Weekly Administration of Docetaxel and Paclitaxel in Metastatic or Advanced Breast Cancer

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Key Words. Breast cancer • Metastatic disease • Taxanes • Chemotherapy

LEARNING OBJECTIVES
After completing this course, the reader will be able to:
1. Identify the response rates to weekly paclitaxel and docetaxel for metastatic breast cancer.
2. Name the recommended doses of each taxane when administered weekly.
3. Learn schemas of phase III adjuvant trials incorporating weekly taxanes.

ABSTRACT
The taxanes docetaxel (Taxotere®; Aventis Pharmaceuticals Inc., Bridgewater, NJ, http://www.aventispharma-us.com) and paclitaxel (Taxol®; Bristol-Myers Squibb, Princeton, NJ, http://www.bms.com) have significant clinical activity in metastatic breast cancer. A number of clinical trials have evaluated the tolerability and efficacy of weekly taxane administration to optimize the benefit-to-risk ratio in metastatic breast cancer. Single-agent studies with docetaxel and paclitaxel in metastatic breast cancer show clinically significant antitumor activity even in advanced, heavily pretreated, resistant, and/or refractory disease. This activity is also evident with taxane-based combination regimens. Severe hematologic and nonhematologic toxicities are infrequent, with other toxicities noted based on the dose and weekly regimen selected. Weekly docetaxel and paclitaxel regimens represent valuable therapeutic options for women with metastatic breast cancer and have entered evaluation as part of adjuvant therapy for this disease. The Oncologist 2005;10:665–685

INTRODUCTION
An estimated 215,990 women will be diagnosed with breast cancer in the U.S. in 2005, and 40,110 deaths are expected to result from the disease [1]. For most women diagnosed with metastatic breast cancer (MBC), median survival durations of 18–36 months after diagnosis are common, with survival longer than 5–10 years reported in some cases [2]. Because palliation is an important component of treatment of systemic disease, the goals of therapy are focused on prolonging life, providing cancer-related symptom relief, minimizing treatment-related toxicity, and improving quality of life [2].
The taxanes docetaxel (Taxotere®; Aventis Pharmaceuticals Inc., Bridgewater, NJ, http://www.aventispharma-us.com) and paclitaxel (Taxol®; Bristol-Myers Squibb, Princeton, NJ, http://www.bms.com) are now a mainstay in the treatment of MBC. The taxanes exert their antitumor activity by binding tubulin and stabilizing non-functional microtubule bundles, thereby blocking normal mitotic spindle development and subsequent cell division [3]. Although synthesis of paclitaxel and its analogue, docetaxel, first began in the late 1970s and early 1980s [3, 4], clinical development of the taxanes for breast cancer treatment burgeoned in the 1990s, when the antitumor activity of single-agent regimens in patients with advanced disease began to be documented in phase II trials [5, 6].

Since then, these agents have rapidly become incorporated into breast cancer treatment regimens based on data from prospective randomized phase III studies. Overall survival with single-agent paclitaxel or docetaxel is comparable with that with the previous gold-standard anthracycline, doxorubicin (Adriamycin®; Bedford Laboratories, Bedford, OH, http://www.bedfordlabs.com) [7–9], but these agents are associated with a more favorable toxicity profile [8, 9]. In fact, both paclitaxel and docetaxel have particular noteworthy clinical activity in anthracycline-resistant disease [10–14].

Currently, the U.S. Food and Drug Administration–approved dosing schedules for the taxanes in MBC are 60–100 mg/m² for docetaxel as a 1-hour i.v. infusion every 3 weeks and 175 mg/m² for paclitaxel as a 3-hour i.v. infusion every 3 weeks. One of the most frequent dose-limiting adverse effects with every-3-weeks taxane therapy is myelosuppression, primarily neutropenia [4, 5]. The most frequent nonhematologic toxicities include neuropathy, myalgias, fatigue, gastrointestinal disturbances, mucosal toxicity, and skin and nail changes [4, 5, 15]. To reduce docetaxel-induced fluid retention and hypersensitivity, corticosteroid premedication is frequently administered [4, 5, 15]. All patients receiving paclitaxel should be pretreated with corticosteroids, diphenhydramine, and H₂-receptor antagonists to prevent hypersensitivity reactions [16].

Studies have evaluated weekly administration of the taxanes as a strategy to maintain or improve upon the efficacies of conventional schedules and to achieve a more favorable toxicity profile [17]. By administering lower doses more frequently, toxicity may be decreased while maintaining the dose intensity necessary for antitumor activity. This review summarizes the extensive clinical data that have been published on the administration of weekly docetaxel and paclitaxel, as single-agent therapy and as part of combination regimens, for the treatment of MBC.

**Materials and Methods**

In an attempt to comprehensively analyze the published evidence regarding the use of weekly taxanes in MBC or advanced breast cancer, we conducted electronic searches using the Ovid MEDLINE database for records using the subject headings “breast neoplasms” and “taxoids” and the key word “weekly.” Additionally, the abstract books from key international meetings, that is, the American Society of Clinical Oncology (ASCO) Annual Meeting, the European Society for Medical Oncology (ESMO) Congress, the San Antonio Breast Cancer Symposium (SABCS), and the St Gallen Primary Therapy of Early Breast Cancer meeting (St Gallen, Switzerland), were manually searched for relevant study reports. We also backtracked relevant references from the identified articles to further refine the search. Because of the large number of abstracts and articles identified, only those studies that we considered most relevant are presented and discussed here.

**Preliminary Data with Weekly Taxanes in Solid Tumors**

Weekly taxane dosing was studied in numerous phase I and II trials of patients with MBC and other advanced solid tumors. Several dosing regimens were evaluated, including: (a) dosing for 2- or 3-week periods followed by a 1-week no-treatment “rest” period [18–20], (b) dosing for 4–6 weeks followed by a 2-week rest period [21, 22], and (c) continuous weekly dosing without a rest period [23–25]. For docetaxel, the infusion duration varied among studies, with the majority using a 1-hour i.v. infusion, which is recommended in current labeling, while two studies used a shorter infusion time (15–30 minutes) [22, 23]. For paclitaxel, the infusion duration was 1 hour in all studies.

The maximum-tolerated dose of docetaxel ranged around 40 mg/m², depending on the dosing frequency. Dose-limiting toxicities (DLTs) included myelosuppression (most commonly neutropenia with and without fever), fatigue, asthenia, and gastrointestinal symptoms including diarrhea; nail changes were also noted. The most frequently recommended dose for future studies was 35–40 mg/m² per week, but lower doses are now being used to improve tolerability. On the other hand, the maximum-tolerated dose of paclitaxel in initial studies was 100–110 mg/m² weekly. The DLT was primarily neutropenia, with and without fever, resulting in recommended doses for future studies of 80–100 mg/m² per week. The antitumor activity observed in these studies was promising, given that all study populations were patients with advanced malignancies, many of whom were refractory to prior chemotherapy regimens.
**Weekly Single-Agent Docetaxel**

Weekly administration of docetaxel has been evaluated in several phase II trials of women with MBC (Table 1) [26–38]. Most patients in those studies had received prior chemotherapy for MBC and most had an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1. Stemmler et al. [34] reported median times to progression (TTPs) of 6.6 months in chemotherapy-naive patients and 5.9 months in pretreated patients; likewise, Aihara et al. [35] and Kim et al. [27] reported a median TTP of 5 months. In patients resistant to anthracyclines, Ramos et al. [29] reported 8.4 months as the median time to disease progression. The median overall survival in these trials ranged from 13–14 months [29, 34–36]. The weekly docetaxel regimens were well tolerated, and grade 4 toxicities were rare. The most common grade 3 toxicities included neutropenia, anemia, and fatigue/asthenia; ocular toxicity manifesting as increased lacrimation resulting from canalicular stenosis [37] and nail toxicities were also notable. Stemmler et al. randomized patients to receive either dexamethasone (Decadron®, Merck & Co., Inc., Whitehouse Station, NJ, http://www.merck.com) premedication or no premedication; patients who received dexamethasone had a significantly lower incidence of nail changes (p = .004) and edema/effusions (p = .017) [34].

More recently, a phase II study performed by the Spanish Breast Cancer Research Group, GEICAM, evaluated weekly docetaxel in the neoadjuvant treatment of stage II and III breast cancer patients, analyzing correlations between response and the expression of cERBB2, estrogen receptor (ER) status, or Ki-67 labeling index [37]. Patients with previously untreated, stage II and III breast cancer received docetaxel (40 mg/m²) i.v. once weekly for the first 6 weeks of an 8-week cycle for two cycles. In a total of 56 patients that were evaluated, the overall clinical response rate (CRR) was 68% (complete and partial responses, 29% and 39%, respectively). Nine patients (16%) achieved pathological complete responses. There was no correlation between response to docetaxel and the expression of molecular markers; however, the majority of the pathological complete responses were observed in patients with cERBB2-negative tumors. Nonhematological toxicity was more common than hematological toxicity, with alopecia and asthenia the most frequently reported adverse events (89% and 77% of patients, respectively).

In summary, these studies show that weekly docetaxel at doses of 35–40 mg/m² has clinical activity in MBC, producing responses in 30%–40% of pretreated patients, with a median TTP of around 7 months. This schedule is associated with a low incidence of the classic grade 3–4 hematologic and nonhematologic toxicities reported with the every-3-weeks schedules.

**Weekly Docetaxel in Older Women**

In view of the favorable tolerability profile of weekly docetaxel, this regimen was tested in older or frail patients. One trial [36] included 41 patients ≥65 years of age or those who were poor candidates for combination chemotherapy. They received docetaxel at a dose of 36 mg/m² weekly for six consecutive weeks, followed by 2 weeks without treatment. The median age of the patients in that trial was 74 years, and 73% of patients had one or more visceral sites of metastasis. Thirteen patients (36%) had objective responses to treatment, and one had a minor response. The median TTP for responding and stable patients was 7 months. The median survival duration for the entire group was 13 months, with 1- and 2-year actuarial survival rates of 61% and 29%, respectively. Grade 3–4 fatigue was the most common toxicity, occurring in 20% of patients.

Another phase II study evaluated the tolerability and activity of docetaxel (36 mg/m² per week) in 47 frail or older patients (over 70 years of age) with MBC who were considered unlikely to tolerate the every-3-weeks regimen [38]. Reasons for ineligibility to the standard every-3-weeks docetaxel (100 mg/m²) regimen were age >70 years, poor hematological reserves, impaired liver function, and intolerance to previous taxanes administered every 3 weeks without demonstrated resistance. There was a median of two prior chemotherapy regimens, and more than half of the patients had a World Health Organization (WHO) performance status score at baseline of 2–3. The incidence of serious adverse events was low. Grade 3–4 neutropenia occurred in 10 patients. Neurotoxicity was mild, and grade 3 paresthesia occurred in one patient. The overall objective response rate in 37 evaluable patients was 30%, and responses were observed in all subgroups of patients.

These results favor the use of weekly docetaxel in frail or elderly patients for which chemotherapy is indicated; it represents an active regimen with a low toxicity profile that offers the clinician a much needed treatment with a better risk-to-benefit ratio that can be safely proposed for elderly patients with extensive visceral disease.

