Paclitaxel-Based Combination Chemotherapy for Breast Cancer

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Clinical trials to develop paclitaxel (Taxol)-containing combinations started in 1992 with several approaches to combine doxorubicin and paclitaxel. Schedule-dependent toxicity limited doses in the initial trials, although antitumor activity was high. More recently, a well-tolerated, highly effective doxorubicin/paclitaxel regimen was developed with the use of bolus anthracycline administration and a 3-hour infusion of paclitaxel. Combinations of paclitaxel with cisplatin have provided mixed results. Paclitaxel combined with fluorouracil (5-FU) and folinic acid proved effective in patients with extensive prior chemotherapy; the addition of mitoxantrone (Novantrone) to this combination was feasible, well tolerated, and possibly enhanced the efficacy of paclitaxel and 5-FU. Combinations of paclitaxel with cyclophosphamide (Cytoxan, Neosar), vinorelbine (Navelbine), edatrexate, and radiation continue in clinical development. [ONCOLOGY 11(Suppl):29-37, 1997]

Introduction

The initial clinical trials with single-agent paclitaxel (Taxol) demonstrated the marked antitumor efficacy of this agent in ovarian and breast cancer.[1,2] Subsequent clinical trials expanded the experience with this agent and showed that paclitaxel retained substantial antitumor efficacy in previously treated patients and that paclitaxel was active against metastatic breast cancer at a variety of doses and schedules of administration.[3-8] Comparative clinical trials to determine the optimal dose and schedule of administration of this agent are completing accrual. Paclitaxel has been extensively evaluated in combination with other cytotoxic agents with demonstrated activity against metastatic breast cancer (Table 1).

Doxorubicin/Paclitaxel Combinations

Soon after the first report of its antitumor activity, the evaluation of paclitaxel-based combinations started. Since doxorubicin, until the appearance of the taxanes, was considered the most active antitumor agent for metastatic breast cancer, the anthracycline/taxane combination was a logical first step. The University of Texas M. D. Anderson Cancer Center and the Medicine Branch of the National Cancer Institute (USA) initiated paclitaxel/doxorubicin combination phase I trials simultaneously.[9-13] Both groups used the longer durations of infusion of paclitaxel, since that was the schedule of administration used for single-agent trials. In addition, to limit cardiac and other nonhematologic toxicity related to anthracyclines, infusion schedules of administration were used for this agent, too (Table 2). Dose-limiting toxicities of these phase I trials included severe mucositis, diarrhea, tiflitis, and neutropenic fevers. Reversing the sequence of administration of doxorubicin and paclitaxel in the M. D. Anderson Cancer Center clinical trials allowed dose escalation by two or three levels, but eventually, the same dose-limiting toxicity was reached. These initial paclitaxel/doxorubicin combinations were clearly effective, with overall response rates ranging from 62% to 80% and with 95% confidence intervals ranging from 38% to 98%. Furthermore, it is noteworthy that no clinically relevant cardiac toxicity was observed; specifically, no instances of congestive heart failure were reported.

As the first reports of these combination trials appeared, other investigators designed new combinations with the same two agents or with other cytotoxic drugs. Shortening the duration of administration of doxorubicin permitted the administration of higher doses, yet a schedule-dependent interaction was noted and confirmed by pharmacokinetic studies.[14-16] Investigators at the Istituto Nazionale Tumori in Milan, Italy, developed a combination based on bolus administration of doxorubicin and a 3-hour administration of paclitaxel. When the two drugs were given in this schedule of administration, there was no apparent
schedule-dependent interaction of clinical relevance, although these authors also confirmed the previously described pharmacokinetic variations related to the sequence of administration. The doses administered could be increased to 60 mg/m² and 200 mg/m² for doxorubicin and paclitaxel, respectively, and the antitumor activity increased markedly, with an overall response rate exceeding 90%, and complete remission rate now greater than 40% (Table 3).[17]

Observers of this trial were concerned by the appearance of congestive heart failure in 20% of patients and a greater than 15% decrease in left-ventricular ejection fraction in as many as 75% of patients. In fact, in 22% of patients who did not develop clinical heart failure, ejection fraction dropped below 50%. A second study that used the same doses and schedule of administration as the Milan group confirmed these results, both in terms of antitumor activity and cardiac toxicity.[18]

Subsequent experience from the Milan group, limiting the total cumulative doxorubicin dose to 360 mg/m² (six cycles), demonstrated the safety of this regimen, with no episodes of heart failure in nearly 40 patients. [L. Gianni, personal communication, December 1996]

