the standard 3-week docetaxel (100 mg/m²) as first-line treatment for MBC, were presented at the ASCO 2008 Annual Meeting (Miles et al 2008). Significant improvements in both progression-free survival (HR 0.79, CI 0.63–0.98, $p = 0.0318$ for bevacizumab at 7.5 mg/kg; HR 0.72, CI 0.57–0.90, $p = 0.0099$ for bevacizumab 15 mg/kg) and ORR (44.4% versus 55.2%, docetaxel alone versus the arm with bevacizumab 7.5 mg/kg, $p = 0.0295$; 44.4% versus 63.1%, docetaxel alone versus the arm with bevacizumab 15 mg/kg, $p = 0.0001$) have been found for the bevacizumab-containing arms compared with the docetaxel-alone arm.

The taxanes

The taxanes, paclitaxel and docetaxel, represent a milestone in the treatment of MBC. Although their synthesis began in the late 1970s, the clinical development for advanced breast cancer treatment burgeoned in the 1990s, when the first phase II trials documented their antitumor activity as single agents (Holmes et al 1991; Ringel et al 1991; D'Andrea et al 1997; Valero et al 1995).

Since then, data from prospective randomized phase III studies confirmed their activity and proved their efficacy, with single-agent paclitaxel and docetaxel providing similar OS rates compared with the previous gold standard anthracycline, doxorubicin (Chan et al 1999; Paridaens et al 2000; Sledge et al 2003). Moreover they demonstrated a significant activity in anthracycline-resistant patients and an acceptable toxicity profile (Ravdin et al 1995; Seidman et al 1995a, b; Nabholz et al 1996, 1997).

In 2005, Gherzi et al published a comprehensive meta-analysis of all published and unpublished trials comparing regimens containing taxanes with those containing non-taxanes in the first-line and further lines of treatment in MBC, and found that taxanes combinations improved OS, time to progression (TTP), and ORR (Gherzi et al 2005). They also conducted a post-hoc sub-group analysis in order to investigate the treatment effect within the type of taxane. Data from the analysis of trials using paclitaxel showed no difference between the two arms for OS (HR 0.97; 95% CI = 0.87–1.07, $p = 0.54$), but when the taxane used was docetaxel there was a statistically significant difference in OS in favor of taxane-containing regimens (HR 0.88; 95% CI = 0.78–0.98, $p = 0.02$).

In previously untreated patients, single-agent docetaxel provides ORR of 40% to 68% (Cortes et al 1995; Valero 1997) while in anthracycline-resistant patients ORR is 53%–57% (Ravdin et al 1995; Valero et al 1995).

The first schedules of administration of docetaxel employed doses ranging from 75 to 100 mg/m² as a 1-hour intravenous infusion every three weeks. The 3-week schedule of docetaxel 100 mg/m², although extremely active, showed an important myelosuppression with more than 90% of cases experiencing grade (G) 3–4 neutropenia (Ravdin et al 1995; Valero et al 1995), with frequent non hematologic side effects including fatigue, alopecia, skin reactions, nails toxicity, fluid retention syndrome.

In pre-treated, elderly or poor performance status patients the 3-week dose of 100 mg/m² must be frequently reduced to 75 mg/m² (O'Brien et al 1999; Salminen et al 1999).

Furthermore, such a toxicity profile made it difficult to combine docetaxel with other active chemotherapeutic agents, limited its use in unfit patients and affected dose-intensity.

In order to go beyond these difficulties new treatment regimens of docetaxel have been proposed and the weekly administration has been widely experimented during the last years.

In fact, the weekly schedule provides a remarkable reduction of toxicities, especially hematologic, while maintaining the high activity of docetaxel. An additional advantage for the weekly schedule might be an equivalent dose intensity of treatment compared with the three-week administration of

docetaxel at the dose of 100 mg/m², so allowing a prolonged exposure to the drug of the different tumor cell clones, preventing the emergence of resistant clones.

Docetaxel is also a potent and potentially specific inhibitor of endothelial cell migration in vitro and angiogenesis in vitro and in vivo. The antiangiogenic activity of docetaxel in vivo was assessed by Hotchkiss et al In this assay, the angiogenic response to fibroblast growth factor 2 was inhibited in vivo by docetaxel with an ID50 of 5.4 mg/kg when injected twice weekly over a 14-day period and angiogenesis was completely blocked in mice that received 10 mg/kg docetaxel (Hotchkiss et al 2002).

Our review focus on the role of the weekly schedule of administration of docetaxel as single agent therapy and as a part of combination regimens for the treatment of MBC patients.

Weekly single-agent docetaxel: phase I studies

Many phase I trials of weekly docetaxel, either as single agent or in combination, have been carried out and published (Table 2).

