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Key Words. Paclitaxel · Antineoplastic agents · Breast neoplasms · Clinical trials

ABSTRACT

Paclitaxel has emerged as an important agent in the treatment of breast cancer. The efficacy and tolerability of this agent, as well as its lack of cross-resistance with anthracyclines, have spurred intensive clinical investigation worldwide. Optimization of paclitaxel dose and scheduling and evaluation of the drug in combination regimens are a central focus of investigations. Recent clinical evidence suggests that optimal dose of single-agent paclitaxel by 3-h infusion is 175 mg/m². Trials evaluating administration schedule have not found either a 24-h or 96-h infusion to be superior to a 3-h infusion. Weekly moderate-dose paclitaxel administration is also generating much interest, given the high relative dose intensity and dose density delivered, yet very modest myelosuppression and manageable neurotoxicity observed.

As first-line therapy in metastatic disease, multiple studies have documented overall response rates in the range of 30%-60%. As second-line or salvage single-agent therapy in metastatic patients, paclitaxel generally affords an overall response rate of 20%-40%, even in anthracycline-resistant patients.

The novel mechanism of action and manageable toxicity of paclitaxel has led to successful incorporation into combination chemotherapy regimens. The combination of paclitaxel and doxorubicin has been the most extensively studied, with the role of this regimen continuing to evolve. Other combination regimens that appear to hold substantial promise as first-line metastatic treatment are paclitaxel with carboplatin and paclitaxel with trastuzumab (anti-HER2 antibody). The favorable results obtained in the metastatic setting have prompted phase II and phase III investigations of paclitaxel in the adjuvant and neoadjuvant settings. In the adjuvant setting, a recent phase III study has indicated that the addition of sequential paclitaxel to standard therapy affords both disease-free and overall survival benefits.

Current investigations with paclitaxel will continue to optimize the role of this agent in the treatment of early- and advanced-stage breast cancer, addressing not only response rates but also survival and quality-of-life issues. The use of paclitaxel on a weekly schedule or with new therapeutic modalities, such as monoclonal antibodies, is also receiving much attention. While it is clear that paclitaxel is a very active agent in the treatment of breast cancer, it is hoped that these innovative trials will further maximize the potential of this agent in patients with breast cancer. The Oncologist 1998;3:373-389

INTRODUCTION

The role of paclitaxel is being investigated in settings ranging from first-line, second-line, and salvage therapy for metastatic disease, as well as adjuvant and neoadjuvant treatment. Paclitaxel’s place in combination chemotherapy, as well as optimal dosing and scheduling, are among the critical issues being addressed in clinical trials worldwide. A number of large-scale, randomized phase III clinical trials have been initiated, and recently several have had preliminary results reported.

Paclitaxel is classified as a taxane, an antimicrotubulin agent with a unique mechanism of action and potent activity against several tumor types, including breast cancer. Unlike other antimicrotubulin agents, paclitaxel achieves its antitumor effect by promoting tubulin dimerization and inhibiting depolymerization of the microtubules [1].

Paclitaxel is active in the treatment of metastatic breast cancer as first-line therapy [2-4], as well as in heavily pretreated patients [3, 5-7]. Especially encouraging is its activity in anthracycline-resistant disease [7, 8]. Recognition of the activity of this agent in advanced breast cancer has led to its study in earlier stages of the disease. Several phase III randomized trials are evaluating the efficacy of paclitaxel in the adjuvant and neoadjuvant settings.
Paclitaxel use is generally associated with manageable toxicity. Neutropenia and peripheral neuropathy are common clinical side effects of paclitaxel [1]. The most common dose-limiting toxicity of paclitaxel, neutropenia, is both dose- and schedule-dependent. Severe neutropenia is typically of short duration and rarely associated with other hematologic toxicities. Cumulative peripheral neurotoxicity is typically mild and often reversible. Hypersensitivity reactions are almost completely prevented by the use of a premedication regimen consisting of corticosteroids, cimetidine or ranitidine, and diphenhydramine.

Paclitaxel infusion schedules of 1 h, 3 h, 24 h, and 96 h have been studied in the treatment of breast cancer patients. Because of its convenience in the outpatient setting, a 3-h infusion is currently the most widely used. Today, clinical studies are typically employing a 3-h infusion at a dose range of 135-250 mg/m² every three weeks. Dosing and scheduling issues have been investigated in a number of clinical trials, summarized in Table 1. The results of several recently reported trials have provided much insight into optimal dosing and scheduling [9-12]. This review will describe completed and ongoing clinical trials of paclitaxel in breast cancer. Promising avenues of further investigation will also be highlighted.

### Metastatic Breast Cancer

#### Single-Agent Therapy

Since chemotherapy in metastatic breast cancer patients remains palliative, both response and tolerability are important considerations in evaluating new agents. Paclitaxel has been shown to achieve comparatively high response rates with an acceptable toxicity profile.

The single-agent activity of paclitaxel in metastatic breast cancer was established in seminal phase II studies. As first- or second-line treatment, a 24-h infusion of 250 mg/m² paclitaxel every 21 days displayed high levels of antitumor activity, with overall response rates of 56% and 62%, as reported by investigators at the MD Anderson Cancer Center (MDACC) and the Memorial Sloan-Kettering Cancer Center (MSKCC), respectively [13, 14]. These studies provided the first evidence that paclitaxel was very active as single-agent therapy for metastatic breast cancer. Phase I studies have indicated that the maximum tolerated dose of paclitaxel given by 24-h infusion every three weeks is 175-200 mg/m² without G-CSF support and 200-250 mg/m² with G-CSF support [15, 16].

#### Phase II Trials of Short Infusion Schedules

Following these early studies, the use of shorter infusion schedules of paclitaxel was investigated. Studies in ovarian cancer patients indicated that a 3-h infusion of paclitaxel every three weeks was safe and was associated with significantly less myelosuppression than a 24 h-infusion [17]. The shorter infusion schedule also allowed for outpatient administration.

Phase II studies with single-agent paclitaxel produced overall response rates of 21%-60% at doses of 135 mg/m² to 225 mg/m² administered by 3-h infusion [3, 4, 8, 18, 19]. Treatment was generally well tolerated, and prophylactic use of hematopoietic growth factors was not required.

As first-line therapy for metastatic disease, overall response rates of 43% and 32% have been reported in two studies administering paclitaxel 250 mg/m² every three weeks [2, 3], and a third study administering 225 mg/m² on the same schedule reported an overall response rate of 60% [4]. Neutropenia was the most common toxicity encountered in these studies. These response rates are comparable to the 29%-43% rates obtained with doxorubicin in first-line regimens [20].