**Weekly Versus Every-3-Weeks Docetaxel Administration: Randomized Phase II Study**

A randomized phase II study was conducted at 10 centers in Spain and Belgium to compare weekly with every-3-weeks docetaxel administration in patients with MBC, and was recently reported in extended form [39]. Eighty-three...
<table>
<thead>
<tr>
<th>Study</th>
<th>Patient characteristics (% of patients)</th>
<th>Treatment regimen</th>
<th>No. of evaluable patients</th>
<th>ORR (CR)</th>
<th>Grade ≥3 toxicity in ≥5% of patients (% of patients)</th>
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<tbody>
<tr>
<td>Burstein et al.</td>
<td>Previously treated MBC (66%); ECOG PS score 0–1 (97%); ER positive (65%); ≥3 metastatic sites (65%)</td>
<td>Docetaxel, 40 mg/m² i.v. weekly × 6 weeks followed by 2-week rest</td>
<td>29</td>
<td>41% (0)</td>
<td>Neutropenia (14%), fatigue/asthenia (14%)</td>
</tr>
<tr>
<td>Stemmler et al.</td>
<td>Previously treated MBC (85%); ECOG PS score ≤2</td>
<td>Docetaxel, 35 mg/m² i.v. weekly × 6 weeks followed by 2-week rest; then docetaxel, 35 mg/m² i.v. weekly × 3 weeks followed by 2-week rest</td>
<td>100</td>
<td>42% (10%)</td>
<td>Neutropenia (1% of cycles), anemia (6% of cycles), alopecia (25%), asthenia (6%), pain (7%)</td>
</tr>
<tr>
<td>Aihara et al.</td>
<td>Previously treated MBC (92%); ECOG PS score 0–1 (97%); ≥2 metastatic sites (52%)</td>
<td>Docetaxel, 40 mg/m² i.v. weekly × 3 weeks; cycles repeated every 4 weeks</td>
<td>37</td>
<td>38% (0)</td>
<td>Neutropenia (19%)</td>
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<td>Hainsworth et al.</td>
<td>Previously treated MBC (25%); median age, 74 years (range, 50–88); ECOG PS score 0–1 (78%); ER-positive (56%)</td>
<td>Docetaxel, 36 mg/m² i.v. weekly × 6 weeks, followed by 2-week rest</td>
<td>36</td>
<td>36% (3%)</td>
<td>Leukopenia (5%), anemia (5%), fatigue/asthenia (20%), diarrhea (10%), nausea/vomiting (7%), peripheral edema (7%)</td>
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<td>Estevez et al.</td>
<td>Previously untreated LABC; median age, 53 years (range, 28–73); ECOG PS score 0 (98%); stage II, 87%; stage III 13%</td>
<td>Docetaxel, 40 mg/m² i.v. weekly for the first 6 weeks of an 8-week cycle for 2 cycles</td>
<td>56</td>
<td>68% (pCR rate)</td>
<td>Neutropenia (4%), asthenia (16%), nail disorders (16%), cutaneous toxicity (14%)</td>
</tr>
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<td>D’Hondt et al.</td>
<td>Heavily pretreated MBC; frail or elderly patients (over 70 years of age); median age, 63 years (range, 43–82); ECOG PS score 1 (34%); 2 (55%), and 3 (9%); ER-positive, 62%</td>
<td>Docetaxel, 36 mg/m² once weekly for the initial 6 weeks, followed by 1-week rest</td>
<td>37</td>
<td>30% (0%)</td>
<td>Neutropenia (22%), thrombocytopenia (6%)</td>
</tr>
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<td>Ford et al.</td>
<td>Anthracycline-exposed MBC; second-line treatment (54%); median age 53 years (range, 34–74)</td>
<td>Docetaxel, 35 mg/m² once weekly × 6 weeks, followed by 2-week rest</td>
<td>42</td>
<td>29% (NR)</td>
<td>Fatigue 16%, stomatitis 7%, diarrhea 14%, cutaneous toxicity 19%</td>
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<td>Ramos et al.</td>
<td>Anthracycline-resistant LABC/MBC</td>
<td>Docetaxel, 40 mg/m² for 6 consecutive weeks, followed by 2-week rest in first 18 patients; reduced to 36 mg/m² for the next 17 patients</td>
<td>35</td>
<td>34% (6%)</td>
<td>Neutropenia (17%), asthenia, nail, ocular, and skin disorders</td>
</tr>
<tr>
<td>Kim et al.</td>
<td>Pretreated recurrent breast cancer; Japanese patients</td>
<td>Docetaxel, 40 mg/m² once weekly × 3 weeks, followed by 1-week rest</td>
<td>36</td>
<td>39% (3.4%)</td>
<td>Neutropenia (16.2%), dysgeusia (18.9%), dacryorhea (16.2%), auditory disturbance (16.2%)</td>
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<td>Jackisch et al.</td>
<td>Pretreated MBC (100%); second-line treatment (98.1%); median age 58 years (range, 31–80); Karnofsky performance status 60%–100%</td>
<td>Weekly docetaxel, 35–40 mg/m²</td>
<td>60</td>
<td>33.4% (6.7%)</td>
<td>Neutropenia (3.5%), alopecia (14.3%)</td>
</tr>
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</table>

Abbreviations: CR, complete response; ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; LABC, locally advanced breast cancer; NR, not reported; ORR, overall response rate; pCR, pathologic complete response; PS, performance status.
patients who had received prior neoadjuvant, adjuvant, and/or first-line chemotherapy for metastatic disease (alkylating agent, anthracycline, or both) were enrolled [39]. Patients were randomized to either the weekly regimen (docetaxel, 40 mg/m² by 30-minute i.v. infusion weekly for six consecutive weeks followed by a 2-week rest) or the every-3-weeks regimen (docetaxel, 100 mg/m² by 1-hour i.v. infusion every 3 weeks). For the weekly regimen, 8 mg dexamethasone (or equivalent) was administered orally in the morning, 1-hour preinfusion, and in the evening of the dosing day. For the every-3-weeks regimen, six 8-mg doses of dexamethasone were administered orally beginning the evening prior to dosing and ending the evening of day 2 [39].

Approximately 20% of patients had received prior chemotherapy for metastatic disease. Two patients achieved complete responses and 12 achieved partial responses, for overall response rates (ORRs) of 34% (95% confidence interval [CI], 21%–51%) in the weekly group and 33% (95% CI, 20%–50%) in the every-3-weeks group. At a median follow-up of 10 months, the median TTP for patients treated with weekly docetaxel was 5.7 months, while it was 5.3 months for those treated with every-3-weeks docetaxel; the median times to treatment failure were 4.1 and 4.9 months, respectively. The incidence of all grade 3–4 adverse events was higher in the every-3-weeks group than in the weekly group (96 versus 44), and the number of patients with grade 3–4 adverse events was also greater in the every-3-weeks group (31 versus 20). The incidences of grade 3–4 adverse events in the weekly and every-3-weeks groups, respectively, were as follows: neutropenia without fever, 2% and 17%; neutropenia, 2% and 17%; febrile neutropenia, 5% and 20%; and stomatitis, 7% and 17%. The weekly and every-3-weeks regimens, respectively, had similar rates of other clinically relevant toxicities, such as fatigue (68% and 81%), nail toxicity (56% and 56%), tearing or watery eyes (53% and 39%), alopecia (78% and 87%), and edema (33% and 33%). Although both schedules were well tolerated, the weekly schedule had lower incidences of grade 3–4 neutropenia, neutropenic fever, stomatitis, and neurosensory toxicity [39].

Another study from Egypt randomized 30 patients to receive either weekly docetaxel (35 mg/m² for 6 weeks then 2 weeks rest) or docetaxel (100 mg/m²) every 3 weeks. The authors observed high response rates in both arms, 86.7% and 73.3%, respectively (p = .326), with less neutropenia for the weekly regimen (p = .02), while fatigue, nausea, vomiting, and fluid retention were more commonly encountered with the standard every-3-weeks schedule [40]. We can conclude that there is randomized evidence that the weekly docetaxel regimen is at least as effective as the every-3-weeks regimen and causes less neutropenia, neutropenic fever, stomatitis, and neurologic toxicity, but requires weekly outpatient visits.

**Weekly Docetaxel-Based Combination Regimens in MBC**

The promising results of studies evaluating weekly docetaxel as a single agent provide the rationale for evaluating weekly docetaxel in combination chemotherapy regimens for MBC. Phase I and phase II trials have assessed weekly docetaxel regimens in combination with anthracyclines [41–44], gemcitabine (Gemzar®; Eli Lilly and Company, Indianapolis, http://www.lilly.com) [45–49], vinorelbine (Navelbine®; GlaxoSmithKline, Philadelphia, http://www.gsk.com) [46, 50], and trastuzumab (Herceptin®; Genentech, Inc., South San Francisco, CA, http://www.gene.com) [51]. The combination of two inhibitors of microtubule function, docetaxel and estramustine (Emcyt®, Pfizer Pharmaceuticals, New York, http://www.pfizer.com) proved to be too toxic to be investigated further [52]. Some of the reported results are summarized in Table 2.

These studies indicate that weekly docetaxel in combination with anthracyclines, gemcitabine, or vinorelbine is feasible. The activity in both previously treated and untreated patients with MBC is impressive (up to 85%–90% in untreated patients [41, 42]). However, this level of activity is achieved at the cost of higher toxicity, with higher percentages of neutropenia, febrile neutropenia, asthenia, and alopecia. These combination regimens may constitute an option for young, fit patients presenting with extensive, life-threatening disease, for whom a rapid and important tumor volume reduction is needed.