Table 2 Selected phase I trials on weekly docetaxel

Author and year of publication	N. of pts (BC pts)	Regimen	MTD – DLT
Weekly single-agent docetaxel			
Tomiak et al 1994	31 (6)	Doc 20–55 mg/m ² d 1, 8 q 21	55 mg/m ² – neutropenia
Hainsworth et al 1996	38 (7)	Doc 20–52 mg/m ² qw × 6w (2 w rest)	43 mg/m ² – fatigue –asthenia
Luck et al 1997	18 (all)	Doc 30–50 mg/m ² qw	MTD not reached – no DLT
Loffler et al 1998	31 (all)	Doc 30–45 mg/m ² qw × 6w (2 w rest)	40–45 mg/m ² – leukopenia
Briasoulis et al 1999	26 (1)	Doc 25–50 mg/m ² qw	50 mg/m ² – leukopenia
Kouroussis et al 2000	26 (19)	Doc 30–45 mg/m ² qw × 3w (1 w rest)	42 mg/m ² – neutropenia
Nisticò et al 2005	28 (all)	Doc 30–40 mg/m ² qw × 24 w	35 mg/m ² – asthenia
Weekly docetaxel in combination with chemotherapeutic agents			
Frasci et al 2000	34 (all)	Doc 30–45 mg/m ² d 1, 8 q 3w with Gem 1000 mg/m ² d 1, 8 q 3w or VNR 25 mg/m ² d 1, 8 q 3w	50 mg/m ² – neutropenia
Ito et al 2001	25	Doc 25–30 mg/m ² qw × 6w with Dox 15–20 mg/m ² qw × 6w	30 mg/m ² – neutropenia
Wenzel et al 2002	13 (all)	Doc 25–40 mg/m ² qw × 6w (1w rest) with Epidox 25–35 mg/m ² qw × 6w (1w rest)	40 mg/m ² – neutropenia
Brugnatelli 2002	18 (all)	Doc 30–40 mg/m ² qw × 3w (1w rest) with Gem 800 mg/m ² qw × 3w (1w rest)	40 mg/m ² – asthenia – stomatitis – leukopenia
Ibrahim et al 2007	11 (all)	Doc 20–25 mg/m ² qw × 3w (1w rest) with Dox 30–40 mg/m ² + Cyc 500 mg/m ² qw × 3w (1w rest)	20 mg/m ² – febrile neutropenia

Abbreviations: Pts, patients; BC, breast cancer; MTD, maximum tolerated dose; DLT, dose limiting toxicity; w, week; Doc, docetaxel; Gem, gemcitabine; VNR, vinorelbine; Epidox, epidoxorubicin; Dox, doxorubicin; Cyc, cyclophosphamide.

In 1994, Tomiak et al evaluated first the weekly administration of docetaxel in 32 patients with advanced refractory cancer, at doses ranging from 20 to 110 mg/m² on days 1 and 8 of a 21-day cycle (Tomiak et al 1994).

The first phase I study, investigating a 6-week consecutive administration of docetaxel with a 2-week rest period, was initiated in 1996 by Hainsworth et al to define the optimum dose of weekly docetaxel. Thirty-eight patients (7 with refractory breast cancer), included in sequential cohorts, received escalating doses of docetaxel (20–52 mg/m²/week) until dose-limiting toxicity (DLT) occurred. They reported fatigue and asthenia as the DLTs for this regimen. No patient showed G4 leucopenia at any dose level. In this study the maximum tolerated dose (MTD) was 43 mg/m²/week (corresponding to a dose-intensity of 126 mg/m² every 3 weeks) (Hainsworth et al 1998).

In 1997, Luck et al performed a phase I trial on 18 pretreated advanced breast cancer patients. Dose levels between 30 and 50 mg/m² were used weekly: no DLT occurred and the MTD was not reached (Luck et al 1997).

Loeffler et al conducted a phase I/II trial on 31 patients with advanced breast cancer. Weekly docetaxel (30–45 mg/m²/week) was administered for 6 consecutive weeks followed by a 2-week rest period. An ORR of 50% was reported. The recommended dose for phase II trials was 40 mg/m²/week (Loeffler et al 1998).

In another subsequent phase I study, Briasoulis et al treated 36 cancer patients with weekly docetaxel at doses ranging from 25 to 50 mg/m²/week. They found myelosuppression and diarrhea being the DLTs and suggested the dose of 40 mg/m²/week for further investigations (Briasoulis et al 1999).

In the study conducted by Kourossis et al in 26 advanced solid tumors patients (19 with MBC), the authors reported an ORR of 39% and recommended a dose of 40 mg/m²/week (Kourossis et al 2000).

Nistico et al conducted a phase I/II trial on 28 patients with pretreated MBC. Weekly docetaxel was administered weekly at a dose range of 30–40 mg/m²/week for 24 consecutive weeks (Nistico et al 2005). The suggested dose for phase II trials was 35 mg/m²/week. Two out of 28 evaluable patients (7.1%) showed complete response (CR), 8 partial response (PR) (28.6%), and 8 stable disease (SD) (28.6%). Median TTP and OS were 5 and 15 months, respectively. Only one G3 neutropenia occurred, while severe asthenia was the main reason for treatment stop (10 patients, 35.5%) before the planned 24 weeks.

Overall, these tested weekly dosages are equivalent to a dose range of 105–120 mg/m² every 3 weeks.

Weekly docetaxel in combination regimens: phase I studies

The favorable results arising from single-agent use prompted its combination with other active drugs (Table 2).

In 2000, Frasci et al studied the association between escalating doses of docetaxel (starting from 30 mg/m²) and either gemcitabine 1000 mg/m² or vinorelbine 25 mg/m², all on days 1 and 8 every three weeks for the treatment of 34 anthracyclines pre-treated MBC patients; 24 out of 34 had received weekly dose-dense paclitaxel as second-line treatment (Frasci et al 2000). Docetaxel at the dose of 40 and 35 mg/m² proved to be safe when combined with gemcitabine and vinorelbine respectively. An ORR of 15% was observed (95% CI: 5%–31%) and only 1 of 24 paclitaxel pretreated patients responded to treatment.