### Table 1. Paclitaxel doses and schedules in selected randomized clinical trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Paclitaxel dose (mg/m²)/schedule</th>
<th>Evaluable patients</th>
<th>Overall response (%)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nabholz [9]</td>
<td>135/3 h</td>
<td>227</td>
<td>22</td>
<td>No difference in overall response; median time to progression favored higher dose.</td>
</tr>
<tr>
<td></td>
<td>175/3 h</td>
<td>223</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>Peretz [33]</td>
<td>175 to MTD/3 h</td>
<td>521*</td>
<td>29</td>
<td>No difference in overall response, survival, or time to progression when adjusted for prognostic factors.</td>
</tr>
<tr>
<td></td>
<td>175 to MTD/24 h</td>
<td></td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>CALGB 9342 [10]</td>
<td>175/3 h</td>
<td>325*</td>
<td>21</td>
<td>No difference in overall response or survival. Improved time to treatment failure with highest dose.</td>
</tr>
<tr>
<td></td>
<td>210/3 h</td>
<td></td>
<td>28</td>
<td>Toxicity profile favored lower dose.</td>
</tr>
<tr>
<td></td>
<td>250/3 h</td>
<td></td>
<td>22</td>
<td></td>
</tr>
<tr>
<td></td>
<td>250/24 h</td>
<td></td>
<td>50</td>
<td>[p = 0.02]</td>
</tr>
<tr>
<td>MDACC [12]</td>
<td>250/3 h</td>
<td>88</td>
<td>23</td>
<td>No difference in response or survival. Toxicity profile and feasibility favored shorter schedule.</td>
</tr>
<tr>
<td></td>
<td>140/96 h</td>
<td>91</td>
<td>30</td>
<td></td>
</tr>
</tbody>
</table>

*All arms combined. CALGB = Cancer and Leukemia Group B; NSABP = National Surgical Adjuvant Breast and Bowel Program; MDACC = MD Anderson Cancer Center.
Response in Anthracycline-Resistant Patients

Heavily pretreated breast cancer patients usually have a very poor prognosis, and few treatment options are available. Most will have failed anthracycline therapy, and anthracycline resistance is an indicator of very poor prognosis. In the pre-taxane era, patients with anthracycline-resistant metastatic breast cancer faced a median survival of about four months. Responses to all other treatment regimens, whether single-agent or combination, were less than 15% [21].

In the phase II setting, response rates of approximately 20%-40% were obtained with single-agent paclitaxel in patients who failed prior anthracycline therapy (Table 2) [3, 7, 8, 18, 19]. In heavily pretreated patients, response rates of up to 22% were achieved [19]; however, in patients who had received ≥2 prior chemotherapy regimens containing doxorubicin or epirubicin, response rates were lower, at 6% [22]. Phase III studies have confirmed the activity of paclitaxel in anthracycline-resistant patients. An overall response rate of 25% was observed in anthracycline-pre-treated patients who received paclitaxel 135 or 175 mg/m² over 3 h [9]. In addition, the intergroup trial E-1193, a phase III study in which patients randomized to received single-agent doxorubicin could be crossed over to receive paclitaxel (24-h infusion) upon disease progression, reported a 22% overall response rate to paclitaxel following anthracycline failure [23, 24].

Weekly Paclitaxel

Another area of considerable interest is the administration of weekly cycles of paclitaxel. With weekly administration of moderate doses of paclitaxel, higher cumulative doses can be achieved than with an every-three-weeks schedule, yet myelosuppression is generally modest [25-29]. Seidman et al. administered paclitaxel 100 mg/m² weekly via 1-h infusion to patients with previously treated metastatic breast cancer and observed a 53% overall response rate, with 10% complete responses [25]. In the subgroup with anthracycline-resistant disease, the response rate was 50%. Therapy was well tolerated, with a lack of cumulative neutropenia and manageable neurotoxicity.

Neurotoxicity, which can be cumulative with paclitaxel treatment, is generally not a problem with weekly paclitaxel doses up to 80 mg/m² [26]. Perez et al. at the Mayo Clinic Jacksonville are currently conducting a multicenter phase II trial of continuous, weekly paclitaxel 80 mg/m² in patients with metastatic breast cancer and to date have not encountered difficulty with cumulative neurotoxicity or myelosuppression.

<table>
<thead>
<tr>
<th>Study</th>
<th>Trial design</th>
<th>Dose/schedule</th>
<th>Evaluable patients</th>
<th>Overall response (%)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase II Trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seidman [3]</td>
<td>Phase II</td>
<td>125 mg/m² i.v., 3-h infusion</td>
<td>24</td>
<td>21</td>
<td>Two or more prior regimens for metastatic disease.</td>
</tr>
<tr>
<td>Seidman [7]</td>
<td>Phase II</td>
<td>200-250 mg/m² i.v., 24-h infusion</td>
<td>76</td>
<td>33</td>
<td>At least one prior therapy for metastatic disease.</td>
</tr>
<tr>
<td>Abrams [6]</td>
<td>NCI treatment referral</td>
<td>135 or 175 mg/m² i.v., 24-h infusion</td>
<td>153</td>
<td>24</td>
<td>Patients had progressed either while on doxorubicin or within 6 months after doxorubicin.</td>
</tr>
<tr>
<td>Fountzilas [8]</td>
<td>Phase II</td>
<td>175 mg/m² i.v., 3-h infusion</td>
<td>33</td>
<td>42</td>
<td>Anthracycline resistant.</td>
</tr>
<tr>
<td>Gianni [18]</td>
<td>Phase II</td>
<td>175 or 225 mg/m² i.v., 3-h infusion</td>
<td>50</td>
<td>38</td>
<td>Up to two prior regimens, one adjuvant and one metastatic.</td>
</tr>
<tr>
<td>Vici [19]</td>
<td>Phase II</td>
<td>135 or 175 mg/m² i.v., 3-h infusion</td>
<td>41</td>
<td>22</td>
<td>Two to five prior therapies for advanced disease.</td>
</tr>
<tr>
<td>Vermorken [22]</td>
<td>European Cancer Center Trial</td>
<td>250-300 mg/m² i.v., 3-h infusion</td>
<td>33</td>
<td>6</td>
<td>Two or more prior anthracycline-containing regimens.</td>
</tr>
<tr>
<td>Phase III Trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nabulzas [9]</td>
<td>Multicenter</td>
<td>135 or 175 mg/m² i.v., 3-h infusion</td>
<td>303</td>
<td>25</td>
<td>One prior regimen, adjuvant or metastatic, or one each adjuvant and metastatic.</td>
</tr>
</tbody>
</table>
A higher-dose weekly paclitaxel regimen, 175 mg/m² by 3-h infusion for six weeks of an eight-week cycle, is under investigation by the Brown University Oncology Group as first-line treatment for locally advanced or metastatic breast cancer. The overall response rate was 78%, with 16% complete responses; however, most patients required dose modification secondary to cumulative toxicities [30, 31].

**Phase III Trials: Dose Response**

Phase III trials have confirmed the high, single-agent activity of paclitaxel in advanced breast cancer. Issues of paclitaxel dose have recently been studied by Nabholtz et al. [9] and CALGB trial 9342 [10]. The trial reported by Nabholtz et al., which compared doses of paclitaxel 135 and 175 mg/m² delivered by 3-h infusion every three weeks, reported overall response rates of 22% and 29%, respectively, and complete response rates of 5% and 2%, for each of the doses, respectively [9]. These differences were not statistically significant; however, there was a significant difference in time to progression, with the higher dose producing a median time to disease progression of 4.2 months, compared with 3.0 months for the lower dose.