**Docetaxel–Trastuzumab Combinations**

Several phase II studies have evaluated the activity and tolerability of weekly docetaxel in combination with trastuzumab in women with MBC overexpressing human epidermal growth factor receptor-2 (HER-2). Esteva and colleagues evaluated docetaxel (35 mg/m² per week) plus trastuzumab (loading dose of 4 mg/kg, followed by 2 mg/kg thereafter) in 30 women with HER-2–overexpressing MBC (Table 2) [51]. Nineteen patients achieved partial responses, for an ORR of 63% (95% CI, 44%–80%) [51]. In the subgroup of 24 patients who were HER-2 positive by fluorescence in situ hybridization (FISH), the ORR was 67% [51]. When response was analyzed by HER-2 extracellular domain level, those with baseline levels >14.9 ng/ml (n = 21) had an ORR of 76%, compared with a 33% response rate in patients with levels below this threshold (p = .04) [51]. The median TTP was 9 months [51]. This
Table 2. Selected phase I/II studies of weekly docetaxel-based combinations in metastatic breast cancer (MBC)

<table>
<thead>
<tr>
<th>Study/phase</th>
<th>Patient characteristics (% of patients)</th>
<th>Treatment regimen</th>
<th>No. of evaluable patients</th>
<th>ORR (CR)</th>
<th>Grade ≥3 toxicity in ≥5% of patients (% of patients)</th>
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<tr>
<td><strong>Anthracyclines</strong></td>
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<tr>
<td>Ito et al. [41]</td>
<td>Previously treated MBC (12%); median age, 51 years (range, 27–68); prior adjuvant CT (20%); ECOG PS score 0–1 (96%); ≥3 metastatic sites (28%)</td>
<td>Docetaxel, 20–30 mg/m² i.v., plus doxorubicin, 15–20 mg/m² i.v. push weekly × 6 weeks</td>
<td>24</td>
<td>56% (0%)</td>
<td>Neutropenia (79%, grade 4 16%), anorexia (8%), vomiting (8%)</td>
</tr>
<tr>
<td>Wenzel et al. [42]</td>
<td>Previously untreated primary (61%) and MBC (39%); median age, 51 years (range, 37–71)</td>
<td>Docetaxel, 25–40 mg/m² i.v., plus epirubicin, 25–35 mg/m² i.v., weekly × 6 weeks followed by 1-week rest for up to 4 cycles</td>
<td>20a 13a</td>
<td>90% (10%) 62% (NR)</td>
<td>Leukopenia (22% of cycles), lymphocytopenia (75% of cycles), alopecia (100% of cycles)</td>
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<tr>
<td>Yardley et al. [43]</td>
<td>Previously untreated LABC (clinical T1c-T4d and/or N0–3 disease); six cases of inflammatory breast cancer</td>
<td>Docetaxel, 30 mg/m², plus gemcitabine, 800 mg/m², given on days 1, 8, and 15; cycles repeated every 21 days × 4 cycles</td>
<td>34</td>
<td>85% (pCR, 24%); 16 patients pN0</td>
<td>Neutropenia (41%), febrile neutropenia (12%), anemia (21%), thrombocytopenia (9%)</td>
</tr>
<tr>
<td>Holmes et al. [44]</td>
<td>Previously treated MBC (50%); median age, 60 years (range, 30–84); prior adjuvant CT (48%); ECOG PS score 0–1 (98%)</td>
<td>Docetaxel, 25 mg/m², and pegylated liposomal doxorubicin, 10 mg/m², weekly for 2 weeks followed by 1-week rest in each 28-day cycle</td>
<td>48</td>
<td>43% (4%)</td>
<td>Fatigue (14%), hand-foot syndrome (6%)</td>
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<td>Brugnatelli et al. [45]</td>
<td>Previously treated MBC (100%); median age, 56 years (range, 33–75); prior anthracyclines (100%); prior taxanes (61%); WHO PS score 0–1 (83%); ≥2 metastatic sites (39%)</td>
<td>Docetaxel, 30–40 mg/m² i.v., plus gemcitabine, 800 mg/m² i.v., days 1, 8, and 15; cycles repeated every 4 weeks × 6 cycles</td>
<td>12</td>
<td>58% (8%)</td>
<td>Leukopenia (50%), thrombocytopenia (22%), asthenia (44%), alopecia (39%), stomatitis (28%), diarrhea (17%)</td>
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<td>Frasci et al. [46]</td>
<td>LABC (24%) or MBC (75%) previously treated with anthracyclines; median age, 49 years (range, 33–70)</td>
<td>Docetaxel, 30–45 mg/m² i.v., plus gemcitabine, 1,000 mg/m² i.v., weekly for 2 weeks followed by 1-week rest × 3–6 cycles</td>
<td>19</td>
<td>15% (0%) 13% (0%)</td>
<td>Neutropenia (37%), thrombocytopenia (16%). Neutropenia (53%), neutropenic sepsis (13%). Thrombocytopenia (26%)</td>
</tr>
<tr>
<td>Kornek et al. [50]</td>
<td>Previously treated (26%) and untreated (74%) MBC; median age, 59 years (range, 36–75); WHO PS score 0–1 (45%); ≥2 metastatic sites (65%)</td>
<td>Docetaxel, 30–40 mg/m² i.v., plus vinorelbine, 25 mg/m² i.v., weekly for 2 weeks followed by 1-week rest × 3–6 cycles</td>
<td>42 (first line) 15 (second line)</td>
<td>64% (19%) 53% (20%)</td>
<td>Leukopenia (53%), neutropenia (64%), alopecia (32%), infection (7%)</td>
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<td>Ghosn et al. [101]</td>
<td>Previously untreated MBC or LABC; median age, 58 years (range, 36–79); WHO PS score 0–1 (100%); prior adjuvant CT (67%)</td>
<td>Docetaxel, 35 mg/m², weekly × 12 weeks after 4 cycles of navelbine and capectabinate (i.v. navelbine, 25 mg/m² on days 1 and 8, plus capectabinate, 825 mg/m² twice a day from days 1–14 every 3 weeks)</td>
<td>30</td>
<td>80% (3%)</td>
<td>Neutropenia (14%), febrile neutropenia (8%)</td>
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<tr>
<td><strong>Gemcitabine/vinorelbine</strong></td>
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<tr>
<td>Frasci et al. [46]</td>
<td>LABC (24%) or MBC (75%) previously treated with anthracyclines; median age, 49 years (range, 33–70)</td>
<td>Docetaxel, 30–45 mg/m² i.v., plus gemcitabine, 1,000 mg/m² i.v., weekly for 2 weeks followed by 1-week rest × 3–6 cycles</td>
<td>19</td>
<td>15% (0%) 13% (0%)</td>
<td>Neutropenia (37%), thrombocytopenia (16%). Neutropenia (53%), neutropenic sepsis (13%). Thrombocytopenia (26%)</td>
</tr>
<tr>
<td>Kornek et al. [50]</td>
<td>Previously treated (26%) and untreated (74%) MBC; median age, 59 years (range, 36–75); WHO PS score 0–1 (45%); ≥2 metastatic sites (65%)</td>
<td>Docetaxel, 30–40 mg/m² i.v., plus vinorelbine, 25 mg/m² i.v., weekly for 2 weeks followed by 1-week rest × 3–6 cycles</td>
<td>42 (first line) 15 (second line)</td>
<td>64% (19%) 53% (20%)</td>
<td>Leukopenia (53%), neutropenia (64%), alopecia (32%), infection (7%)</td>
</tr>
<tr>
<td>Ghosn et al. [101]</td>
<td>Previously untreated MBC or LABC; median age, 58 years (range, 36–79); WHO PS score 0–1 (100%); prior adjuvant CT (67%)</td>
<td>Docetaxel, 35 mg/m², weekly × 12 weeks after 4 cycles of navelbine and capectabinate (i.v. navelbine, 25 mg/m² on days 1 and 8, plus capectabinate, 825 mg/m² twice a day from days 1–14 every 3 weeks)</td>
<td>30</td>
<td>80% (3%)</td>
<td>Neutropenia (14%), febrile neutropenia (8%)</td>
</tr>
<tr>
<td><strong>Trastuzumab</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esteva et al. [51]</td>
<td>HER-2–positive MBC; median age, 45 years (range, 33–78); prior adjuvant CT (63%); prior CT for MBC (19%); KPS 80–90 (83%); ≥2 metastatic sites (82%)</td>
<td>Docetaxel, 35 mg/m² i.v., plus trastuzumab, 4 mg/kg i.v. loading dose, then 2 mg/kg i.v. following docetaxel; doses repeated weekly × 3 weeks followed by 1-week rest until PD or toxicity</td>
<td>30</td>
<td>63% (0%)</td>
<td>Granulocytopenia (26%), fatigue (20%), diarrhea (6%), hypersensitivity (6%)</td>
</tr>
</tbody>
</table>
Table 2. (continued)

<table>
<thead>
<tr>
<th>Study/phase</th>
<th>Patient characteristics (% of patients)</th>
<th>Treatment regimen</th>
<th>No. of evaluable patients</th>
<th>ORR (CR)</th>
<th>Grade ≥3 toxicity in ≥5% of patients (% of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eniu et al. [53]</td>
<td>HER-2–positive MBC; median age, 53 years (range, 35–73); prior adjuvant CT (52%); prior CT for MBC (24%)</td>
<td>Docetaxel, 35 mg/m² i.v., plus trastuzumab, 4 mg/kg i.v. loading dose, then 2 mg/kg i.v.; doses repeated weekly × 6 weeks followed by 2-week rest</td>
<td>19</td>
<td>63% (11%)</td>
<td>Neutropenia (5%), fatigue (14%), diarrhea (14%), nausea (5%), vomiting (5%), motor neuropathy (5%), sensory neuropathy (5%), dyspepsia (5%)</td>
</tr>
<tr>
<td>Raab et al. [54]</td>
<td>HER-2–positive MBC; prior adjuvant anthracycline therapy</td>
<td>Every-3-weeks group: median age, 49 years (range, 25–62); WHO PS score 0 (69%)</td>
<td>Docetaxel, 100 mg/m² i.v., every 3 weeks plus trastuzumab, 4 mg/kg i.v. loading dose day 1, then 2 mg/kg i.v. weekly</td>
<td>13</td>
<td>69% (NR)</td>
</tr>
<tr>
<td>Tedesco et al. [55]</td>
<td>HER-2–positive MBC; median age, 53 years (range, 35–73); ECOG PS score 0 (54%); prior adjuvant CT (38%); prior CT for MBC (15%)</td>
<td>Docetaxel, 35 mg/m² weekly × 6 weeks with 2-week rest × 3 cycles plus trastuzumab, 4 mg/kg i.v. loading dose daily, then 2 mg/kg i.v. weekly</td>
<td>26</td>
<td>50% (8%)</td>
<td>Leukopenia (8%), neutropenia (12%), neuropathy (8%), fatigue (12%), altered taste/smell (8%), pleural effusion (8%)</td>
</tr>
<tr>
<td>Bines et al. [56]</td>
<td>HER-2–positive stage III previously untreated LABC; median age, 45 years (range, 21–63)</td>
<td>Docetaxel, 36 mg/m² 2 weeks × 6 followed by 2-week break for 2 cycles, plus trastuzumab, 4 mg/kg 1 week, followed by 2 mg/kg weekly × 14</td>
<td>33</td>
<td>70% (24%)</td>
<td>pCR, 12%</td>
</tr>
<tr>
<td>Raff et al. [57]</td>
<td>HER-2–positive MBC; prior adjuvant CT (NR); prior CT for MBC (NR)</td>
<td>Docetaxel, either 33 mg/m² or 40 mg/m² weekly × 3 weeks plus trastuzumab, 4 mg/kg on day 1 then 2 mg/kg on days 8 and 15 of each 28-day cycle</td>
<td>17</td>
<td>59% (NR)</td>
<td>Neutropenia (21%), pulmonary toxicity (12%), hyperglycemia (10%)</td>
</tr>
<tr>
<td>Yardley et al. [58]</td>
<td>HER-2–positive MBC; prior adjuvant CT (9 patients); median age, 58 years (range, 41–79)</td>
<td>Docetaxel, either 33 mg/m² or 40 mg/m² weekly × 3 weeks with 1-week break</td>
<td>35</td>
<td>21% (NR)</td>
<td></td>
</tr>
<tr>
<td>Wenzel et al. [59]</td>
<td>HER-2–positive MBC; previously untreated; median age, 59.5 years (range, 36–78)</td>
<td>Docetaxel, 35 mg/m², and epirubicin, 30 mg/m², weekly × 6 weeks followed by 1 week off therapy plus weekly trastuzumab, 4 mg/kg body weight loading dose, 2 mg/kg/week maintenance dose</td>
<td>14</td>
<td>86% (NR)</td>
<td>pCR, 7%</td>
</tr>
</tbody>
</table>

*20 patients received neoadjuvant therapy and 13 patients received therapy for metastatic disease.