Twenty-five patients with advanced breast cancer were treated by Ito et al with an intravenous bolus of doxorubicin (15–20 mg/m²), immediately followed by a 1-h infusion of docetaxel (25–30 mg/m²), every week for 6 weeks (Ito et al 2001). MTD was 20 mg/m² and 30 mg/m² for doxorubicin and docetaxel, respectively. Overall, modest neutropenia was reported with no febrile episodes with doxorubicin 15 or 20 mg/m² and docetaxel 25 mg/m² or lower. Reported G3 non-hematologic toxicities included asthenia in 4% of patients, anorexia in 8%, and vomiting in 8%. The ORR was 56% (14/25 with partial response). The recommended dose for further investigation was 20 mg/m² of doxorubicin and 25 mg/m² of docetaxel.

Weekly epidoxorubicin (25–35 mg/m²) and docetaxel (25–40 mg/m²) given once a week for 6 weeks followed by 1-week rest were evaluated for the preoperative and palliative treatment of patients with breast cancer by Wenzel et al DLT was neutropenic fever, occurring with 35 mg/m² of epidoxorubicin and 40 mg/m² of docetaxel. Epidoxorubicin 30 mg/m² and docetaxel 35 mg/m² were suggested for further evaluations (Wenzel et al 2002).

In order to determine the maximum tolerable dose of docetaxel in association with gemcitabine, both given on a weekly schedule, Brugnattelli et al designed a phase I study using three escalating doses of docetaxel (30, 35, and 40 mg/m²) followed by a fixed dose of gemcitabine, 800 mg/m², on days 1, 8, and 15 of a 28-day cycle (Brugnattelli et al 2002). Asthenia, stomatitis, and leukopenia were the main DLTs. An objective response rate of 58% was found and the dose of 35 mg/m² was proposed for further phase II evaluation.

In a recent phase I trial, 11 MBC patients were enrolled in an open, single-arm phase I escalation trial in 3–6 patients/cohort (Ibrahim et al 2007). The treatment schedule was: docetaxel 20 mg/m² (or 25, depending on dose level assignment) on day 1, 8, 15 in association with doxorubicin 40 or 50 mg/m² and cyclophosphamide 500 mg/m² on day 1, every 4 weeks. Five patients were allocated to dose level 20/50 (docetaxel/doxorubicin) and 6 to dose level 20/40. MTD was defined at 20 mg/m² for docetaxel in combination with doxorubicin 40 mg/m² and cyclophosphamide 500 mg/m², due to DLT febrile neutropenia.

Weekly single-agent docetaxel: phase II studies

Several phase II trials have evaluated the weekly administration of single-agent docetaxel in MBC patients (Table 3).

In 2000 Burstein et al published the results of a study of weekly docetaxel administered at the dose of 40 mg/m²/week to 29 patients (Burstein et al 2000). The authors reported an ORR of 41% (all PRs), with similar results for both first- and second-line treatment (21% of second-line patients). Grade 3 toxicities, most commonly neutropenia and fatigue, were reported in 28% of patients, whereas fatigue, fluid retention, and eye tearing/conjunctivitis were found to be related to cumulative dose. Dose reductions were required for 8 patients, mostly due to fatigue.

Jackisch et al (2000) presented, in abstract form, the preliminary results of a multicentric phase II study designed

to determine response rate and toxicity of weekly docetaxel 35–40 mg/m² in 60 MBC patients (second line 1.9%, third line 98.1%). Overall 24 patients (42.9%) were pretreated with anthracyclines for MBC. The reported ORR was 33.4% including 4/60 CR (6.7%) and 16/60 PR (26.7%). Regarding toxicity, 23/652 (3.5%) cycles were associated with G3 neutropenia, and 2/652 (0.3%) cycles with G3/4 thrombocytopenia. Non-hematologic G3 side effects were: 14.3% alopecia, 1.2% skin disorder, 0.8% neurotoxicity, 0.8% mucositis, 0.8% nausea/vomiting, 1% fluid retention, with no G4 non-hematologic toxicities. The authors found this schedule safe and feasible, achieving good response rates in heavily pretreated MBC patients.

Stemmler et al (2001) conducted a phase II trial in 35 previously treated MBC patients. Docetaxel 35 mg/m²/week for 6 weeks followed by 2 weeks of rest was administered with an ORR of 34%. A median survival of 11 months and a progression-free survival of 2.6 months were reported. G3 neutropenia was observed in 3 patients.

Hainsworth et al (2001) tested a weekly schedule of docetaxel 36 mg/m²/week in 41 elderly (median age 74 years) or poor performance status MBC patients (75% as first-line treatment). In this cohort 36% had an ORR, median TTP was 7 months, and median survival was 13 months. Fatigue was the most common G3/4 non-hematologic toxicity.

In another phase II study, 37 MBC patients (previously treated in 92% of cases) received docetaxel at 40 mg/m²/week for 3 consecutive weeks with 1-week rest (Aihara et al 2002).

Table 3 Recent selected phase II trials on weekly docetaxel

Author and year of publication	N. of pts (line)	Regimen	ORR
Weekly single-agent docetaxel			
Burstein et al 2000	29 (21% 2nd line)	40 mg/m ² qw	41%
Jackisch et al 2000	60 (93.3% 2nd or > line)	35–40 mg/m ² qw	33.4%
Stemmler et al 2001	35 (all 2nd or > line)	35 mg/m ² qw × 6w (2 w rest)	34%
Aihara et al 2002	37 (all 2nd or > line)	40 mg/m ² qw × 3w (1 w rest)	38% (32 evaluable pts)
Hainsworth et al 2001	41 (25% 2nd or > line)	36 mg/m ² qw	36%
Ramos et al 2003	35 (all Anthra resistant)	36–40 mg/m ² qw × 6w (2 w rest)	34%
D'Hondt et al 2004	47 (79% 2nd or > line)	36 mg/m ² qw × 6w (1 w rest)	30% (37 evaluable pts)
Stemmler et al 2005	54 (all 1st line)	35 mg/m ² qw × 6w (2 w rest)	48.1%
Ford et al 2006	42 (62% 2nd line)	35mg/m ² qw × 6w (2 w rest)	26%
Weekly versus 3-week single-agent docetaxel			
Sedky et al 2002	30 (overall 40% 2nd line)	35 mg/m ² qw × 6w (2w rest) versus 100 mg/m ² d 1 q 21	86.7% versus 73.3%
Tabernero et al 2004	41 (17% 2nd line)	40 mg/m ² qw versus 100 mg/m ²	34% versus 33%
	42 (20% 2nd line)	d 1 q 21	

Abbreviations: Pts, patients; ORR, complete + partial response; w, week; Anthra, anthracycline.