Preliminary results of CALGB 9342 have recently been reported [10, 32]. In this phase III trial, single-agent paclitaxel doses of 175, 210, and 250 mg/m² were administered as a 3-h infusion every three weeks to patients who had received up to one prior therapy for metastatic disease. In updated results presented at the 1998 American Society of Clinical Oncology (ASCO) annual meeting in Los Angeles, response rates and overall survival were not statistically different among the three arms; however, time to treatment failure was statistically longer for patients receiving the highest dose. Although all dose levels were well tolerated and overall quality of life was not different among the three arms of the trial, grade III neurosensory toxicity and grade IV hematologic toxicity were more frequent with the 250 mg/m² dose than with either 175 or 210 mg/m².

These studies have not shown a clear-cut dose-response relationship for paclitaxel in the treatment of metastatic breast cancer. Although time to treatment failure may favor higher doses, there have been no differences in overall response or survival between arms of the studies. Given this information, it appears that a dose and schedule of 175 mg/m² by 3-h infusion every 21 days is both effective and well tolerated, and a reasonable therapeutic choice.

**Phase III Trials: Infusion Schedule**

Two phase III trials have addressed the issue of comparative efficacy and safety of 3-h versus 24-h paclitaxel infusions in patients with advanced breast cancer. A preliminary report by Perez et al. of the results of a European phase III trial evaluating 3-h versus 24-h paclitaxel infusion, each at 175 mg/m², did not show either schedule superior [33]. Patients were stratified according to no prior chemotherapy, adjuvant chemotherapy, or chemotherapy for advanced disease. Overall, there were no differences in cumulative response rates, median progression-free survival, or overall survival between the two groups when adjusted for prognostic factors. In the salvage setting, the 24-h infusion had some efficacy advantage, but did not confer a significantly greater patient benefit when compared with 3-h infusion. More grade 3 and 4 neutropenia was reported in patients receiving the 24-h infusion, while peripheral neuropathy was more common in the 3-h schedule.

Preliminary results of NSABP B-26, which compared a 3-h versus 24-h infusion of paclitaxel 250 mg/m² have recently been reported [11], with updated data presented at the 1998 ASCO meeting [34]. Patients enrolled had stage IIIB or IV breast cancer, and only prior adjuvant chemotherapy was allowed. The overall response rate for all patients was significantly higher in the 24-h infusion group (50%) than in the 3-h group (40%) [11]. For the subset of patients with stage IV disease, the overall response rates were 48% and 36% for the 24-h and 3-h infusions, respectively. The median time to progression was 7.1 months for the 24-h arm, and 6.4 months for the 3-h arm [34]. Despite the difference in response, there was no difference in overall survival between the 24-h infusion (21 months) and the 3-h infusion (20.7 months). Although the median overall survival for the subset of patients with stage IIIB disease had not been reached at the time of presentation in May 1998, the median overall survival for stage IV patients was 18.2 months for the 24-h infusion and 20.3 months for the 3-h infusion arm. As with the European phase III trial, the 24-h schedule was
associated with more severe hematologic toxicity, and severe neurotoxicity was more common with 3-h infusions. The authors concluded that although the 24-h schedule offered a higher overall response rate, this did not translate to an increase in event-free or overall survival as compared with the 3-h arm. Because of the increased toxicity and costs associated with the 24-h infusion, the authors concluded that the 3-h infusion was generally preferable.

A third phase III multicenter trial, coordinated by MDACC, evaluated 3-h versus 96-h infusions of paclitaxel in metastatic breast cancer [12]. Doses of 250 mg/m² by 3-h infusion and 140 mg/m² for the 96-h infusion were administered every three weeks. There were no differences in overall response, response duration, or overall survival between study arms. The investigators concluded that the extra logistical support required for 96-h infusion was not justified.

### Phase III Trials: Comparison Studies

**Paclitaxel versus CMFP**

Preliminary results of a phase III study from New Zealand and Australia reported by Bishop et al. indicate that single-agent paclitaxel yields response rates equivalent to standard combination cyclophosphamide/methotrexate/5-fluorouracil (5-FU)/prednisolone (CMFP) at equitoxic doses in patients with previously untreated metastatic breast cancer [35-37]. In their preliminary report, the overall response rate was 30% with paclitaxel and 36% with CMFP [35]. Median time to progression was 5.3 months for paclitaxel and 6.5 months for CMFP. Paclitaxel was associated with significantly less severe leukopenia, thrombocytopenia, mucositis, infections, and nausea/vomiting. Alopecia, peripheral neuropathy, and myalgia/arthritis were more frequent with paclitaxel. Patient assessment of quality of life appeared to improve with paclitaxel, but deteriorate with CMFP. The investigators concluded that single-agent paclitaxel is well tolerated, has efficacy comparable to CMFP, and may have additional benefits with respect to quality of life.

**Paclitaxel versus Doxorubicin**

Results were recently reported from another multi-institutional phase III trial comparing paclitaxel with doxorubicin, each as single agents, as first-line treatment of metastatic breast cancer [38]. In this European Organization for Research and Treatment of Cancer (EORTC) trial of 331 anthracycline-naive patients, doxorubicin 75 mg/m² produced a higher response rate, 41%, and longer progression-free survival, 7.3 months, as compared with paclitaxel 200 mg/m² by 3-h infusion, which demonstrated a 25% overall response rate and 4.0 months progression-free survival. However, the doxorubicin arm was associated with greater hematologic, gastrointestinal, and cardiac toxicities, suggesting that the drugs were not compared in equitoxic doses.

In contrast to the EORTC study, U.S. Intergroup Study E-1193, a randomized Phase III trial, failed to reveal any difference between doxorubicin and paclitaxel as single agents in overall response rate, time to disease progression, or overall survival [23, 24]. This three-arm study compared doxorubicin 60 mg/m² with paclitaxel 175 mg/m² by 24-h infusion versus a combination of doxorubicin 50 mg/m² and paclitaxel 150 mg/m² by 24-h infusion. In the preliminary report, overall response rates prior to any crossover therapy were 36% for single-agent doxorubicin, 34% for single-agent paclitaxel, and 47% for the combination. The combination had a statistically superior response; however, there was no statistical difference in response between the two single-agent arms.

**Paclitaxel has demonstrated significant activity in patients with anthracycline-resistant breast cancer.**

An ongoing U.S. multicenter trial is comparing paclitaxel 175 mg/m² by 3-h infusion with docetaxel 100 mg/m² by 1-h infusion as first- or second-line therapy of advanced breast cancer [39]. The question of an equitoxic dose comparison arises, as the maximum tolerated dose for docetaxel is 100 mg/m², while paclitaxel has been shown to be well tolerated up to 250 mg/m². While the paclitaxel dose appears reasonable based on current information, the optimal dose of docetaxel, in terms of efficacy and toxicity, is not yet defined and awaits the results of a separate trial evaluating docetaxel 60 mg/m² versus 75 mg/m² versus 100 mg/m².

In summary, paclitaxel has substantial activity as a single agent in the treatment of metastatic breast cancer. While response rates are highest in the first-line setting, single-agent paclitaxel maintains very good activity as second-line and salvage therapy. The response rate to single-agent paclitaxel is reasonably comparable to that of single-agent doxorubicin. Of importance, paclitaxel has demonstrated significant activity in patients with anthracycline-resistant breast cancer. Although a well-defined dose-response relationship has not been established for 3-h infusions of paclitaxel on an every-three-weeks schedule, a dose of 175 mg/m² appears to offer the best balance of efficacy and tolerability. With regard to infusion schedule, when overall survival is considered, neither 24-h nor 96-h schedules appear to offer survival benefits over a 3-h schedule. Although the 24-h
schedule has been associated with a higher overall response rate, this did not translate into a survival difference. Overall, a 3-h schedule of paclitaxel 175 mg/m² every three weeks appears to be a reasonable option for the treatment of breast cancer. Weekly studies with moderate-dose, single-agent paclitaxel appear very promising in terms of both efficacy and tolerability. A relatively high rate of dose delivery combined with a remarkably tolerable toxicity profile has been observed, encouraging continued investigation.