*G-CSF given depending on absolute neutrophil count (1,000–2,000/ml) on day of therapy.

Abbreviations: CR, complete response; CT, chemotherapy; ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; KPS, Karnofsky performance status; LABC, locally advanced breast cancer; NR, not reported; ORR, overall response rate; PD, progressive disease; PS, performance status; WHO, World Health Organization.
suggests that the level of HER-2 extracellular domain should be investigated as a predictive factor in HER-2–overexpressing patients.

In a second phase II trial, a similar regimen was investigated, and preliminary data from 21 patients (total, 69 cycles; median follow-up, 9 months) were reported [53]. The ORR in 19 evaluable patients was 63%, and only one grade 3–4 hematologic toxicity occurred (grade 3 neutropenia). Fatigue and diarrhea were the most common grade 3 non-hematologic toxicities (each occurring in three patients), and one case of grade 4 dyspepsia/ulcer was reported [53].

A phase II multicenter randomized study conducted in Germany compared every-3-weeks docetaxel and trastuzumab with a weekly regimen as first-line therapy for patients with anthracycline-pretreated, HER-2–overexpressing MBC (Table 2) [54]. The ORRs were 69% (95% CI, 39%–91%) in the every-3-weeks group and 54% (95% CI, 23%–83%) in the weekly group [54]. The median TTPs were 215 days and 335 days in the every-3-weeks and weekly groups, respectively. Grade 3–4 hematologic toxicities were frequent in the every-3-weeks group, including neutropenia, leukopenia, febrile neutropenia, and anemia. Only one grade 3–4 hematologic toxicity (leukopenia) occurred in the weekly group [54].

A multi-institutional phase II trial conducted in the U.S. reported an ORR of 50%, including two complete responses and 11 partial responses, with a weekly docetaxel–trastuzumab regimen as first- or second-line therapy for 26 women with previously treated, HER-2–overexpressing MBC (Table 2) [55]. Among patients that were HER-2 3+ by immunohistochemistry (IHC) (n = 19), the ORR was 63%, compared with a 14% response rate (one of seven patients) among those with HER-2 2+ tumors. The ORR among patients with HER-2–positive tumors by FISH was 64%. For the whole studied population, the median TTP was 12.4 months, and the median overall survival was 22.1 months. The regimen was well tolerated. A Brazilian multicenter phase II study evaluated weekly docetaxel and trastuzumab as primary therapy in 33 patients with locally advanced, stage III HER-2–overexpressing breast cancer for response rate, pathologic response, and safety [56]. The patients were 70% stage IIIIB and 30% stage IIIA–large T3 tumors, all HER-2 3+ as determined by IHC (HercepTest™; DakoCytomation, Glostrup, Denmark, http://www.dako.dk). In this untreated patient population, the ORR was 70% (23/33), with a 46% partial response rate and a 24% complete response rate. The pathological complete response rate was 12% (4/33). Eight patients (24%) had negative nodes at the time of surgery. The treatment was well tolerated with only one patient (4%) experiencing grade 4 toxicity (anasarca). The most frequent grade 3 adverse events were alopecia (15%), neutropenia (9%), and headache (9%). Another phase II study was designed to determine the efficacy and toxicity of weekly docetaxel in MBC patients when given alone (for HER-2–negative disease) or with trastuzumab (for HER-2–overexpressing disease) [57]. Patients with MBC received docetaxel given on two different schedules, either 33 mg/m2 or 40 mg/m2, weekly for 3 weeks with 1 week off. Patients with HER-2–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. Fifty-two patients were treated with docetaxel alone (35 patients) or in combination with trastuzumab (17 patients). Partial responses occurred in 7 of the 35 patients treated with docetaxel alone, including 3 of the 19 taxane-pretreated patients and 4 of the 16 taxane-naïve patients. Partial responses occurred in 10 of 17 patients (59%; 95% CI, 34%–82%) treated with docetaxel and trastuzumab. The most common grade 3–4 toxicities, occurring in at least 10% of patients, included neutropenia (21%), pulmonary toxicity (12%), and hyperglycemia (10%). The median times to disease progression were 4.5 months (95% CI, 2.5–6.5 months) in the docetaxel group and 8.5 months (95% CI, 4.5–12.5 months) in the docetaxel–trastuzumab group.

Building on preclinical data suggesting synergism between vinorelbine and docetaxel plus trastuzumab, Yardley et al. performed a phase II trial evaluating weekly trastuzumab administered with docetaxel and vinorelbine as first-line therapy of HER-2–positive MBC patients [58]. Patients received vinorelbine (25 mg/m2) and docetaxel (30 mg/m2) on days 1 and 8 every 21 days. Trastuzumab was given at a dose of 4 mg/kg on day 1 followed by 2 mg/kg per week thereafter. Grade 3–4 toxicities included neutropenia (70%), febrile neutropenia (21%), fatigue (14%), hyperglycemia (10%), and myalgias (7%). At the time of the analysis of 29 evaluable patients, the response rate was 75%, with 10 (42%) partial responses and eight (33%) complete responses. Four patients had stable disease and two had disease progression. Three deaths resulting from intercurrent illness were noted (myocardial infarction, renal failure, and gastrointestinal bleed). The progression-free survival duration was 11.3 months.

To further improve the clinical and pathologic response rates, a pilot study evaluated the safety and efficacy of preoperative epidoxorubicin (epirubicin; Ellence®, Pfizer Pharmaceuticals) and docetaxel plus trastuzumab in 14 outpatient breast cancer patients [59]. Preoperative treatment consisted of weekly trastuzumab (4 mg/kg body weight loading dose, 2 mg/kg per week maintenance dose) in combination with weekly epidoxorubicin (30 mg/m2) and docetaxel (35 mg/m2) once a week for 6 weeks.
lowed by 1 week off therapy. Because of possible cardiotoxic effects of the anthracycline-containing regimen in combination with trastuzumab, left ventricular ejection fraction (LVEF) was monitored twice during treatment (at the beginning and end of treatment) and every 6 months after finishing therapy. Outpatient epidoxorubicin and docetaxel plus trastuzumab were well tolerated. In two patients, WHO grade IV leukocytopenia was observed. WHO grade III toxicities consisted of leukocytopenia (10%) and stomatitis (3%). Cardiac toxicity or allergic reactions were not observed in any of the patients. Twelve (86%) of the 14 patients responded, leading to breast-conserving surgery in 11 of 14 patients (79%), with one pathological complete response.

In summary, there is compelling evidence that the docetaxel–trastuzumab combination is extremely active when used as a weekly treatment in HER-2–positive patients, with response rates in the range of 55%–75%, even in pretreated patients. The toxicity profile is very favorable, with few grade 3–4 toxicities, supporting the use of this regimen as a front-line treatment for this patient population.

**Randomized Phase III Trials of Weekly Docetaxel**

In an attempt to supply data for the optimal management of MBC, a phase III trial was designed in Germany for MBC patients no longer eligible for anthracyclines [60]. Randomized patients received either docetaxel (35 mg/m²) or vinorelbine (30 mg/m²) weekly—6 for four cycles of 8 weeks’ duration. Crossover was offered after progression. The primary end point was TTP; other end points were survival, response, toxicity, and quality of life. Of the reported 112 patients, 57 received vinorelbine, and 55 received docetaxel. Sixty-five patients crossed over because of progressive disease and received vinorelbine (31 patients) or docetaxel (34 patients) as second therapy. The overall median follow-up was 230 days (5–1,588). Before or without crossing over, vinorelbine patients had a median of seven doses for a TTP of 81 days (95% CI, 67–99), while docetaxel patients had a median of 11 doses. Overall survival for initial vinorelbine versus docetaxel was 253 days (95% CI, 173–331) versus 288 days (95% CI, 231–424), (p = not significant [ns]). The 1-year survival rates were 31% for vinorelbine (95% CI, 20%–46%) and 44% for docetaxel (95% CI, 30%–60%). More vinorelbine patients (42%) than docetaxel patients (18%) had disease progression as their best response (p = .00751). After crossing over, docetaxel led to a higher objective response rate (35% versus 3%, p ≤ .0014, Fisher’s exact test, double sided), but again without significant benefit in terms of TTP or overall survival. Generally, vinorelbine resulted in more treatment delays (76% versus 46%) and more leukopenia (61% versus 10%) and neutropenia (43% versus 7%), grade 3–4, but less mucositis/stomatitis (1% versus 8%, all p < .05, Fisher’s exact test, double sided).

**Weekly Paclitaxel in MBC**

**Weekly Single-Agent Paclitaxel**

Like docetaxel, paclitaxel administered on a weekly schedule has been studied extensively both as a single agent and in combination chemotherapy. Common toxicities associated with every-3-weeks paclitaxel dosing include neutropenia, neuropathy, and arthralgia/myalgia. Weekly dosing of paclitaxel has been evaluated as a means to increase dose density and improve tolerability.

Several phase II studies have evaluated weekly paclitaxel administration as single-agent therapy in patients with MBC (Table 3). Seidman and colleagues evaluated continuous paclitaxel therapy, 100 mg/m² per week, in 30 women with MBC who had received prior adjuvant and/or metastatic therapy (Table 3) [61]. Three patients in that study achieved complete responses (10%) and 16 achieved partial responses (43%) for an ORR of 53% (95% CI, 34%–72%). Therapy was generally well tolerated. Grade 3–4 neutropenia occurred in four patients, with no episodes of febrile neutropenia. There was no evidence of cumulative neutropenia and no cases of thrombocytopenia. The only frequent grade 3 nonhematologic toxicity was neurosensory toxicity in seven patients (24%), five of whom had received paclitaxel doses of 110–120 mg/m² [61].

A phase II trial reported on the use of weekly paclitaxel (100 mg/m²) administered as first-line chemotherapy for MBC [62]. Thirty-five patients, who may previously have received adjuvant chemotherapy (but not taxane-containing regimens), were treated with a median of 14 infusions per patient, at a mean delivered dose intensity of 94 mg/m² per week. In 33 assessable patients, a complete response was observed in one patient and partial responses were seen in 12 patients, producing an ORR of 40%. Stable disease was observed in 17 patients, nine of whom were stabilized for more than 24 weeks. Thus, clinical benefit was observed in 67% of the patients. TTP was 189 days, the duration of response was 180 days, and overall survival was 544 days. Five patients developed grade 3 neutropenia and five patients developed grade 3 neurotoxicity.