An ORR of 38% (14 partial responses) was found, with a TTP of 5 months and an OS of 12 months. Regarding toxicity, 19% of patients experienced G3/4 neutropenia with no case of febrile neutropenia. Although degree of toxicity was not severe in many cases, it was the most common cause for delay of the treatment and dose reduction. None of the patients showed G3/4 non-hematologic toxicity. Fatigue and asthenia, generally mild, were observed in 35% of patients and generally mild. Gastrointestinal side effects and skin/nails changes were relatively frequent (38% and 39% respectively).

In 2003, Ramos et al (2003) reported on 35 MBC patients resistant to prior anthracycline chemotherapy treated with docetaxel 40 mg/m² for 6 consecutive weeks followed by a 2-week rest, then reduced to 36 mg/m² due to non-hematologic toxicity (28% G3/4 asthenia). ORR was 34% (2 CR and 10 PR). After a median follow-up of 11.4 months, median TTP was 8.4 months, while median OS was 13.6 months. The most severe hematologic toxicity (17% of patients) was neutropenia whereas asthenia, nail, ocular, and skin disorders were the main non-hematologic toxicities. One treatment-related death occurred during further follow-up (pulmonary fibrosis).

In order to evaluate the safety and efficacy of weekly docetaxel in frail and/or elderly patients, who were ineligible for the standard 3-weekly docetaxel (100 mg/m²) regimen, D'Hondt et al (2004) performed a phase II study for the treatment of 47 MBC patients. Docetaxel was given at the dose of 36 mg/m² weekly for 6 weeks followed by a 1-week rest. There was a median of 2 prior chemotherapy regimens and more than 60% had a WHO performance score at baseline of 2–3. Noteworthy, the ORR, in 37 evaluable patients, was 30%. Six patients experienced G3 and 4 patients G4 neutropenia. Of these 10 patients, 4 developed neutropenic fever. Neurotoxicity was mild and G3 paraesthesia occurred in 1 patient. The authors conclude that weekly docetaxel (36 mg/m²) is active, safe and overall well tolerated also in heavily pretreated frail/elderly patients.

In a multicenter phase II study published in 2005, Stemmler et al (2005) prospectively analyzed the activity of weekly docetaxel in 54 first-line MBC patients. Docetaxel was given at a dose of 35 mg/m² weekly for 6 weeks followed by 2 weeks of rest with an ORR of 48.1%. Median survival was 15.8 months, while median TTP was 5.9 months. G3 neutropenia was reported in 3.7% of patients with no case of febrile neutropenia. Among the non hematologic toxicities G3/4 asthenia was observed in 5.6% and nausea/vomiting in 3.7% of cases. The toxicity profile did not differ significantly between younger (<65 years) and elderly

patients (>65 years), except for fluid retention syndrome and neurotoxicity that showed an increased incidence in the younger patients.

In 2006 Ford et al (2006) evaluated docetaxel 35 mg/m² weekly for 6 weeks followed by a 2-week rest, in 42 anthracycline-pretreated MBC patients (second-line treatment in 62% of patients). They reported an ORR of 26% (11 partial responses); 5 of these responding patients had relapsed <12 months after the end of previous anthracycline-based chemotherapy. Myelosuppression was rare, with only 2 patients (5%) experiencing G3 neutropenia (no G4 neutropenia). Non-hematologic G3 toxicities were: fatigue 17%, neuropathy 0%, hyperlacrimation 5%, stomatitis 7%, diarrhoea 14%, and cutaneous toxicity 19% (limb/palmar-plantar erythematous reactions, or fixed-plaque erythrodysesthesia). The authors do not recommend this weekly regimen due to the significant non-hematological toxicities associated with the treatment.

Sedky et al (2002) conducted a randomized phase II trial, presented in an abstract form, to compare weekly docetaxel at a dose of 35 mg/m² for 6 weeks followed by 2 weeks rest, with docetaxel at a dose of 100 mg/m² every 3 weeks in 30 MBC patients. There was no statistical difference between the weekly and the every 3-week treatment arms for ORR (86.7% versus 73.3% respectively), neutropenia being less with the weekly regimen.

A randomized phase II study (Tabernero et al 2004) was performed to compare weekly versus every 3-week docetaxel at a dose of 40 mg/m² and 100 mg/m², respectively, in 83 MBC patients. ORR was 34% in the weekly and 33% in the every-3-week arm; median TTP was 5.7 versus 5.3 months, while the median time to treatment failure was 4.1 and 4.9 months, respectively. In terms of tolerability, the incidence of all G3/4 adverse events was higher in the every-3-week arm. In particular G3/4 neutropenia, neutropenic fever, stomatitis, and neurosensory toxicity had a lower incidence in the weekly docetaxel arm.

Weekly docetaxel in combination regimens: phase II studies

Since encouraging results came from phase II studies on weekly single-agent docetaxel, it has been investigated in combination with either chemotherapeutic or biological agents (Table 4).