Combination Chemotherapy

Combination chemotherapy is the standard approach to the treatment of breast cancer. Multidrug regimens have generally resulted in higher complete and overall response rates, with improvements in response durations. The novel mechanism of action of paclitaxel, its demonstrated single-agent activity, and its manageable toxicity profile make it an attractive candidate for inclusion in combination chemotherapy regimens.

Paclitaxel has been studied in combination with a number of other agents effective in breast cancer. The largest number of studies have been conducted with the paclitaxel/doxorubicin combination as first-line therapy in advanced breast cancer [24, 40-48]. Other combinations for both first-line and salvage therapy have included paclitaxel and 5-fluorouracil (5-FU) [49, 50], paclitaxel and cyclophosphamide [51-55], and paclitaxel with a platinum compound [56-65].

New insights in molecular biology have led to combination chemotherapy and antibody studies. With respect to breast cancer in particular, the investigation of combination paclitaxel or anthracycline/cyclophosphamide with anti-HER2 antibody has generated much interest.

Paclitaxel/Anthracycline or Anthracenedione Combinations

Paclitaxel and Doxorubicin

The high individual activity of doxorubicin and paclitaxel in breast cancer and their incomplete clinical cross-resistance make combination therapy with these two agents an attractive option for first-line treatment of metastatic breast cancer. This combination has been extensively evaluated in phase II trials of breast cancer patients worldwide. Response rates—among the highest reported for first-line metastatic treatment—have been encouraging (Table 3).

The first two trials of combination doxorubicin and paclitaxel involved administration of both drugs as prolonged infusions. In a National Cancer Institute study, paclitaxel and doxorubicin were administered concurrently as a 72-h infusion. The overall response rate was 72% [66]. An MDACC trial of paclitaxel by 24-h infusion and doxorubicin by 48-h infusion also investigated the effect of drug sequencing. As reported by Holmes et al., the overall response rate was higher (80%) when paclitaxel preceded doxorubicin versus 57% when the order was reversed, but tolerability was clearly lower [67]. Mucositis, fever, neutropenia, and diarrhea were dose-limiting in the above trials. A pharmacokinetic study revealed that when paclitaxel administration preceded that of doxorubicin, the clearance of doxorubicin was decreased by 32% [68]. An Eastern Cooperative Oncology Group (ECOG) study also observed substantially more mucositis when paclitaxel by 24-h infusion preceded a doxorubicin bolus than when the drugs were administered in the reverse order [69]. Moreover, preclinical studies had shown that doxorubicin followed by paclitaxel has a synergistic or additive effect in primary breast cancer cell cultures or breast cancer cell lines [70]. Consequently, the sequence of doxorubicin followed by paclitaxel has been preferred in subsequent trials.

The desire to deliver paclitaxel and doxorubicin in combination on an outpatient basis led to studies of shorter administration times [40-44, 48]. These short-infusion studies provided evidence of high overall and complete response rates (Table 3).

In all trials conducted to date, the paclitaxel/doxorubicin combination has resulted in high rates of response. However, in trials reported by Gianni et al. [40] and Gehl et al. [41], high response rates were accompanied by an increased incidence of congestive heart failure (CHF), an incidence much higher than expected in light of the cumulative doses of doxorubicin administered. A pharmacokinetic analysis revealed apparent interference by paclitaxel in the elimination of doxorubicin, resulting in increased concentrations of both doxorubicin and its major metabolite, doxorubicinol [71]. Other investigations have also documented a pharmacokinetic interaction between paclitaxel and doxorubicin [68, 72].

Recently, the international experience with combination paclitaxel and doxorubicin therapy in patients with advanced breast cancer has been analyzed with respect to cardiac toxicity [73]. Of the total of 656 patients treated on a combination of 10 different trials, 31 patients (5%) developed CHF. In patients receiving a cumulative doxorubicin dose of up to 380 mg/m², the incidence of CHF was less than 5%, similar to that expected with doxorubicin alone. Above this dose, an increase in CHF was apparent. Therefore, the current recommendation for combination doxorubicin/paclitaxel therapy is to limit the maximum cumulative doses of doxorubicin to 380 mg/m², with a maximum single dose of 50-60 mg/m².

Data from the only phase III trial of combination paclitaxel and doxorubicin, the Intergroup study E-1193, were included in the above analysis [23, 24]. As has been noted, this trial allowed for comparison of efficacy and toxicity of paclitaxel and doxorubicin, each as single agents, to the
combination of the two. For patients enrolled on either single-agent arm, crossover to the other agent was allowed at disease progression. In this trial, the concurrent administration of paclitaxel and doxorubicin was not associated with any greater cardiac toxicity than that observed with single-agent doxorubicin. With respect to response, the combination had an overall response rate of 47%, statistically higher than either paclitaxel (34%) or doxorubicin (36%) as single agents. The crossover design resulted in a similar survival rate in the three study arms, independent of randomization assignment [24]. Also, analysis of the crossover responses revealed that 22% of patients responded to paclitaxel following progression on doxorubicin, and that 20% of patients responded to doxorubicin after progression on paclitaxel.

In addition to limiting the cumulative dose of doxorubicin, several other avenues aimed at reducing the risk of cardiac toxicity are under investigation [74]. These include adjusting the timeframe between doxorubicin and paclitaxel administration, [42, 75], and evaluation of the use of cardioprotective agents [76]. Studies are also evaluating the combination of paclitaxel with epirubicin, a reputedly less cardiotoxic anthracycline [77].

The combination of paclitaxel and doxorubicin is highly active in the treatment of advanced and metastatic breast cancer. Due to cardiac toxicity considerations, it is recommended that the cumulative dose of doxorubicin not exceed