An Italian phase II study reported a single-institution experience with paclitaxel administered weekly at a dose of 90 mg/m² [63] in 58 patients with advanced breast cancer or MBC without prior taxane exposure. The authors observed a response rate of 44% in the subpopulation of patients previously treated with anthracyclines (52 patients).
Table 3. Selected phase II/III studies of weekly single-agent paclitaxel in metastatic breast cancer (MBC)

<table>
<thead>
<tr>
<th>Study/phase</th>
<th>Patient characteristics (% of patients)</th>
<th>Treatment regimen</th>
<th>No. of evaluable patients</th>
<th>ORR (CR)</th>
<th>Grade ≥3 toxicity in ≥5% of patients (% of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seidman et al. [61] Phase II</td>
<td>Previously treated (43%) and untreated (57%) MBC; median age, 57 years (range, 35–74); median KPS, 90 (range, 70–100); ≥3 metastatic sites (24%)</td>
<td>Paclitaxel, 100 mg/m² i.v. weekly until progression</td>
<td>30</td>
<td>53% (10%)</td>
<td>Leukopenia (17%), neutropenia (14%), neurosensory (24%), hyperglycemia (7%)</td>
</tr>
<tr>
<td>Wist et al. [62] Phase II</td>
<td>Previously untreated MBC; median age, 53 (range, 33–68); prior adjuvant CT (60%); no prior CT for MBC; ≥2 metastatic sites (40%)</td>
<td>Paclitaxel, 100 mg/m² i.v. weekly until progression</td>
<td>33</td>
<td>40% (3%)</td>
<td>Neutropenia (14%), neurotoxicity (14%)</td>
</tr>
<tr>
<td>Akerley et al. [68] Phase II</td>
<td>Previously untreated MBC or unresectable LABC; median age, 58 years</td>
<td>Paclitaxel, 175 mg/m² i.v. weekly × 6 weeks followed by 2-week break; cycles repeated until PD</td>
<td>MBC: 18</td>
<td>78% (11%)</td>
<td>Neutropenia (65%), grade 2–3 myalgia (25%), grade 2–3 hyperglycemia (19%), grade 2–3 rash (16%), grade 2–3 mucositis (16%), grade 2–3 nausea (13%), grade 2–3 diarrhea (13%)</td>
</tr>
<tr>
<td>Perez et al. [69] Phase II</td>
<td>Previously treated (69%) and untreated (31%) MBC; mean age, 60 years (range, 31–88); ECOG PS score 0–1 (88%); ≥3 metastatic sites (46%); prior anthracyclines (72%); prior taxanes (25%)</td>
<td>Paclitaxel, 80 mg/m² i.v. weekly × 4 weeks; cycles repeated until PD or prohibitive toxicity</td>
<td>177</td>
<td>22% (2%)</td>
<td>Neutropenia (15%), anemia (9%), neuropathy (9%)</td>
</tr>
<tr>
<td>ten Tije et al. [71] Phase II</td>
<td>Hormone-refractory elderly (≥70 years) MBC; median age, 77 (range, 71–84); prior adjuvant CT (5%); no prior CT for MBC; ≥3 metastatic sites (50%)</td>
<td>Paclitaxel, 80 mg/m² administered weekly on days 1, 8, and 15 of a 28-day cycle</td>
<td>23</td>
<td>38% (0%)</td>
<td>Neutropenia (12%), anemia (12%), neuropathy (4%)</td>
</tr>
<tr>
<td>Sikov et al. [72] Phase III</td>
<td>MBC; median age, 57 years (range, 30–86); prior adjuvant CT (57%); prior CT for MBC (14%)</td>
<td>Paclitaxel, 150 mg/m² i.v. weekly × 6 weeks followed by 2-week rest; cycles repeated every 8 weeks × 2</td>
<td>72</td>
<td>50% (NR)</td>
<td>Neutropenia (67%), febrile neutropenia (8%), anemia (6%), neuropathy (17%), diarrhea (5%)</td>
</tr>
<tr>
<td>Lombardi et al. [63] Phase III</td>
<td>Previously treated MBC; anthracycline exposure (90%); median age, 54 years (range, 38–72)</td>
<td>Paclitaxel, 150 mg/m² i.v. weekly × 2 followed by 1-week rest; cycles repeated every 3 weeks × 5</td>
<td>70</td>
<td>50% (NR)</td>
<td>Neutropenia (69%), febrile neutropenia (14%), anemia (7%), neuropathy (21%), diarrhea (19%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Paclitaxel, 80 mg/m² weekly × 15 weeks</td>
<td>74</td>
<td>42% (NR)</td>
<td>Neutropenia (18%), anemia (8%), neuropathy (7%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Paclitaxel, 90 mg/m² i.v. weekly</td>
<td>58</td>
<td>48% (8%)</td>
<td>Neutropenia (15%)</td>
</tr>
</tbody>
</table>

*Paclitaxel doses could be increased or decreased at 10-mg/m² increments after 4 weeks, then every 2 weeks.

Abbreviations: CR, complete response; CT, chemotherapy; ECOG, Eastern Cooperative Oncology Group; KPS, Karnofsky performance status; LABC, locally advanced breast cancer; NR, not reported; ORR, overall response rate; PD, progressive disease; PS, performance status.
A multicenter study from Japan enrolled 74 patients with advanced breast cancer or MBC, of which 66.2% had received prior anthracyclines, in a study of weekly paclitaxel (80 mg/m²) for 3 weeks followed by a 1-week rest [64]. The ORR was 40.5%, including a 4.1% complete response rate, with a median overall survival of 15.8 months.

Other studies reported similar results [65–67]. High-dose weekly paclitaxel (175 mg/m² per week) without prophylactic growth factor support was evaluated in 34 patients with previously untreated metastatic or unresectable locally advanced breast cancer (LABC) (Table 3) [68]. The ORR was 78% (95% CI, 60%–91%), with five complete responses (16%) [68]. No significant difference in response was observed between patients with metastatic disease and those with LABC, between those with visceral disease and those with soft tissue disease, or between those who had had prior anthracycline-based adjuvant therapy and those who had not [68]. Grade 3–4 neutropenia developed in 22 patients (65%), with two patients requiring hospitalization for febrile neutropenia; grade 3 neurotoxicity was observed in four patients. This high-dose weekly regimen more than doubled the dose intensity delivered with standard every-3-weeks paclitaxel and achieved response rates comparable with those produced by combination chemotherapy.

A large, multicenter phase II study by Perez and colleagues investigated the activity and tolerability of weekly paclitaxel (80 mg/m² per week) in 212 women with previously treated MBC (Table 3) [69]. Overall, 25% of the patients had previously received taxanes using an every-3-weeks or every-4-weeks schedule, 25% had undergone two prior chemotherapy regimens for MBC, and 9% had received treatment with high-dose chemotherapy and stem cell transplant. In addition, 11% of enrolled patients presented with brain metastases. Paclitaxel was administered once weekly, without breaks, until disease progression or intolerable toxicity. In 177 evaluable patients, the ORR was 21.5% (95% CI, 15.4%–27.5%), with four complete responses [69]. The median TTP and overall survival duration were 142 days and 387 days, respectively. Grade 3–4 toxicities were limited to neutropenia, anemia, and neuropathy, and were seen in 9% of patients [69].

In summary, weekly paclitaxel produced response rates in the range of 22%–53% in pretreated patients, with a median TTP of 5–6 months. The toxicity associated with this regimen was mild and consisted mainly of neutropenia and neuropathy.

**Weekly Paclitaxel in Older Women**

An analysis was conducted on the subset of patients 65 years or older (<65 years \[n = 139, 66\%\] versus ≥65 years \[n = 73, 34\%\]) from the multicenter phase II study of Perez et al. [69] that investigated the activity and tolerability of weekly paclitaxel (80 mg/m² per week) (Table 3) [69]. Paclitaxel was administered once weekly without breaks until disease progression or intolerable toxicity. Baseline characteristics were similar in the two age groups; however, older patients were less likely to have received prior chemotherapy, less likely to have received prior anthracycline- or taxane-based chemotherapy, and more likely to have received prior hormonal therapy (\(p < .005\) compared with the younger patient group for all) [70]. The ORRs were not significantly different statistically between the age groups, and the tolerability profiles were similar [70]. Grade 3–4 neutropenia occurred in 15% of patients of both age groups, and grade 3 neuropathy occurred in 12% and 9% of the older and younger patients, respectively. Other toxicities of a serious nature were uncommon [70].

Similar results were recently reported from another multicenter phase II study performed in The Netherlands, which specifically evaluated the activity and toxicity of weekly paclitaxel as first-line chemotherapy in elderly patients (>70 years of age) with hormone-refractory MBC [71]. Twenty-six patients with MBC received 80 mg/m² paclitaxel administered weekly on days 1, 8, and 15 of a 28-day cycle. Additional cycles were given until disease progression or unacceptable toxicity. The protocol allowed for a dose increase to 90 mg/m² in the absence of toxicity. In 23 patients who were evaluable for response, there were 10 partial responses (38%), nine patients with stable disease (35%), and four patients with disease progression (15%). The median duration of response was 194 days (>6 months). Overall, treatment was relatively well tolerated, but eight patients (32%) had to prematurely discontinue treatment because of fatigue. Neuropathy greater than grade 1 was noted only after five or more cycles in four patients.

Along with aging of the population, breast cancer in elderly patients constitutes a major health problem that will increase in the future. As the paclitaxel weekly regimen seems to be associated with less toxicity than the every-3-weeks schedule, these weekly regimens are very attractive for elderly breast cancer patients.

**Weekly Versus Every-3-Weeks Paclitaxel Administration: Randomized Phase III Study**

A large phase III randomized study compared the efficacy and tolerability of two high-dose weekly paclitaxel regimens with a standard-dose weekly regimen in patients with previously treated or untreated MBC (Table 3) [72]. Patients were stratified according to prior chemotherapy and presence of liver metastases prior to randomization. The mean delivered dose intensities for the 6-week, 2-week, and 15-week regimens were 100.7 mg/m², 108 mg/m², and 76 mg/m² per week,
respectively, with the 6-week and 2-week regimens delivering 25% and 46% higher dose intensities, respectively, than the 15-week regimen. The 6-week and 2-week regimens were associated with greater incidences of neutropenia (grade 4, 40% and 45%, respectively), febrile neutropenia (9% and 13%, respectively), and grade 3 sensory neuropathy (16% and 20%, respectively) than the 15-week regimen (8%, 1%, and 8%, respectively) [72]. High-dose weekly paclitaxel (6-week and 2-week regimens) did not produce a significantly higher ORR or prolong survival, and it was associated with greater toxicity, including neutropenia and neuropathy.

In an effort to determine the relative efficacy of weekly versus every-3-weeks paclitaxel dosing, a randomized phase III Cancer and Leukemia Group B study compared paclitaxel (100 mg/m², modified to 80 mg/m² after the initial weeks of therapy) once weekly with paclitaxel (175 mg/m²) every 3 weeks as first-line therapy for 577 women with MBC [73]. Patients received trastuzumab if the tumor was HER-2 positive; if the tumor was HER-2 negative, patients were randomized to either receive trastuzumab or not. Weekly paclitaxel led to an ORR of 40%, compared with a response rate of 28% for the every-3-weeks regimen (odds ratio, 1.61; *p* = .017). The median TTPs were 9 months and 5 months for the weekly and every-3-weeks regimens, respectively (*p* = .0008). Weekly paclitaxel dosing resulted in more grade 3 sensory neuropathy (23% versus 12%, *p* = .001) and motor neuropathy (8% versus 4%, *p* = .04), but less grade ≥3 granulocytopenia (8% versus 15%, *p* = .013). Trastuzumab did not improve overall response in patients with HER-2–negative MBC.