The combination of weekly docetaxel and vinorelbine was investigated in 57 MBC patients (first line in 42 cases) (Kornek et al 2001). Therapy consisted of vinorelbine 30 mg/m² on days 1 and 15 and docetaxel 30 mg/m² on

Table 4 Recent selected phase II trials on weekly docetaxel in combination regimens

Author and year of publication	N. of pts (line)	Regimen	ORR
Kornek et al 2001	57 (26% 2nd line)	VNR 30 mg/m ² d1,15 q 4w with Doc 30 mg/m ² d1,8,15 q 4w	64% as 1st line 53% as 2nd line
Palmeri et al 2005	58 (1st line)	Doc 35 mg/m ² d1,8,15 q 4w with Gem 800 mg/m ² d1,8,15 q 4w	64% (56 pts evaluable)
Mrozek et al 2006	39	Doc 30 mg/m ² qw × 3w (1 w rest) with Cap 800 mg/m ² bid d1-21 q 4w	44%
Esteva et al 2002	30 (19% 2nd line)	Doc 35 mg/m ² qw × 3w (1 w rest) with T 2 mg/kg qw × 3w (1w rest)	63%
Raab et al 2002	13 (1st line) 12	Doc 35 mg/m ² qw × 6w (2 w rest) + T 2 mg/kg/qw versus Doc 100 mg/m ² d1 q21 + T 2 mg/kg/qw	Overall 63%
Tedesco et al 2004	26 (15% 2nd line)	Doc 35 mg/m ² qw × 6w with T 2 mg/kg qw × 3w	50%
Raaf et al 2004	21 + 14	Doc 33 mg/m ² d1,8,15 q 4w	21%
	+ 17 (Her2 +)	Doc 40 mg/m ² d1,8,15 q 4w + T 2 mg/kg d8,15 q 4w (T only for 17 additional Her2 + pts)	59%
Ramaswamy et al 2006	27 (22% 2nd line)	Doc 35 mg/m ² d1,8,15 q 4w with B 10 mg/kg d1,15 q 4w	52%
Ghosn et al 2008	63 (1st line)	NAVCAP 8 cycles versus NAVCAP 4 cycles + Doc qw × 12 wk	(Overall 65% after first 4 cycle of NAVCAP) Not yet available
Peacock et al 2008	61 (1st line)	Doc 30 mg/m ² d1,8 q 3w with VNR 25/mg/m ² d1,8 q3w with T 2 mg/kg qw	67%
Rosati et al 2008	20 + 28	Doc 30 mg/m ² qw × 3w (1 w rest) or P 50 mg/m ² qw × 3w (1 w rest)	Overall 73%
	(All 1st line)	with NPL-Anthra 25 mg/m ² qw × 3w (1 w rest)	
Waterhouse et al 2008	33 (55% 1st line)	Doc 30 mg/m ² qw × 3w (1w rest) with Imatinib 600 mg daily	20% (18 evaluable pts)

Abbreviations: Pts, patients; ORR, complete + partial response; w, week; VNR, vinorelbine; Doc, docetaxel; G, gemcitabine; Cap, capecitabine; T, trastuzumab; P, paclitaxel; B, bevacizumab; NAVCAP, VNR 25 mg/m² d1, 8 + Cap 825 mg/m² bid D1-14 q3w; NPL-Anthra, non-pegylated liposomal anthracycline.

days 1, 8, and 15 every 28 days. Depending on the absolute neutrophil count on the day of scheduled administration, a 5-day course of G-CSF 5 µg/kg/d was given. ORR was 64.3% in patients receiving docetaxel plus vinorelbine as first-line chemotherapy, including 8 CR (19%) and 19 PR (45.3%); 11 patients (26.2%) had disease stabilization and 4 (9.5%) experienced disease progression. As second-line treatment, this regimen resulted in 8 (53.3%) objective responses. Median TTP was 12 months in the first-line and 9.8 months in the second-line setting. After a median follow-up of 18 months, 38 patients (65%) were still alive (with metastatic disease). Regarding hematologic side effects, G3 or G4 neutropenia occurred in 18 patients (32%) and was

complicated by septicemia in 4 cases; G3 or G4 thrombocytopenia was reported in 2 patients (4%) and G3 anemia was seen in 1 patient (2%). Severe (G3) non-hematologic toxicities, except for alopecia, were rarely observed and included nausea/vomiting in 2 patients (4%) and stomatitis, peripheral neuropathy, and skin toxicity, each in 1 case.

A multicenter phase II study focused on weekly docetaxel 35 mg/m² in combination with gemcitabine 800 mg/m² on days 1, 8, 15 of an every-28-days cycle as first-line treatment in 58 MBC patients (Palmeri et al 2005). At least 1 visceral site of metastasis was present in 45 (77.6%) patients. In the 56 assessable patients, ORR was 64.3% with 9 patients (16.1%) achieving a CR, 27 (48.2%) a PR, and 12 (21.4%) patients SD.

Median survival was 22.10 months, with 43 (74.1%) patients still alive at the cut-off date of 36 months. Noteworthy, TTP was 13.6 months. Median time to treatment failure was 8.6 months (95% CI: 4.79–12.41). At the time of cut off, 24 patients had experienced progressive disease (PD). Median duration of response in patients with SD was 19.27 months. Furthermore, median survival of patients who achieved PR was 29.30 months. G3/4 neutropenia occurred in 8 patients (14%). Regarding non-hematologic toxicity, G3 alopecia was experienced by 5 patients (9%). No case of fluid retention syndrome was seen.