<table>
<thead>
<tr>
<th>Study</th>
<th>Dose/schedule</th>
<th>Evaluable patients</th>
<th>Response (%)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gianni [40]</td>
<td>T 200 mg/m² i.v., 3-h infusion A 60 mg/m² i.v. bolus Cycles repeated q 3 wk, maximum 8 cycles</td>
<td>32</td>
<td>41 53 94</td>
<td>No prior chemotherapy.</td>
</tr>
<tr>
<td>Gehl [41]</td>
<td>T 155-200 mg/m² i.v., 2-3-h infusion A 30 mg/m² i.v. bolus, d 1 and 8 Cycles repeated q 3 wk</td>
<td>29</td>
<td>24 59 83</td>
<td>≤1 prior adjuvant regimen; no prior anthracycline.</td>
</tr>
<tr>
<td>Amadori [42]</td>
<td>A 50 mg/m² i.v. bolus 16 h before T T 130-250 mg/m² i.v. 3-h infusion Cycles repeated q 3 wk</td>
<td>32</td>
<td>31 47 78</td>
<td>No prior chemotherapy for metastatic disease; adjuvant chemotherapy allowed.</td>
</tr>
<tr>
<td>Schwartzmann [43]</td>
<td>T 250 mg/m² i.v., 2-3-h infusion A 60 mg/m² i.v. bolus Cycles repeated q 3 wk, maximum 6 cycles</td>
<td>25</td>
<td>28 52 80</td>
<td>No prior chemotherapy for metastatic disease; adjuvant chemotherapy allowed.</td>
</tr>
<tr>
<td>Sparano [48]</td>
<td>A 60 mg/m² i.v. bolus T 200 mg/m² i.v., 3-h infusion 15 min after A Cycles repeated q 3 wk, maximum 6 cycles</td>
<td>47</td>
<td>6 47 53</td>
<td>No prior chemotherapy for metastatic disease; adjuvant chemotherapy allowed other than A or T.</td>
</tr>
<tr>
<td>Jovtis [44]</td>
<td>A 50 mg/m² i.v. short infusion T 200 mg/m² i.v., 1-h infusion after A Cycles repeated q 3 wk, maximum 10 cycles</td>
<td>50</td>
<td>NR NR 72</td>
<td>No prior chemotherapy for metastatic disease; adjuvant chemotherapy (without anthracyclines) allowed.</td>
</tr>
<tr>
<td>Latorre [45]</td>
<td>A 50 mg/m² i.v. bolus 1 d before T T 130-250 mg/m² i.v. 3-h infusion Cycles repeated q 3 wk</td>
<td>30</td>
<td>23 47 70</td>
<td>No prior chemotherapy for metastatic disease; adjuvant chemotherapy allowed.</td>
</tr>
<tr>
<td>Sledge [24]</td>
<td>A 60 mg/m² or T 175 mg/m²/24 h or A+T, 50 mg/m² and 150 mg/m²/24 h</td>
<td>230</td>
<td>NR NR 47</td>
<td>First-line therapy; adjuvant chemotherapy allowed other than A or T.</td>
</tr>
</tbody>
</table>

Abbreviations: T = paclitaxel; A = doxorubicin; NR = not reported; CR = complete response; PR = partial response; OR = overall response.
Therefore, a regimen of paclitaxel 175 mg/m² by 3-h infusion with doxorubicin 50 to 60 mg/m² every three weeks for four to six cycles is a reasonable option. Ongoing clinical trials will further define the role of combination paclitaxel and doxorubicin in advanced breast cancer.

Two European phase III trials are comparing paclitaxel/anthracycline combinations with cyclophosphamide/anthracycline combinations. EORTC 10961 is evaluating a paclitaxel/doxorubicin combination in comparison with a cyclophosphamide/doxorubicin combination as first-line metastatic therapy. An MRC-UK Coordinating Committee on Cancer Research trial (AB01) is conducting a similar comparison using epirubicin as the anthracycline agent.

Paclitaxel and Epirubicin

Epirubicin, a stereoisomer of doxorubicin, is associated with a comparatively lower rate of cardiotoxicity. Although this agent is not currently available in the United States, it had been studied in combination with paclitaxel in Europe and South America [77-84]. As first-line therapy for metastatic disease, overall response rates of 43%-85%, with complete responses of 0%-29%, have been reported [77-84]. In two of the studies, cardiotoxicity was encountered, but, in general, clinical cardiotoxicity has been low.

Paclitaxel and Mitoxantrone

Paclitaxel has also been studied in combination with the anthracenedione mitoxantrone [85-87]. Overall response rates of 56%-69% were observed in patients with advanced disease. As first-line therapy, the combination resulted in a 69% overall response rate, with a 25% complete response rate [87]. Therapy was generally well tolerated.

Paclitaxel/Platinum Compound Combinations

Paclitaxel has been investigated with both cisplatin and carboplatin as first-line therapy and salvage therapy in patients with metastatic breast cancer. The combination of paclitaxel with a platinum agent is familiar in the setting of lung cancer and ovarian cancer. Unlike cisplatin, carboplatin does not share the potential for overlapping neurotoxicity with paclitaxel [88], and may be the preferred platinum for combination studies.

Overall, while the combination of paclitaxel and cisplatin is active in patients with advanced breast cancer, serious toxicity concerns, particularly neurotoxicity, preclude its general use.

Paclitaxel and Cisplatin

First-line therapy with paclitaxel and cisplatin therapy has had variable results. Gelmon et al. reported a response rate of 85% with a novel paclitaxel/cisplatin combination in which both agents were administered biweekly at modestly reduced doses (90 mg/m² and 60 mg/m², respectively) [56]. However, two confirmatory trials by the ECOG and Hoosier Oncology Group using the same doses and schedule as first-line therapy for metastatic cancer failed to achieve comparable response rates, and severe and life-threatening toxicity occurred in 38% and 50% of the patients, respectively [57, 65]. In the ECOG study, the overall response rate was only 21% [65]. In another phase II study, significant dose-limiting neurotoxicity was an issue [59].

In patients previously treated with anthracyclines, the combination of paclitaxel and cisplatin has been shown to be active, but not without toxicity. In one study of 17 patients, a relatively low dose of paclitaxel, 135 mg/m², was administered with cisplatin, and although an 89% overall response rate was attained, three patients had to be withdrawn from the study due to toxicity [89]. In a more recent study using the same dosages of the paclitaxel/cisplatin combination in anthracycline-resistant relapsing patients, a response rate of only 35% was observed [64].

Overall, while the combination of paclitaxel and cisplatin is active in patients with advanced breast cancer, serious toxicity concerns, particularly neurotoxicity, preclude its general use.

Paclitaxel and Carboplatin

Carboplatin is a derivative of cisplatin that offers an improved toxicity profile. The renal, neurologic, ototoxic, and emetic effects of carboplatin are substantially reduced compared with those of cisplatin. Carboplatin as a single agent is active in metastatic breast cancer, with response rates of 25%-35% in previously treated patients and 37% in untreated patients [90, 91].

Early results of the combination of paclitaxel/carboplatin as first-line metastatic treatment are promising [58, 60, 61]. The combination appears to be tolerable, with less hematopoietic toxicity than expected based on the expected toxicities of each agent [92]. In a multi-institutional phase II trial conducted by the North Central Cancer Treatment Group.
(NCCTG), treatment with paclitaxel (200 mg/m² over 3 h) followed by carboplatin AUC 6 resulted in a 62% overall response rate; median survival time had not been reached but was >16 months. Therapy was well tolerated, with a low incidence of serious leukopenia and neurotoxicity. These results are similar to those reported by Fountzilas et al., who administered paclitaxel 175 mg/m² with carboplatin AUC 6 every three weeks, and reported an overall response rate of 53% [60]. In a separate study, Fountzilas et al. also evaluated a slightly different schedule, paclitaxel 200 mg/m² with carboplatin AUC 7 every four weeks with G-CSF support, in anthracycline-resistant advanced breast cancer patients [61]. The overall response rate was 43%, with a median overall survival of 11.1 months. Again, therapy was well tolerated, with 71% of cycles delivered on schedule. Clearly, paclitaxel in combination with carboplatin is an active and well-tolerated regimen deserving of continued study.