These findings indicate that paclitaxel has greater efficacy in the management of MBC when administered weekly rather than every 3 weeks and that trastuzumab does not appear to improve the efficacy of paclitaxel in patients with HER-2–negative disease. Based on these data, the standard-dose weekly paclitaxel regimen is recommended over the every-3-weeks schedule as the better regimen for the treatment of MBC because of higher activity and less toxicity.

**Weekly Paclitaxel-Based Combination Regimens in MBC**

The encouraging results observed in the single-agent trials evaluating weekly paclitaxel in MBC provide the basis for assessing this administration schedule in combination regimens. Weekly paclitaxel has been studied in combination with anthracyclines, platinum agents, and trastuzumab (Table 4) [74–78].

Collectively, these studies showed that paclitaxel in combination with anthracyclines or platinum can achieve response rates from 42% up to 82%, with a median TTP of several months. The most frequent grade 3–4 toxicities recorded were neutropenia, alopecia, and neuropathy. These initial phase I/II studies proved the feasibility of the different schedules to be further evaluated in randomized phase III trials.

**Weekly Paclitaxel– Anthracycline– Platinum Triplets**

The Southern Italian Cooperative Oncology Group (SICOG) evaluated the triple combination of weekly paclitaxel, epirubicin, and cisplatin (Platinol®; Bristol-Myers Squibb) in a series of phase I, phase II, and phase III trials [79, 80]. The phase I trial enrolled 63 women with LABC or MBC who had not received prior therapy for metastatic disease [79]. Patients received escalating doses of paclitaxel, 55 mg/m² to 120 mg/m² per week; and epirubicin, 20 mg/m² to 50 mg/m² per week; and a fixed dose of cisplatin of 30 mg/m². The ORR was 82% (95% CI, 71%–91%), with 15 complete responses. The primary DLTs were neutropenia and neuropathy. The recommended dosages used in the subsequent SICOG phase II trial were paclitaxel, 120 mg/m² per week, epirubicin, 50 mg/m² per week, and cisplatin, 30 mg/m² per week, with growth factor support [79–81]. That trial included 47 women with stage IIB and 33 women with stage IV disease [81]. The ORR in all patients was 87% (95% CI, 76%–94%), with 21 complete responses; the ORR for the stage IIB patients was 98%, and for the stage IV patients it was 79% [46, 81]. For the stage IIB patients, 20 complete responses (50%), 19 partial responses (48%), and one minor response were recorded, giving a 98% response rate (95% CI, 84%–100%) [81]. Among the patients with MBC at a median follow-up of 11 months (range, 3–19 months), the median progression-free survival duration was 14 months [80]. The primary grade 3–4 toxicities observed were neutropenia, anemia, mucositis, and loss of appetite.

The results of that study encouraged the group to perform a phase III study to compare the weekly paclitaxel–epirubicin–cisplatin (PET) regimen with a standard paclitaxel–epirubicin (ET) every-3-weeks regimen in women with previously untreated LABC and MBC [82, 83]. Women were randomized to receive 12 cycles of weekly PET chemotherapy (cisplatin, 30 mg/m² per week, plus epirubicin, 50 mg/m² per week, plus paclitaxel, 120 mg/m² per week, plus G-CSF) or four triweekly cycles of the ET doublet (epirubicin, 90 mg/m², plus paclitaxel, 175 mg/m²). The group reported separately the analysis of LABC [82] and MBC patients [83]. For the LABC patients, pathological complete response was the primary end point. The first analysis of the study reported on the first 140 evaluable LABC patients. Twenty complete (29%) and 41 partial (59%) responses were recorded in the PET arm, giving an 88% ORR. Eleven complete (15%) and 44 partial (62%) responses were observed in
Table 4. Phase I/II studies of weekly paclitaxel-based combinations in metastatic breast cancer (MBC)

<table>
<thead>
<tr>
<th>Study phase</th>
<th>Patient characteristics (% of patients)</th>
<th>Treatment regimen</th>
<th>No. of evaluable patients</th>
<th>ORR (CR)</th>
<th>Grade ≥3 toxicity in % of patients (% of patients)</th>
</tr>
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<tbody>
<tr>
<td><strong>Anthracyclines</strong></td>
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<tr>
<td>Panday et al. [74]</td>
<td>Previously untreated MBC; median age, 53 years (range, 43–61); median WHO PS score, 1; ≥2 metastatic sites (29%)</td>
<td>Paclitaxel, 80 mg/m² i.v. weekly, plus doxorubicin, 12 mg/m² i.v. weekly × 6 weeks followed by 3-week rest</td>
<td>7</td>
<td>48% (0%)</td>
<td>Leukopenia (13% of 119 cycles), neutropenia (16% of 119 cycles)</td>
</tr>
<tr>
<td>Kohler et al. [75]</td>
<td>MBC; median age, 53 years (range, 33–68); prior CT for MBC (63%)</td>
<td>Paclitaxel, 80 mg/m² i.v., plus epirubicin, 35 mg/m² i.v., weekly × 6 weeks followed by 2-week rest</td>
<td>35</td>
<td>51% (20%)</td>
<td>Neutropenia (30% of 123 cycles), alopecia (72% of 123 cycles)</td>
</tr>
<tr>
<td>Cals et al. [76]</td>
<td>Inflammatory or T4 breast cancer; no prior therapy; median age, 50 years (range 32–67); ER negative (68%)</td>
<td>Paclitaxel, 80 mg/m² given as a 1-hr infusion, and epirubicin, 40 mg/m² weekly × 6 consecutive weeks, 8-week cycle, × 2 cycles</td>
<td>19</td>
<td>72% (14%)</td>
<td>Neutropenia (8%)</td>
</tr>
<tr>
<td>Schwonzen et al. [77]</td>
<td>Previously treated MBC; median age, 59 years (range, 44–74); median WHO PS score, 1</td>
<td>Pegylated liposomal doxorubicin, 20 mg/m² i.v., plus paclitaxel, 100 mg/m² i.v., weekly × 2 weeks followed by 1-week rest; cycles repeated every 3 weeks × 3 cycles then 3 additional cycles based on response</td>
<td>21</td>
<td>48% (10%)</td>
<td>Neutropenia (62%), skin toxicity (29%), neurotoxicity (24%), mucositis (14%)</td>
</tr>
<tr>
<td>Fulfar et al. [78]</td>
<td>Previously untreated MBC; prior adjuvant CT allowed</td>
<td>Paclitaxel, 70 mg/m² weekly, days 1, 8, and 15, and pegylated liposomal doxorubicin, 30 mg/m² every 4 weeks</td>
<td>9</td>
<td>55% (11%)</td>
<td>No grade 3–4 toxicities reported</td>
</tr>
<tr>
<td><strong>Platinum agents</strong></td>
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<tr>
<td>Frasci et al. [99]</td>
<td>Previously untreated MBC; prior adjuvant CT (49%); ECOG PS score 0–1 (72%); ≥2 metastatic sites (28%)</td>
<td>Paclitaxel, 75–85 mg/m² i.v., plus cisplatin, 40 mg/m², weekly × 6 weeks (then an additional 6 weeks in patients without PD) plus G-CSF, 5 μg/kg/d s.c. days 3–5 each week</td>
<td>27 (no prior adjuvant CT)</td>
<td>81% (26%)</td>
<td>Neutropenia (9%), thrombocytopenia (7%), anemia (7%), fatigue (12%), vomiting (9%), neuropathy (7%)</td>
</tr>
<tr>
<td>Loesch et al. [84]</td>
<td>Previously untreated MBC or LABC; median age, 59 years (range, 33–89); ECOG PS score 0–1 (94%); prior adjuvant CT (61%)</td>
<td>Paclitaxel, 100–135 mg/m² weekly, plus carboplatin, AUC 2 weekly, × 3 weeks followed by 1-week rest</td>
<td>95</td>
<td>62% (8%)</td>
<td>Neutropenia (35%), leukopenia (17%), neuropathy (11%), weakness (6%), infection (6%), anemia (5%)</td>
</tr>
<tr>
<td><strong>Nonanthracycline combinations</strong></td>
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<tr>
<td>Bouillet et al. [100]</td>
<td>Anthracycline-pretreated MBC; median age, 64 years (range, 51–74); prior CT for MBC (65%); ECOG PS score 0–1 (94%)</td>
<td>Paclitaxel, 80 mg/m² weekly, and biweekly vinorelbine, 25 mg/m², as 8-week course with 2-week rest</td>
<td>18</td>
<td>55% (5%)</td>
<td>Neutropenia (70%), febrile neutropenia (25%), thrombocytopenia (5%), neurotoxicity (5%), nausea/vomiting (5%)</td>
</tr>
<tr>
<td><strong>Anthracyclines/platinum Agents</strong></td>
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<tr>
<td>Frasci et al. [79]</td>
<td>Previously untreated MBC (n = 39) or LABC (n = 24); median age, 51 years (range, 38–74); ECOG PS score 0–1 (79%); prior adjuvant CT (32%); ≥3 metastatic sites (47%)</td>
<td>Paclitaxel, 55–120 mg/m², plus epirubicin, 20–50 mg/m², plus cisplatin, 30 mg/m², weekly × 6–12 weeks; G-CSF, 5 μg/kg/d s.c. days 3–5 each week at paclitaxel doses &gt;85 mg/m² and epirubicin doses &gt;40 mg/m²/week</td>
<td>63</td>
<td>82% (24%)</td>
<td>Neutropenia (12% of 506 cycles)</td>
</tr>
<tr>
<td>Frasci et al. [80]</td>
<td>Previously untreated MBC (n = 33) or LABC (n = 47); median age, 51 years (range, 38–74); ECOG PS score 0–1 (69%); prior adjuvant CT (27%); ≥3 metastatic sites (61%)</td>
<td>Paclitaxel, 120 mg/m², plus epirubicin, 50 mg/m², plus cisplatin, 30 mg/m², weekly × 6–12 weeks plus G-CSF, 5 mg/kg/d s.c. days 3–5 each week</td>
<td>68</td>
<td>87% (31%)</td>
<td>Neutropenia (32%), anemia (10%), mucositis (10%), loss of appetite (10%), diarrhea (9%), skin toxicity (9%)</td>
</tr>
</tbody>
</table>
### Table 4. continued