The activity and tolerability of weekly docetaxel (30 mg/m² on days 1, 8, and 15) and capecitabine (800 mg/m² twice daily on days 1–21) repeated every 28 days was evaluated in 39 patients with MBC (Mrozek et al 2006). ORR was 44%, with a median duration of response of 9.1 months. Median TTP was 5.5 months. G3 non-hematologic toxicities were asthenia (18%), diarrhea (18%), nausea/vomiting (13%), stomatitis (13%), and hand-foot syndrome (10%); among the hematological toxicities, 13% of patients experienced neutropenia. There were 2 G4 toxicities (febrile neutropenia and pulmonary embolism).

In HER-2 overexpressing MBC patients, weekly docetaxel has been largely evaluated in combination with trastuzumab.

A phase II study was performed in 30 MBC women (19% in second line) with a median age of 45 years (Esteva et al 2002). The authors evaluated docetaxel 35 mg/m²/week and trastuzumab (loading dose of 4 mg/kg followed by 2 mg/kg) weekly for 3 weeks followed by 1-week rest. They reported an ORR of 63% (RP in 19 patients); according to the HER-2 extracellular domain level, 21 patients with baseline levels >14.9 ng/ml had an ORR of 76% while those with normal levels had an ORR of 33%. The median TTP was 9 months. The main G3/4 toxicities were granulocytopenia (26%), fatigue (20%), and diarrhea (6%).

A phase II randomized study compared every-3-week docetaxel and trastuzumab with a weekly regimen (docetaxel 35 mg/m² for 6 weeks with 2-week rest) as first-line treatment in 25 patients with anthracycline-pretreated, HER-2 overexpressing MBC (Raab et al 2002). Overall the ORR was 63% and median TTP was 8.3 months. G3/4 hematologic side effects were frequent in the every-3-week group, including leukopenia, neutropenia (92%), and febrile neutropenia (23%).

A phase II study evaluated the combination of weekly docetaxel (35 mg/m²/week for 6 weeks) and trastuzumab (4 mg/kg load; 2 mg/kg/week) as first- or second-line (15%) therapy in 26 women with HER-2-overexpressing

MBC (Tedesco et al 2004). ORR was 50%. With regard to HER-2 3+ patients, the reported ORR was 63%, compared with a 14% response rate for HER-2 2+ patients ($p = 0.07$). Patients with FISH-positive tumors experienced an ORR of 64%. Median time to progression was 12.4 months for the entire group and median survival was 22.1 months. G4 toxicities occurred in 4 patients.

The combination of weekly docetaxel and trastuzumab was also evaluated in 52 MBC patients (Raff et al 2004). They received docetaxel given on 2 different schedules: 21 patients in group 1A, 33 mg/m² weekly; 14 in group 1B, 40 mg/m² weekly for 3 weeks with 1-week rest. Patients with HER-2/neu overexpressing disease also received trastuzumab 4 mg/kg on day 1, then 2 mg/kg on days 8 and 15 of each 28-day cycle (group 2). Previous every-3-week taxane therapy had been used for metastatic disease in 19 of 35 patients (54%) in group 1A/B and in 2 of 17 patients (12%) in group 2. ORR (PR) was 21% in patients treated with docetaxel alone, including 3 of 19 taxane-pretreated patients (16%) and 4 of 16 taxane-naïve patients (25%). Partial response occurred in 59% of cases treated with docetaxel/trastuzumab. Median TTP was 4.5 months in the docetaxel group and 8.5 months in the docetaxel/trastuzumab group. The main G3/4 toxicities (>10% of patients) observed were neutropenia (21%), pulmonary toxicity (12%), and hyperglycemia (10%).

Finally, a pilot study of preoperative weekly trastuzumab (4 mg/kg loading dose, then 2 mg/kg/week), in association with weekly epirubicin 30 mg/m²/week and docetaxel 35 mg/m²/week for 6 weeks with 1 week was conducted on 14 consecutive patients (Wenzel et al 2004). Overall the regimen was well tolerated, with major responses observed in 12 out of 14 patients (86%) leading to breast-conserving surgery in 11 of 14 patients (79%).

The safety and efficacy of bevacizumab and weekly docetaxel as first or second line treatment was evaluated in 27 MBC patients (Ramaswamy et al 2006). ORR was 52% and the median progression-free survival was 7.5 months. The most common G4 toxicities were: pulmonary embolus (7%), febrile neutropenia (4%), and infection (4%).

Four recent studies evaluating weekly docetaxel in combination with both chemotherapeutic and/or biological agents, for the treatment of MBC were presented at the 2008 ASCO annual meeting, demonstrating the growing interest for such a feasible and active schedule.

On the basis of a proven prolonged TTP and OS of the sequential use of vinorelbine (25 mg/m² d1,8) and capecitabine (825 mg/m² bid d1–14) (NAVCAP)

every 3 weeks for 4 cycles followed by 12 consecutive weeks of docetaxel (25 mg/m²/w) in the first-line treatment of MBC, Ghosn et al (2008b) designed and conducted a further phase II randomized trial. Preliminary data from this study have been also presented in abstract form (Ghosn et al 2008a). Sixty-three first-line HER-2/neu negative MBC patients were enrolled and 44 have been randomized after the first 4 cycles of NAVCAP to receive either 4 more cycles of NAVCAP (25 patients) or 12 weekly docetaxel (19 patients). Overall, after the first 4 cycles of NAVCAP an ORR of 65% with 17% of CR was registered (SD 21%). Nineteen and 12 patients had completed the treatment plan at the time writing. With regard to tolerability, patients treated with NAVCAP experienced G3 neutropenia in 8% of cases, G3/4 anemia in 6%, and 1 patient had G3 hand-foot syndrome; in patients treated with docetaxel, 11% had G4 liver enzymes elevation and 1 patient had G4 creatinine elevation. No long-term follow-up data were available in order to determine whether maintenance docetaxel will have an added value versus maintenance NAVCAP.