**Paclitaxel/Other Agent Combinations**

Paclitaxel and 5-FU

The combination of paclitaxel and 5-FU with leucovorin has been evaluated in several studies and is considered by many to be an option for patients who have already received their maximum lifetime anthracycline dose or for whom anthracycline-based therapy is not desirable. Several phase II trials have evaluated the paclitaxel/5-FU combination in previously treated patients (including heavily pretreated patients and patients with anthracycline exposure or resistance) and have demonstrated overall response rates of 52%-54%, including 50%-55% response rates in patients previously treated with anthracyclines [49, 50]. Treatment was well tolerated.

However, the triple combination paclitaxel/5-FU/mitoxantrone, while producing an overall response rate of 51% in patients receiving first- or second-line metastatic therapy, was associated with unexpectedly severe myelosuppression, with 76% of cycles resulting in grade 3 or 4 leukopenia. Four treatment deaths were reported [93].

Klassen et al. reported a trial of first-line treatment of weekly high-dose 5-FU plus leucovorin combined with cisplatin 50 mg/m² on days 1 and 22 and paclitaxel 175 mg/m² on days 0 and 21 of a 50-day cycle [94]. An overall response rate of 83%, with a complete response rate of 29%, was observed and although generally tolerable, the regimen was associated with mild to moderate cumulative neurotoxicity.

A recent phase II trial of weekly paclitaxel 80 mg/m² with weekly 5-FU/leucovorin reported an overall response of 47% as first-line therapy for metastatic breast cancer [95]. Toxicity was moderate, with dose reductions necessary by week 4 in many patients secondary to neutropenia.

Other Agents

Other agents with which paclitaxel is being investigated in metastatic breast cancer include cyclophosphamide, vinorelbine, and gemcitabine. These studies are still preliminary, and it is not yet clear what role such combinations will play in therapy.

As with doxorubicin and cisplatin, a sequence-dependent toxicity has been observed with the paclitaxel/cyclophosphamide combination [52]. More severe toxicity was seen in courses in which paclitaxel was administered first. In a pilot study of this combination, the overall response rate was 64%, with 29% complete responses; however, 88% of patients required hospitalization for neutropenic fever [96]. Another study revealed more modest antitumor activity, with overall response rates of 25% and 50%, respectively, in patients with and without prior chemotherapy for metastatic disease [97]. The response rate in women with anthracycline-resistant disease was 8%.

Vinorelbine acts primarily at the level of microtubules and the mitotic spindle. Its action is distinct from that of paclitaxel, and the two agents have been tested as a combination. Both drugs cause neurotoxicity. In two phase II combination trials, paclitaxel was administered at the relatively low dose of 135 mg/m², resulting in 35%-43% overall response rates [98, 99]. In both studies, the complete response rate was 7%. Although an overall response rate of 53% was seen in anthracycline-resistant patients in one of the studies, life-threatening dehydration occurred in 3% of patients [99]. In a study of paclitaxel and vinorelbine as first-line treatment, the response rate was 76%, with 14% complete remissions [100].

Preliminary results from a phase II trial in which paclitaxel and gemcitabine, a nucleoside analog, were administered in a biweekly schedule to anthracycline-resistant patients indicated a response rate of 41%, with 9% complete responses [101]. One reversible episode of cardiac toxicity was observed.

**Combination Chemotherapy/Monoclonal Antibody Therapy**

**Paclitaxel and Anti-HER2 Antibody**

A trial that has recently generated much notice is the combination of the anti-HER2 antibody, trastuzumab (Herceptin®), with chemotherapy in patients with metastatic breast cancer overexpressing the HER2 receptor [102]. In this multinational controlled phase III trial, patients were treated with either combination doxorubicin 60 mg/m² or epirubicin 75 mg/m² with cyclophosphamide 600 mg/m², or with paclitaxel 175 mg/m² by 3-h infusion if they had already received adjuvant anthracycline therapy. Patients in each group were then stratified to receive anti-HER2 antibody therapy in addition to chemotherapy. A total of 469 patients were enrolled. The overall response rate to all chemotherapy with anti-HER2
antibody was 48%, with a median time to progression of 7.6 months, higher than chemotherapy without the antibody (overall response 32%, median time to progression 4.6 months, \( p = 0.001 \)). Specifically for paclitaxel, the overall response rate with antibody was 42%, with a time to progression of 6.9 months, statistically greater than paclitaxel alone, which had an overall response rate of 16% (\( p = 0.001 \)) and a three-month median time to progression (\( p = 0.0001 \)).

Although the overall response rate for paclitaxel alone was low, it may have been a result of prior selection for anthracycline-pretreated patients along with the impact of tumors that overexpressed HER2. For the combination of doxorubicin and cyclophosphamide, the overall response rate was 52% with anti-HER2 antibody and 43% without (\( p = 0.0025 \)), with median time to progression of 8.1 months and 6.1 months (not statistically different), respectively. Of concern, the incidence of symptomatic cardiac toxicity (NYHC CHF grade III-IV) was higher than expected, 16%, in patients who had received anthracycline and cyclophosphamide with antibody as compared with those who received no antibody, 2%. Cardiac toxicity was not increased in the paclitaxel-treated patients, with 0% incidence of symptomatic cardiac toxicity observed in the paclitaxel-alone arm and a 2% incidence in the patients receiving paclitaxel with anti-HER2 antibody.

The exact mechanism underlying the increased incidence of cardiac events in the anthracycline/cyclophosphamide plus anti-HER2 antibody arm has not been fully elucidated; however, it does appear that this increased incidence is related to concurrent administration of the agents. Because of concerns of cardiac toxicity when the antibody was combined with anthracycline/cyclophosphamide, it was suggested that future studies administering concurrent chemoimmunotherapy with anti-HER2 antibody focus on paclitaxel-based therapy.

Currently, clinical trials of paclitaxel and anti-HER2 antibody are being developed for patients with locally advanced breast cancer, as well as trials of doxorubicin/cyclophosphamide with dextrazoxane and anti-HER2 antibody. Along with these agents, combination antibody therapy with other drugs, such as carboplatin, may be warranted. It is clear that evaluation of chemotherapy/antibody trials in breast cancer will be a priority in the coming years.

**Paclitaxel in Adjuvant Therapy**

While the majority of breast cancer patients present with disease confined to the breast, many subsequently relapse and eventually succumb to metastatic disease. Accordingly, a major goal of adjuvant chemotherapy is elimination of micrometastatic disease likely to be present at the time of initial diagnosis. The importance of adjuvant treatment for breast cancer has been widely accepted since the 1970s. Further evidence supporting this view was a 1992 worldwide meta-analysis of 10-year follow-up results from randomized trials, which revealed significant improvements in disease-free and overall survival in patients receiving adjuvant chemotherapy [103].

The activity and tolerability of paclitaxel in metastatic disease has led to the investigation of this agent in the adjuvant and neoadjuvant settings. The feasibility of including paclitaxel in adjuvant regimens for node-positive breast cancer patients was demonstrated in a pilot trial using a dose-intensified regimen of doxorubicin/cyclophosphamide with granulocyte colony-stimulating factor (G-CSF) support followed by paclitaxel in high-risk patients with multiple positive nodes [104].

Randomized clinical trials incorporating paclitaxel have been initiated, with one phase III trial recently reporting preliminary results and a second to complete accrual in the near future. Trials such as these often require three to four years to complete accrual.