<table>
<thead>
<tr>
<th>Study/phase</th>
<th>Patient characteristics (% of patients)</th>
<th>Treatment regimen</th>
<th>No. of evaluable patients</th>
<th>ORR (CR)</th>
<th>Grade ≥3 toxicity in ≥5% of patients (% of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthracyclines/platinum Agents (continued)</td>
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</tr>
<tr>
<td>Maiorino et al. [83] Phase III</td>
<td>Previously untreated MBC</td>
<td>PET (cisplatin, 30 mg/m²/week + epirubicin, 50 mg/m²/week, + paclitaxel, 120 mg/m²/week + G-CSF) weekly for 12 cycles versus ET (epirubicin, 90 mg/m², + paclitaxel, 175 mg/m²) triweekly for 4 cycles</td>
<td>120</td>
<td>PET arm, 80% (20%); ET arm, 50% (12%)</td>
<td>Anemia, mucositis, peripheral neuropathy, and gastrointestinal toxicity more frequent in the PET arm</td>
</tr>
<tr>
<td>Comella et al. [82] Phase III</td>
<td>Previously untreated LABC (T4 and/or N3)</td>
<td>PET (cisplatin, 30 mg/m²/week + epirubicin, 50 mg/m²/week, + paclitaxel, 120 mg/m²/week + G-CSF) weekly ×12 cycles versus ET (epirubicin, 90 mg/m², + paclitaxel, 175 mg/m²) triweekly for 4 cycles</td>
<td>140 (PET = 69; ET = 71)</td>
<td>PET arm, 88% (29%); ET arm, 77% (15%)</td>
<td>No differences in terms of severe neutropenia and thrombocytopenia were observed between the two arms</td>
</tr>
<tr>
<td>Trastuzumab</td>
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<tr>
<td>Seidman et al. [86] Phase II</td>
<td>Previously treated HER-2–positive MBC; median age, 51 years (range, 28–68); median KPS, 90; prior CT for MBC (30%); prior adjuvant CT (77%); ≥3 metastatic sites (32%)</td>
<td>Paclitaxel, 90 mg/m² i.v. weekly, plus trastuzumab, 4 mg/kg i.v. loading dose, then 2 mg/kg weekly; cycles repeated until PD or prohibitive toxicity</td>
<td>95</td>
<td>57% (5%)</td>
<td>Neutropenia (6%), neuropathy (29%), asthenia (7%), edema (5%)</td>
</tr>
<tr>
<td>Fountzilas et al. [87] Phase II</td>
<td>HER-2–positive MBC; median age, 48 years (range, 28–76); ECOG PS score 0–1 (94%); prior adjuvant CT (74%); ≥3 metastatic sites (33%)</td>
<td>Paclitaxel, 90 mg/m² i.v. weekly, plus trastuzumab, 4 mg/kg i.v. loading dose, then 2 mg/kg weekly × 12 weeks; G-CSF allowed for grade ≥2 neutropenia or febrile neutropenia</td>
<td>34</td>
<td>62% (12%)</td>
<td>Neutropenia (9%), alopecia (33%)</td>
</tr>
<tr>
<td>Burris et al. [93] Phase II</td>
<td>Previously untreated HER-2–positive MBC; median age, 52 years (range, 34–81); ECOG PS score 0–1 (95%); positive by FISH (46%); prior adjuvant CT (87%)</td>
<td>Trastuzumab, 8 mg/kg i.v. loading dose then 4 mg/kg i.v. weekly for 8–16 weeks, then paclitaxel, 70 mg/m² i.v., plus carboplatin, AUC 2 i.v., plus trastuzumab, 2 mg/kg i.v. weekly × 6 weeks followed by 2-week rest</td>
<td>38</td>
<td>71% (24%)</td>
<td>Leukopenia (33%), neuropathy (14%)</td>
</tr>
<tr>
<td>John et al. [90] Phase II</td>
<td>Previously treated HER-2–positive MBC; median age, 59 years (range, 29–76); prior CT for MBC (39%); HercepTest™ 2+ (88%), positive by FISH (12%); prior anthracyclines (100%); median number of metastatic sites (2)</td>
<td>Paclitaxel, 90 mg/m² i.v. weekly weeks 1–6 and 8–13, plus trastuzumab, 2 mg/kg i.v. weekly up to 48 weeks</td>
<td>77</td>
<td>69% (19%)</td>
<td>Allergic reaction (3 cases)</td>
</tr>
<tr>
<td>Gasparini et al. [91] Phase II</td>
<td>Previously untreated HER-2–positive MBC; median age, 53 years (range, 30–69); HER-2 over-expression (2+/3+) by HercepTest™</td>
<td>Paclitaxel, 80 mg/m² weekly versus Paclitaxel and trastuzumab (loading dose of 4 mg/kg, followed by weekly doses of 2 mg/kg)</td>
<td>Total 62</td>
<td>70.8% (NR)</td>
<td>Neutropenia (12.5%)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>24</td>
<td>73.7% (NR)</td>
<td>Neutropenia (14.2%)</td>
</tr>
<tr>
<td>Gori et al. [92]</td>
<td>Previously treated HER-2–positive MBC; median age, 43 years (range, 29–64); prior anthracyclines (100%); prior taxanes (80%); HER-2 over-expression by IHC</td>
<td>Paclitaxel, 60–90 mg/m² i.v. weekly, plus trastuzumab, 4 mg/kg i.v. loading dose followed by 2 mg/kg i.v. weekly</td>
<td>25</td>
<td>56% (16%)</td>
<td>Cardiotoxicity (8%)</td>
</tr>
<tr>
<td>Trigo et al. [94]</td>
<td>Previously untreated HER-2–positive MBC or LABC; HER-2 overexpression (2+/3+) by IHC</td>
<td>Paclitaxel, 80 mg/m², and trastuzumab, 2 mg/kg, both weekly, and liposomal doxorubicin, 50 mg/m² every 3 weeks × 6</td>
<td>32</td>
<td>87% (46%)</td>
<td>Febrile neutropenia (8 cases), infections (7 cases)</td>
</tr>
</tbody>
</table>

Abbreviations: AUC, area under the concentration–time curve; CR, complete response; CT, chemotherapy; ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; KPS, Karnofsky performance status; LABC, locally advanced breast cancer; NR, not reported; ORR, overall response rate; PD, progressive disease; PS, performance status; WHO, World Health Organization.
the ET arm, giving a 77% ORR. The difference between the two arms was significant for the CRR (29% versus 15%; \( p = .05 \)), while there was a trend in favor of the PET arm for the ORR (88% versus 77%; \( p = .09 \)). From the 130 patients that were submitted to surgery, the absence of invasive tumor in the breast (pT0+pTis) was observed in 14 and 10 patients in the PET and ET arms, respectively (\( p = \text{ns} \)). Negative axillary nodes (pN0) were found in 17 PET and 14 ET patients (\( p = \text{ns} \)). However, a complete regression of the tumor in both the breast and axilla (pT0+pTis+N0) was observed in 11 PET (16%) patients but in only three ET (4%) patients (\( p = .03 \)). No differences in terms of severe neutropenia and thrombocytopenia were observed between the two arms. However, severe anemia, mucositis, peripheral neuropathy, and gastrointestinal toxicity were substantially more frequent in the PET arm.

In the analysis of MBC patients [83], the time to treatment failure was considered the main end point. An accrual of 120 patients per arm was planned, with an interim analysis on the first 60 evaluable patients of each arm. Overall, 132 patients have been recruited (64 in the PET arm and 68 in the ET arm). Of the 120 evaluable patients, 11 complete (20%) and 34 partial (60%) responses were recorded in the PET arm, giving an 80% ORR. In the ET arm, eight complete (12%) and 24 partial (38%) responses were registered, for a 50% ORR (\( p = .0004 \)). At a median follow-up of 21 months, 78 failures had occurred (38 in the PET arm and 40 in the ET arm), with median times to treatment failure of 13.2 months and 14 months in the PET and ET arms, respectively (\( p = .97 \)). Only 43 deaths occurred (PET, 18; ET, 25), with 4-year survival probabilities of 44% for the PET arm and 39% for the ET arm. Anemia, mucositis, peripheral neuropathy, and gastrointestinal toxicity were substantially more frequent in the PET arm. The higher toxicity, together with the lack of survival benefit, limit the use of this combination.

**Randomized Phase II Studies of Weekly Paclitaxel**

As a continuation of their previous phase II study testing weekly paclitaxel and carboplatin (Paraplatin®; Bristol-Myers Squibb) in first-line MBC [84], investigators from the US Oncology group evaluated single-agent weekly paclitaxel and the combination of weekly paclitaxel and carboplatin in patients with previously untreated MBC [85]. One hundred forty-one patients were randomized to receive, on a weekly basis, paclitaxel (100 mg/m²) either alone or with carboplatin with an area under the concentration–time curve (AUC) of 2. Chemotherapy was given on days 1, 8, and 15 of a 28-day cycle. About half of the patients (55%) had received prior adjuvant chemotherapy for breast cancer, and 56% of the patients were ER-positive. Patients who were HER-2 3+ by IHC or HER-2 positive by FISH were excluded. For this initial analysis, 84 patients were evaluable for response and TTP. The response rates (complete plus partial responses) were 35.0% with paclitaxel and 42.5% with the combination (\( p = .64 \)). The median TTPs were 5 months with paclitaxel alone and 7.7 months with the paclitaxel–carboplatin combination (\( p = .054 \)). In terms of grade 3–4 toxicities, the combination was associated with more neutropenia (38% versus 14%; \( p = .002 \)). Preliminary results of this randomized phase II trial show a nonsignificant trend toward a higher response rate and longer TTP for paclitaxel and carboplatin versus paclitaxel alone.

**Weekly Paclitaxel–Trastuzumab Combinations**

Weekly paclitaxel plus trastuzumab was evaluated in several phase II trials involving MBC patients with HER-2–overexpressing tumors (Table 4) [86–89]. In two of the trials, patients received paclitaxel and trastuzumab weekly; one trial continued treatment until progressive disease or toxicity [86], and the other continued for 12 weeks [87]. Seidman et al. evaluated this combination in 95 patients, including 30% who had received prior treatment for MBC (Table 4) [86]. The ORR was 57%, with a complete response rate of 5%. The median response duration was 7 months. Fountzilas et al. [87] evaluated this combination as first-line therapy for MBC in 34 patients; the ORR was 62%, with a complete response rate of 12%. At a median follow-up of 14.4 months, the median TTP was 9 months [87]. In both trials, weekly paclitaxel plus trastuzumab was well tolerated, with rare grade 3–4 hematologic or nonhematologic toxicities. Seidman et al. [86] reported three cases of cardiac complications, which occurred in patients who had received prior anthracycline therapy.

A German trial evaluated the same dose of paclitaxel administered weekly in weeks 1–6 and 8–13, with trastuzumab given weekly for up to 48 weeks (Table 4) [90]. Seventy-seven MBC patients, all with anthracycline pretreatment, were enrolled. Eighty-eight percent had tumors with IHC 3+ overexpression of HER-2 (by the HercepTest™), with the rest being HER-2 positive by FISH. After a median duration of 24 weeks of treatment, an objective response rate of 69% was achieved, including complete remissions in 19%. Common Toxicity Criteria grade 2 toxicities were leukopenia, anemia, and peripheral neuropathy (15% of patients), and there were three cases of severe allergic reactions [90]. The question of whether the weekly paclitaxel–trastuzumab combination is superior to weekly paclitaxel was addressed by an Italian study that enrolled 89 untreated MBC patients with HER-2 overexpression (2+/3+ by HercepTest™) [91]. Scheduled treatment consisted of weekly paclitaxel (80 mg/m²) versus paclitaxel and trastuzumab. Both treatment arms were well tolerated. Grade 3 neurop-
Weekly Administration of Docetaxel and Paclitaxel

athy was observed in 2.3% of patients in the combination arm versus 3.1% of patients in the paclitaxel alone arm; the incidences of grade 3 neutropenia were 14.2% in the combination arm and 12.5% in the paclitaxel-alone arm; no grade 4 toxicity occurred. LVEF did not decrease during the treatment in either of the arms, and no symptomatic cardiac event was observed. Sixty-two patients were evaluable for response. Somewhat surprisingly, the ORRs (70.8% versus 73.7%) and preliminary median TTPs (171 days versus 198 days) were similar in the two arms. However, the addition of trastuzumab induced a better overall response than paclitaxel alone in patients with HER-2 3+ disease (83.4% versus 62.6%) and in those with visceral disease (74.1% versus 63.2%).