The feasibility and safety of a 3-drug combination of trastuzumab, docetaxel, and vinorelbine as first-line therapy was investigated in 61 HER-2 positive MBC. The schedule included docetaxel 30 mg/m² and vinorelbine 25 mg/m² on days 1 and 8 of a 3-week cycle in association with weekly trastuzumab (4 mg/kg loading dose followed by 2 mg/kg/week) (Peacock et al 2008). The reported ORR was 67% (CR 26%, PR 41%). After a median follow-up of 58 months, median progression-free survival was 11.3 months and median OS was 39.1 months. The most common hematologic toxicity was neutropenia (G4 in 72%); 8 patients (13%) were hospitalized for febrile neutropenia. Other G3/4 toxicities included fatigue (12%), hyperglycemia (7%), and myalgias (7%).

Rosati et al (2008) presented results of their phase I/II trial in first-line MBC patients (adjuvant anthracyclines and taxanes were allowed). The dose-finding study examined the safety and activity of weekly combination (d 1, 8, 15 q4w) of paclitaxel (n = 28 patients) or docetaxel (n = 20 patients) with non-pegylated liposomal anthracycline. DLT was 50 mg/m² and 30 mg/m² for paclitaxel and docetaxel respectively, combined with 25 mg/m² of non-pegylated liposomal anthracycline. A phase II trial followed and 48 patients were enrolled. The reported ORR was 73% (12.5% CR and 60.41% PR), with a clinical benefit of 85.41%. Median TTP was 10.68 months. No survival differences were recorded between paclitaxel and docetaxel groups. G3/4 toxicities included neutropenia (68.75%) and alopecia (60.41%).

Overall the following non-hematologic toxicities were significantly higher for docetaxel than paclitaxel: mucositis 12.53% versus 8.3%, onycholysis 22.91% versus 10.41%, and peripheral sensory neuropathy 25% versus 14.58%. The authors concluded that weekly administration of taxane and non-pegylated liposomal anthracycline is well tolerated and clinical benefit data encourage a phase III study design.

The association between weekly docetaxel and imatinib mesilate has been studied in a phase II study designed to investigate whether adding imatinib could ameliorate docetaxel performance in first- or second-line MBC patients (Waterhouse et al 2008).

Docetaxel was given weekly 30 mg/m² days 1, 8, and 15 q28 for 6 cycles with daily oral imatinib 600 mg until PD. To date, only data on toxicity of 33 patients have been published (55% first line and 42% second line; 13 patients had prior taxanes). Overall, hematologic side effects were mild with G3/4 neutropenia 12% (1 febrile neutropenia) and anemia 9%. On the other hand, G3/4 non-hematologic, especially gastrointestinal, toxicity prompted imatinib dose modification to 400 mg after the first 14 patients. No improvement in gastrointestinal toxicity has been recorded despite dose reduction: G3/4 diarrhea 21%, nausea 18%, and vomiting 12%, with 9 patients requiring treatment-related hospitalizations (gastrointestinal toxicity 4, febrile neutropenia 1, pleural effusion 2, and pneumonia 2). Only 5 patients went on to maintenance imatinib with a median of 6 cycles. Four out of 18 evaluable patients had PR, 8 patients SD, while 6 patients progressed. Median TTP and OS were 3 and 10 months, respectively. Although presented data are preliminary, no therapeutic advantage resulted from adding imatinib to weekly docetaxel in MBC.

Weekly single-agent docetaxel: phase III studies

To date only 3 phase III randomized trials have been performed to investigate the efficacy of weekly docetaxel (Table 5).

In 2004, Meier et al reported, in abstract form, a planned interim analysis of a phase III trial comparing weekly vinorelbine versus weekly docetaxel for metastatic breast cancer failing anthracyclines (Meier et al 2004). Crossing-over was allowed on disease progression. They analyzed data from 120 of 240 patients accrued from November 1998 until July 2003 and randomized to receive either vinorelbine 30 mg/m² or docetaxel 35 mg/m² weekly for 6 consecutive weeks of a 8-week cycle. At the time of the analysis 112 patients were evaluable. TTP was the main endpoint of the study: 81 days

Table 5 Phase III trials

Author and year of publication	N. of pts	Regimen	TTP (months)	PFS	OS
Meier et al 2004	55	Doc 35 mg/m ² qw × 6w (2w rest) versus VNR 30 mg/m ² qw × 6w (2w rest)	2.7 versus 3.4 (p = 0.1178)	Not reported	9.6 months versus 8.43 months (p = 0.1895)
Burstein et al 2007	40	Doc 35 mg/m ² × 8w/P 80 mg/m ² × 8w + T 2mg/kg qw versus VNR mg/m ² + T 2 mg/kg qw	6 versus 8.5 (p = 0.09)	Not reported	Not reported
Rivera et al 2008	59	Doc 75 mg/m ² d 1 q 21 versus Doc 35 mg/m ² d 1,8,15 q 28	Not reported	5.7 months versus 5.5 (p = 0.46)	18.3 months versus 18.6 (p = 0.34).

Abbreviations: Pts, patients; BC, breast cancer; TTP, time to progression; OS, overall survival; w, week; Doc, docetaxel; VNR, vinorelbine.