**Adjuvant Clinical Trials**

Pilot trials have been completed at MSKCC evaluating the addition of paclitaxel to sequential regimens of doxorubicin and cyclophosphamide in node-positive breast cancer patients. The initial pilot trial evaluated treatment with doxorubicin followed by paclitaxel followed by cyclophosphamide compared with the sequence of doxorubicin followed by cyclophosphamide, as used in a previous MSKCC trial. Recipients of the paclitaxel-containing regimen achieved a disease-free survival rate of 81% [105]. By comparison, the disease-free survival rate was 58% among patients in the earlier trial who did not receive paclitaxel. The toxicity of the paclitaxel-containing regimen was significant but manageable, necessitating hospitalization in 69% of patients and 17% of total cycles [106]. However, cardiotoxicity was not observed.

A second pilot trial at MSKCC evaluated a regimen of doxorubicin followed by paclitaxel followed by cyclophosphamide, compared with the sequence of doxorubicin followed by concurrent paclitaxel/cyclophosphamide [51]. With a median follow-up time of 10 months, no relapses were observed. The regimen delivering the three drugs sequentially was found to be more tolerable than the regimen using concurrent paclitaxel/cyclophosphamide [51].

As summarized in Table 4, current clinical trials are focusing on adjuvant therapy using differing sequences of standard chemotherapeutic agents with and without the addition of paclitaxel to the regimens. Preliminary results of CALGB 9344 were recently made available [107]. This trial investigated the effects of doxorubicin dose intensification as well as sequential therapy with paclitaxel in women with resected, node-positive breast cancer. In the 3 \( \times \) 2 factorial design, patients were randomized to receive
doxorubicin 60, 75, or 90 mg/m² with cyclophosphamide 600 mg/m², and then randomized again to receive continued therapy with paclitaxel 175 mg/m² by 3-h infusion for four cycles or no further therapy. The trial enrolled 3,170 patients. The interim analysis reported results at a median of 18 months’ follow-up, where it was found that the addition of paclitaxel to doxorubicin/cyclophosphamide resulted in statistically significant increases in both disease-free ($p = 0.0077$) and overall survival ($p = 0.039$) (Table 4).

The dose level of doxorubicin administered had no impact on survival. No unexpected toxicities were observed, and therapy was well tolerated overall. The authors concluded that the addition of paclitaxel to standard therapy with doxorubicin and cyclophosphamide significantly improved survival outcomes at the time of analysis. Reports of results at longer follow-up intervals are eagerly awaited to better define the impact of sequential paclitaxel therapy in these patients.

NSABP study B-28 is also evaluating the effect of the addition of sequential paclitaxel to doxorubicin/cyclophosphamide therapy in patients with resected, node-positive breast cancer. The target accrual for the study, over 3,000 patients, has been met; data analyses are pending [108].

A phase III trial in progress at the Istituto Nazionale Tumori of Milan is comparing a treatment sequence consisting of doxorubicin/paclitaxel followed by cyclophosphamide/methotrexate/5-FU (CMF) with an otherwise identical regimen omitting paclitaxel. This trial involves previously untreated stage II/III breast cancer patients with tumors exceeding 2 cm in maximum diameter.

The Southwest Oncology Group (SWOG) is leading a randomized multicenter phase III Intergroup trial (S9623) comparing a regimen of sequential doxorubicin, paclitaxel, and cyclophosphamide with a regimen of concurrent standard-dose doxorubicin/cyclophosphamide followed by high-dose cyclophosphamide/cisplatin/carmustine (STAMP I) or cyclophosphamide/carboplatin/thiotepa (STAMP V) with autologous stem cell rescue. Study participants are previously untreated stage I/IIIA breast cancer patients with involvement of four to nine axillary lymph nodes.

Accrual commenced in late 1997 for a randomized Intergroup trial (CALGB C9741) of adjuvant therapy in previously untreated node-positive, stage II/IIIA breast cancer patients. The sequence of doxorubicin followed by paclitaxel followed by cyclophosphamide is being compared with a regimen of concurrent doxorubicin/cyclophosphamide followed by paclitaxel. In addition to comparing two different sequences of administration of the chemotherapeutic agents, CALGB C9741 will compare a shorter, more dose-dense intertreatment interval of 14 d with an interval of 21 d.

### Neoadjuvant Clinical Trials

Novel chemotherapeutic strategies that prove successful in the metastatic and adjuvant settings may potentially also find application in neoadjuvant treatment. By diminishing primary tumor size, neoadjuvant therapy may allow a patient to undergo more conservative surgery or even render an otherwise inoperable patient operable. Also, therapy may impact local and distant relapse [109]. Neoadjuvant paclitaxel treatment is under study in a number of clinical trials (Table 5).

#### Table 4. Adjuvant paclitaxel clinical trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Design</th>
<th>Patients</th>
<th>Chemotherapy</th>
<th>Criteria</th>
<th>DFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completed trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CALGB 9344 [107]</td>
<td>Phase III</td>
<td>3,170</td>
<td>AC versus AC + T</td>
<td>Resected, n &gt; 0</td>
<td>86%</td>
<td>95%</td>
</tr>
<tr>
<td>MSKCC [51, 105, 106]</td>
<td>Pilot trials</td>
<td>112</td>
<td>A + C versus A + T + C; A + T + C versus A + T</td>
<td>Resected, n &gt; 0</td>
<td>Addition of paclitaxel resulted in improved disease-free survival rate. Sequential therapy better tolerated than combination.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Current trials</th>
<th>Design</th>
<th>Patients</th>
<th>Chemotherapy</th>
<th>Criteria</th>
<th>DFS</th>
<th>OS</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td>NSABP-B-28 [108]</td>
<td>Phase III</td>
<td>3,050</td>
<td>AC versus AC + T</td>
<td>Resected (stage II/IIIA), n &gt; 0</td>
<td>Ongoing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Milan (INT-23/96)*</td>
<td>Phase III</td>
<td>900**</td>
<td>A + CMF versus AT + CMF</td>
<td>Operable (stage II/III), tumor &gt;2 cm</td>
<td>Ongoing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SWOG-S9623</td>
<td>Phase III</td>
<td>1,000</td>
<td>A + T + C versus AC + STAMP I or V</td>
<td>Resected (stage II/IIIA), N4-9</td>
<td>Ongoing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CALGB C9741</td>
<td>Phase III</td>
<td>1,584</td>
<td>A + T + C versus AC + T</td>
<td>Operable (stage II/IIIA), N1-2</td>
<td>Ongoing</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: A = doxorubicin; C = cyclophosphamide; T = paclitaxel; M = methotrexate; F = 5-FU; STAMP I = cyclophosphamide/cisplatin/carmustine; STAMP V = cyclophosphamide/carboplatin/thiotepa; DFS = disease-free survival; OS = overall survival.

*Neoadjuvant arm of this trial summarized in Table 5; **450 in each arm.
Follow-up is ongoing in a prospective randomized trial at MDACC, evaluating neoadjuvant paclitaxel versus 5-FU/doxorubicin/cyclophosphamide (FAC) in patients with operable breast cancer [110]. Preliminary data suggest that paclitaxel alone is comparable in antitumor activity to FAC in the treatment of early breast cancer. The extent of cytoreduction was similar with the two induction regimens, both of which were well tolerated. However, paclitaxel treatment was associated with an increased incidence of neutropenic fever.