To explore the activity of the paclitaxel–trastuzumab combination in anthracycline- and taxane-pretreated patients, a phase II trial was performed by an Italian group [92]. They enrolled 25 HER-2–overexpressing MBC patients in a phase II study. The treatment was planned to continue until disease progression or prohibitive toxicity; in patients with responsive or stable disease, after months of therapy, the decision to stop paclitaxel while continuing weekly trastuzumab was left to the physicians’ judgment. At a median follow-up of 19.6 months, the group reported a 16% complete response rate, a 40% partial response rate, a 16% stable disease rate, and a 28% disease progression rate. The ORR was 56% (95% CI, 36.5%–75.5%). The median TTP was 8.6 months (range, 2.5–24.2). The toxicity was mild; two patients (8%) came off study for grade 3 cardiotoxicity (after 9 weeks and 17 weeks of treatment, respectively); both had already received anthracyclines and taxanes.

In a recently published multicenter phase II trial of the Minnie Pearl Cancer Research Network, a sequential design was favored to explore several questions (Table 4) [93]. The purpose of the study was to determine the response rate of trastuzumab as first-line therapy in patients with HER-2–overexpressing MBC and to assess the feasibility and toxicity of weekly paclitaxel plus carboplatin with or without trastuzumab following initial treatment with trastuzumab. Sixty-one patients received trastuzumab (8 mg/kg followed by 4 mg/kg per week) for 8 weeks. Responding patients received eight additional weeks of trastuzumab (4 mg/kg per week), and then proceeded to receive trastuzumab (2 mg/kg) in combination with paclitaxel (70 mg/m²) and carboplatin (AUC, 2) weekly for 6 weeks followed by 2 weeks’ rest. Stable patients after the initial 8 weeks of trastuzumab proceeded to treatment with trastuzumab, paclitaxel, and carboplatin. Patients with disease progression during the initial 8 weeks had the trastuzumab discontinued and were treated with weekly paclitaxel plus carboplatin. Weekly paclitaxel plus carboplatin, with or without trastuzumab, was well tolerated. Grade 3–4 toxicities consisted of neutropenia in 17 patients (41 episodes), thrombocytopenia in two patients (five episodes), and anemia in three patients, with fatigue and nausea as the most common nonhematologic toxicities reported. Fifty-two patients were assessable for response, and all 61 patients were assessable for survival. Seventeen (33%) of the 52 patients experienced a minor/partial response to single-agent trastuzumab and received 8 additional weeks of single-agent trastuzumab. Fifteen (29%) of 52 patients had stable disease and proceeded to receive the paclitaxel–carboplatin–trastuzumab combination. Thirty-one patients with measurable disease were assessable for response after initial single-agent trastuzumab followed by paclitaxel, carboplatin, and trastuzumab. An ORR of 84% (8 complete responses, 18 partial responses), median TTP of 14.2 months, and median overall survival of 32.2 months were reported with the triplet combination. In the patients treated with paclitaxel and carboplatin alone after disease progression on initial single-agent trastuzumab, an ORR of 69% (one complete response, 10 partial responses), median TTP of 8.3 months, and median overall survival of 22.2 months were reported. The median TTP for all 61 patients was 10 months and the median overall survival was 26.7 months. Overall, these results are very encouraging and prompted the evaluation of weekly paclitaxel–trastuzumab combinations in phase II and randomized phase III trials [86, 87].

The triple combination of weekly paclitaxel and trastuzumab plus liposomal doxorubicin (Myocet®; Zeneus Pharma Ltd, Herts, UK, http://www.zeneuspharma.com) every 3 weeks was examined in a phase II trial that enrolled 41 previously untreated HER-2–positive (3+ by IHC or positive by FISH) patients with MBC or LABC (Table 4) [94]. Cardiac function was assessed every 3 weeks. The authors reported an ORR of 87.5% (15 complete responses and 13 partial responses); a further four patients had stable disease. Nineteen serious adverse events were observed in 14 patients. The most common events were febrile neutropenia (eight patients) and infections (seven patients); one case of cardiac insufficiency was reported but was judged to be not related to therapy. The North Central Cancer Treatment Group (NCCTG) 98-32-52 trial was a multicenter, randomized phase II trial of weekly versus every-3-weeks paclitaxel, carboplatin, and trastuzumab in women with HER-2–positive MBC led by Perez and colleagues [95]. The primary goal of the study was to evaluate the therapeutic ratio (balance of efficacy and toxicity) between the two schedules. Patients were required to have HER-2–positive MBC, defined as an IHC staining score of 3+ or positive for HER-2 gene amplification by FISH evaluated at the Mayo Clinic’s central laboratory. Patients received either pacli-
taxel (200 mg/m²), carboplatin (AUC, 6), and trastuzumab (initial dose, 4 mg/kg; subsequent doses, 2 mg/kg), later modified to every 21 days for 8 cycles (n = 43), or weekly therapy (n = 48) consisting of paclitaxel (80 mg/m²) and carboplatin (AUC, 2) for 3 of 4 weeks, with weekly trastuzumab (initial dose, 4 mg/kg; subsequent doses, 2 mg/kg) administered every 4 weeks for six cycles. Trastuzumab was continued until disease progression or other discontinuation event. Baseline patient characteristics were well balanced between the study arms. In both arms, there were a substantial number of patients with visceral-dominant disease (68% in the every-3-weeks arm versus 84% in the weekly arm). The efficacies of the two dosing schedules were similar, with ORRs of 65% (90% CI, 51%–77%) and 81% (90% CI, 58%–81%), median TTPs of 9.2+ months and 12.5+ months, and median overall survival times of 23.5+ months and 37.9+ for the every-3-weeks and weekly therapy, respectively. Hematologic and nonhematologic toxicities occurred less frequently with weekly therapy. Grade 3–4 neutropenia was reported in 88% and 59% of patients, grade 3 thrombocytopenia was reported in 30% and 5% of patients, and grade 3 neurosensory toxicity was reported in 19% and 2% of patients receiving every-3-weeks and weekly therapy, respectively. Overall, the every-3-weeks and weekly paclitaxel, carboplatin, and trastuzumab regimens were highly active in women with HER-2–positive MBC. However, substantial differences in the toxicity profiles favor weekly administration.

In summary, paclitaxel in combination with trastuzumab represents a highly active regimen that is able to shrink tumors in 56%–86% of the HER-2–positive breast cancer patients, with a low incidence of grade 3–4 toxicities. It provides a safe and effective treatment that is able to provide 8–12 months of progression-free survival for the subgroup of patients overexpressing HER-2.

### Cross-Resistance Among Taxanes

Despite belonging to the same class of drugs with similar mechanisms of actions, paclitaxel and docetaxel are not entirely cross-resistant. An interesting study from a Japanese group reported, retrospectively, the benefit of paclitaxel in 44 MBC patients that had progressed under docetaxel [96]. The patients received paclitaxel (80 mg/m²) weekly until progression. The authors observed no complete responses, but 14 of the 44 patients responded (ORR, 31.8%; 95% CI, 17.5%–46.1%). Seven of 14 responders never responded to docetaxel therapy. The median duration of response was 6.1 months (range, 2.1–12.7), and the reported median TTP was 5.0 months. Grade 3–4 toxicity included neutropenia (27.2%), leukopenia (25.0%), neuropathy (13.6%), and febrile neutropenia (6.8%). The authors concluded that the two taxanes are incompletely cross-resistant and the toxicity seemed to be noncumulative.

Building on the idea that the two taxanes are drugs with different toxicities and activities, an Italian group investigated the feasibility of a regimen combining weekly paclitaxel (60 mg/m²) with docetaxel at the same dose [97]. Because of toxicity, the doses were subsequently reduced to 25 mg/m² for docetaxel and 40 mg/m² for paclitaxel. Although the 26 included patients received different schedules, the authors were able to observe an ORR of 68% (95% CI, 50%–86%), with a median duration of response of 10 months (range, 2–18+ months), with acceptable toxicity.

A pilot phase II study conducted at Memorial Sloan-Kettering Cancer Center to assess the feasibility of dose-dense 5-fluourouracil–epirubicin–cyclophosphamide (FEC) chemotherapy followed by alternating weekly docetaxel (35 mg/m²) and paclitaxel (80 mg/m²) had to be stopped early because of toxicity [98].

### Ongoing Trials of Weekly Taxanes in MBC

A number of ongoing trials are evaluating weekly docetaxel or paclitaxel as single agents or in various combinations for the treatment of MBC. Two phase III randomized studies are evaluating weekly versus every-3-weeks docetaxel, one in previously treated patients (MDA-ID-99242) and one in chemotherapy-naïve patients (UW 0201). Likewise, randomized phase II/III trials are comparing weekly with every-3-weeks schedules of paclitaxel-based combinations. In addition, a randomized phase II trial is comparing weekly paclitaxel with weekly paclitaxel and carboplatin in previously untreated elderly patients with MBC.

Data are emerging on the use of newer formulations of taxanes (such as ABI-007 [Abraxane®, American Pharmaceutical Partners, Inc., Schaumburg, IL, http://www.appdrugs.com] and Tocosol® [Sonus Pharmaceuticals, Bothell, WA, http://www.sonuspharma.com]) that are less allergenic, can be administered more quickly, and obviate the need for steroids to prevent allergic reactions. These new taxanes are already being tested in clinical trials with promising results.

### Conclusions

Optimizing the dose and schedule of taxane therapy to maximize antitumor activity while maintaining a favorable toxicity profile remains an important goal in MBC [17]. Weekly, rather than the standard every-3-weeks, dosing of docetaxel and paclitaxel at lower doses is one way to provide an efficacious method of drug delivery while maintaining a favorable toxicity profile. Various studies support weekly taxane dosing as an active regimen in MBC, even in heavily pretreated, refractory disease and...
in elderly patients or those with poor performance status. Importantly, this regimen is associated with a low incidence of severe hematologic toxicities and acute nonhematologic toxicities.

Ongoing studies will continue to evaluate weekly versus standard every-3-weeks docetaxel and paclitaxel dosing regimens as single-agent therapy or as part of combination regimens that include trastuzumab and/or carboplatin and other novel agents. In conclusion, published data to date support the administration of taxanes by weekly infusion as a valuable therapeutic option for patients with MBC; data on their incorporation in adjuvant trials are eagerly awaited.

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