(CI: 67–99) versus 103 days (CI: 98–119) were registered for vinorelbine versus docetaxel ($p = 0.1178$). OS was 253 (CI: 173–331) versus 288 days (CI: 231–424) for initial vinorelbine versus docetaxel ($p = 0.1895$). Significantly more patients receiving vinorelbine (42%) had disease progression as best response than patients receiving docetaxel (18%) ($p = 0.00751$). Moreover, vinorelbine resulted in more treatment delays (76% versus 46%), more leukopenia (61% versus 10%) and G3/4 neutropenia (43% versus 7%), but less mucositis/stomatitis (1% versus 8%) (all $p < 0.05$). The authors found weekly docetaxel more efficient at response and less toxic than weekly vinorelbine, but more mature data are needed in order to clarify the benefit. To our knowledge, no definitive data are available to date.

Burstein et al studied the combination of trastuzumab with either vinorelbine or a taxane as first-line treatment in 81 out of the 250 originally planned HER-2 positive MBC patients (the study was terminated early because of poor accrual) (Burstein et al 2007). The primary endpoint was ORR. Patients were randomized 1:1 to receive either trastuzumab 4 mg/kg loading dose and then 2 mg/kg/week with weekly vinorelbine (25 mg/m² q week for 8 weeks) or weekly taxanes (paclitaxel 80 mg/m² q week for 8 weeks or docetaxel 35 mg/m² q week for 8 weeks at the investigator's choice). Forty-one patients and 40 patients were randomized to the vinorelbine/trastuzumab and the taxane/trastuzumab arm, respectively (docetaxel $n = 24$; paclitaxel $n = 14$, with 2 more patients receiving paclitaxel and carboplatin). Overall, ORR was 51% in the vinorelbine/trastuzumab arm and 40% in the taxane/trastuzumab arm ($p = 0.37$). Median TTP was not significantly different between the vinorelbine- and taxane-based arms (8.5 versus 6.0 months, $p = 0.09$). Noteworthy chemotherapy administration delays

were more frequent in the vinorelbine containing arm (82% of patients experienced at least 1 week of delay) than the taxane-based arm (overall 60%, 56% for paclitaxel and 63% for docetaxel). With regard to tolerability, anemia and neutropenia were more common with vinorelbine treatment. Alopecia, rash, and nail changes were reported to be more frequently associated with taxane-containing therapy. Among patients treated with docetaxel, 2 had fluid retention syndrome and 5 hyperlacrimation. In the vinorelbine arm, 2 patients went off study for cardiac toxicity. The authors concluded that either weekly vinorelbine/trastuzumab or weekly taxane/trastuzumab are active and feasible and can be considered for the first-line treatment of HER-2 overexpressing MBC patients, even if some caution is required when interpreting these results due to the small proportion of patients included leading to the early termination of the study.

A recent phase III trial was conducted randomizing 118 MBC patients to receive docetaxel on an every-3-week versus weekly basis (Rivera et al 2008). Fifty-nine patients received docetaxel 75 mg/m² every 3 weeks and 59 docetaxel 35 mg/m² for 3 consecutive weeks with 1 week of rest. ORR was 35.6% for the 3-week versus 20.3% for the weekly schedule. No statistically significant difference was observed both in terms of progression-free survival (5.7 months versus 5.5, $p = 0.46$) and OS (18.3 versus 18.6 months, $p = 0.34$). A significantly higher toxicity rate, G3/4, was found in the every-3-week treatment arm versus the weekly treatment arm (88.1% versus 55.9%, respectively; $p = 0.0001$). The trial was terminated early after an interim analysis performed in June 2005 because of a slow accrual rate.

Due to the early termination this study was significantly underpowered even in the authors' opinion, so that it remains unknown whether a larger phase III study could demonstrate

differences in OS and/or progression-free survival. Nevertheless, modest increases in response rate are unlikely to affect OS in patients with advanced MBC.

Conclusion

Since the main goal of MBC management remains palliation, maximizing the antitumor activity and maintaining a favorable toxicity profile appears of paramount relevance in this setting. To date, combinations containing the taxanes represent the standard of care for first-line treatment of these patients. Both docetaxel and paclitaxel can be administered weekly, achieving comparable efficacy results with lower toxicity compared with standard schedules (Zimatore et al 2002).

Particularly, several docetaxel-containing schedules and associations have been tested: overall, weekly, rather than the standard every-3-week dosing can provide good efficacy results and better tolerability, even in heavily pretreated patients with refractory disease and/or in elderly/poor PS women. Unfortunately because there is a great difference between the various experimented weekly schedules (ie, d1,8 q21 or d1,8,15 q28 or 6 consecutive weeks) and the doses employed are vary greatly as well (range from 25 to 40 mg/m²), it is not possible to draw any definitive conclusion on which is the best dose and timing of administration.

Reviewing the main phase II studies results, it has been highlighted that the obtained ORR can vary between 26% and 86% or 20% and 73% with docetaxel as a single agent or in combination, respectively, depending on doses, associations, and line of treatment.

Furthermore, the lower incidence of severe hematologic toxicities and acute non-hematologic side-effects allows its use in most MBC patients both as single-agent and as part of combination regimens.

The association with biological agents (trastuzumab, bevacizumab) represents a promising therapeutic option given the favorable toxicity profile of these drugs.

Overall, published data support the administration of weekly docetaxel for the treatment of MBC patients even with the lack of data from phase III randomized trials, and keeping in mind the drawbacks of weekly regimens (eg, more frequent hospital visits).

The choice of the best docetaxel weekly schedule in patients with MBC should be based on patient characteristics and on the risk of developing toxic effects. In elderly or unfit patients weekly docetaxel could be preferred.

Disclosures

The authors have no conflicts of interest to disclose.

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