The previously described trial at the Istituto Nazionale Tumori of Milan includes a neoadjuvant arm. The trial is investigating neoadjuvant doxorubicin/paclitaxel followed by CMF in patients with operable stage II/III breast cancer.

An Austrian multicenter, open-label, dose-escalating phase II trial of neoadjuvant paclitaxel has been completed [111]. An overall response rate of 61% was observed in patients treated with paclitaxel 250 mg/m² for a minimum of four cycles or best response, followed by surgery. Among the 33 study patients, neoadjuvant paclitaxel allowed modified radical mastectomy to be performed in 23 and partial resection in eight. Three of the nine patients originally with T3 disease were able to be downstaged.

An ongoing phase II trial of neoadjuvant paclitaxel in patients with locally advanced or metastatic disease is being carried out by investigators at Brown University [31, 110]. This dose-intensive regimen delivers weekly paclitaxel 175 mg/m² by 3-h infusion for six weeks of an eight-week cycle. Of 14 evaluable patients with locally advanced disease, three achieved a complete remission and eight had partial responses. Hematologic toxicity was manageable. Patients experiencing neurotoxicity improved with interruption of paclitaxel therapy, and dose reductions allowed patients to continue treatment with stable or improving neurologic symptoms.

A phase II trial of neoadjuvant weekly paclitaxel during radiation therapy is being conducted in patients with locally advanced breast cancer by investigators at the University of Southern California (USC) and Mayo Clinic Jacksonville. Patients will receive paclitaxel 30 mg/m² over 1 h twice weekly during radiation therapy and prior to surgery. This approach may gain advantage from the radiosensitizing activity of paclitaxel. The endpoints of the trial will be the pathologic assessment of tumor response at mastectomy and evaluation of cellular and molecular correlates associated with pathologic response. These endpoints will also be assessed in a pilot trial at USC, New York University (NYU) and Mayo Clinic Jacksonville of neoadjuvant paclitaxel therapy in T2 premenopausal breast cancer patients.

**CONCLUSIONS**

Paclitaxel is among the most effective agents in the treatment of breast cancer. Both as a single agent and in combination regimens, paclitaxel is effective as first-line therapy and as salvage therapy in patients with advanced disease. Paclitaxel has also demonstrated efficacy in patients who have received prior anthracycline therapy and those with anthracycline-resistant disease. In the adjuvant setting, data from a randomized study have supported the sequential use of paclitaxel after therapy with doxorubicin and cyclophosphamide for patients with node-positive disease.

The unique mechanism of action of paclitaxel and its relatively well-tolerated toxicity profile have made it a candidate for combination therapy with other active agents in breast cancer. Combination regimens with paclitaxel and

---

**Table 5. Neoadjuvant paclitaxel clinical trials**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Design</th>
<th>Patients</th>
<th>Chemotherapy</th>
<th>Criteria</th>
<th>Status</th>
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</thead>
<tbody>
<tr>
<td>Austrian Multicenter</td>
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<td>33</td>
<td>T</td>
<td>Stage T3-4, N0-3, M0</td>
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<td>Brown University</td>
<td>Phase II</td>
<td>39</td>
<td>T</td>
<td>Locally advanced or metastatic</td>
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<td>Oncology Group</td>
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<tr>
<td>Mayo/USC</td>
<td>Phase II</td>
<td>40</td>
<td>T</td>
<td>Stage T2-3</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Mayo/USC</td>
<td>Phase II</td>
<td>40</td>
<td>T (biweekly with RT)</td>
<td>Locally advanced</td>
<td>Ongoing</td>
</tr>
<tr>
<td>MDACC</td>
<td>Phase III</td>
<td>104</td>
<td>FAC versus T</td>
<td>Stages T2-3, N0-1, M0</td>
<td>Fully accrued; in follow-up.</td>
</tr>
<tr>
<td>Milan (INT-23/96)*</td>
<td>Phase III</td>
<td>450</td>
<td>AT +CMF</td>
<td>Operable (stage II/III), tumor &gt; 2 cm</td>
<td>Ongoing</td>
</tr>
</tbody>
</table>

Abbreviations: F = 5-FU; A = doxorubicin; C = cyclophosphamide; T = paclitaxel; M = methotrexate; RT = radiation therapy.

*Adjuvant arms of this trial summarized in Table 4.
anthracyclines have demonstrated very good response rates. With doxorubicin, however, one must be aware of the potential for undue cardiac effects and limit the cumulative doxorubicin dose to 380 mg/m^2 or lower. In Europe, combination therapy with epirubicin has produced promising results; these may be of particular interest to clinicians in the U.S. as epirubicin may soon become available in this country.

With respect to platinum agents, combination paclitaxel and carboplatin has produced very high response rates as first-line therapy in patients with metastatic disease. The combination is also effective in patients who have failed anthracycline therapy. Combination therapy with cisplatin, while potentially active, is associated with an undesirable rate of toxicity. Combination regimens with other agents, including 5-FU, vinorelbine, and gemcitabine also appear to be promising.

Recent phase III studies have helped define the optimal dose and schedule of paclitaxel in advanced breast cancer. CALGB 9342 did not detect a dose-response relationship in either overall response or overall survival among doses of 175, 210, or 225 mg/m^2 by 3-h infusion. Given that hematologic and neurologic toxicities increased with dose, a recommendation for a paclitaxel dose of 175 mg/m^2 was made. NSABP study B-26 and a trial at MDACC evaluated the effect of schedule on paclitaxel efficacy. Although the overall response rate in NSABP B-26 was higher with the 24-h schedule than with the 3-h schedule, no survival advantage was observed. In the MDACC study of 3 h versus 96 h of paclitaxel, no difference in response or survival was observed. As a result, the 3-h schedule of paclitaxel was deemed more appropriate, considering the logistics and hematologic toxicities encountered with the longer schedules. Taken together, a dose of 175 mg/m^2 by 3-h infusion every three weeks appears to be very reasonable in the treatment of advanced breast cancer. In combination therapy, this dose is often easily combined with other agents, producing manageable toxicity and not usually requiring hematopoietic growth factor support.

The issue of weekly paclitaxel is particularly intriguing, as it appears that this schedule allows for a greater dose density while disassociating from a common toxicity, neutropenia. Trials with moderate-dose weekly paclitaxel (80-100 mg/m^2) have observed very good response rates with remarkably little toxicity, even in heavily pretreated patients. Neutropenia is generally mild, and neuropathy, although more common, is generally less than grade 2. Further investigation into the role of weekly paclitaxel, both as a single agent and as part of combination and sequential therapy, is ongoing.

Finally, the addition of paclitaxel to anti-HER2 antibody therapy has resulted in much interest over the response and tolerability of this combination. This trial not only demonstrates the improved efficacy of combination antibody therapy with traditional chemotherapy in advanced breast cancer, it heralds the arrival of a new and anxiously awaited class of anticancer agents. Much activity in this area is expected in the coming years.

In summary, paclitaxel is effective in the treatment of breast cancer on a number of different levels. It has proven efficacy in the advanced and metastatic settings as well as in adjuvant treatment. The drug may be used as a single agent, as sequential therapy, or in combination with other chemotherapy agents and immunologic agents. Therapy on weekly and every-three-week schedules has been effective. Ongoing trials will continue to define the optimal role of paclitaxel in the treatment of breast cancer.

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