Currently, several confirmatory trials are ongoing. These trials employ the same schedule of administration of paclitaxel and anthracycline (in some studies, epirubicin was substituted for doxorubicin), and although substantial antitumor activity has been reported, these studies are not mature enough to fully assess the results in terms of antitumor activity and toxicity. A randomized phase II study is being conducted at The University of Texas M. D. Anderson Cancer Center, in which doxorubicin (60 mg/m²) is administered as an intravenous bolus followed immediately by paclitaxel (200 mg/m²), either by 1- or 3-hour administration. The study's major focus is close cardiac monitoring to identify whether this combination can be administered safely, to determine the regimen's degree of cardiac toxicity, and to see if the associated cardiac toxicity is the result of synergistic effects of these drugs. Elements of the study include clinical evaluation, noninvasive cardiac functional tests, and endomyocardial biopsies.

**Paclitaxel/Cisplatin Combinations**

Cisplatin (Platinol) is reported to have marked antitumor activity in previously untreated metastatic breast cancer.[19] In addition, cisplatin is less myelosuppressive than many other useful agents against metastatic breast cancer and is considered a good candidate for combination with paclitaxel. One group developed a regimen in which cisplatin was given at 60 mg/m² with the appropriate premedication and hydration, while paclitaxel was administered at 90 mg/m² as a 3-hour infusion.[20] The combination was repeated at 14-day intervals.

In an exploratory study that included mostly patients who had previously received an anthracycline, there was an overall response rate of 85%, including an 11% complete response rate (Table 4). Tolerance was acceptable. There were no episodes of grade 4 nonhematologic toxicity, although grade 2 to 3 fatigue, peripheral neuropathy, and nausea were reported. Myelosuppression and neutropenic fevers were also seen.

Wasserheit et al used higher dosages of both cisplatin and paclitaxel at 3-week intervals.[21] The activity of this regimen was less impressive than that reported by Gelmon and collaborators, and the toxicity was considerably higher. Other investigators have also reported successful combinations of cisplatin and paclitaxel. The optimal dose and schedule of administration for this combination remain to be established.

**Paclitaxel/Cyclophosphamide Combinations**

Because the mechanisms of action of alkylating agents and taxanes are different, as are many of the side effects and mechanisms of resistance, and because cyclophosphamide (Cytoxan, Neosar) is an integral part of most commonly used combination regimens for breast cancer, this was another logical combination to explore. Some of these combinations used standard doses of cyclophosphamide, while others increased the dose of the alkylating agent to two- to sixfold the standard dose[22-25] (Table 5). Because myelosuppression is an overlapping toxicity of the two agents, hematopoietic growth factors were used in all these trials.

Tolcher et al reported the results of his dose-escalation study, which demonstrated a 62% overall response rate in 56 patients treated with 160 mg/m² of paclitaxel infused over 72 hours and 3,300 mg/m² of cyclophosphamide.[23] Although the combination is clearly active, myelosuppression is quite considerable, and the need for the systematic addition of granulocyte colony-stimulating factor (G-CSF [Neupogen]) makes this combination less attractive than other paclitaxel-based regimens. Paclitaxel has also been combined with vinorelbine (Navelbine). This new nor-vinblastine analog is substantially active in metastatic breast cancer, and it is very well tolerated when administered.
weekly as a single agent.[26] Vinorelbine is a tubulin-active agent, and it was anticipated on the basis of preclinical experiments that the sequence of administration with a taxane would be an important consideration.[27]

Several phase I or exploratory trials of the vinorelbine/paclitaxel combination are in progress. The University of Texas M. D. Anderson Cancer Center group used a simultaneous schedule of administration for vinorelbine and paclitaxel: both were given as a 3-hour IV infusion every 3 weeks.[28] Dose-limiting toxicities were neutropenic fever and cumulative neuropathy. With hematopoietic growth factor (G-CSF) support, additional dose escalation was possible, and neuropathy became the dose-limiting event.[29] This combination was also active, with objective response rates in the 50% to 65% range.

In other centers, paclitaxel and vinorelbine are being evaluated in sequential schedules of administration.[30-32] Although no definitive results have been reported, peripheral neuropathy appears to be a less prominent problem in these trials.

**Other Combinations**

Additional combinations include fluorouracil (5-FU), mitoxantrone (Novantrone), or combinations of both (Table 6). These combinations appear to have substantial antitumor activity, even in patients with extensive prior chemotherapy exposure.[33-35]

**Combinations With Investigational Agents**

Paclitaxel combinations with edatrexate, losoxantrone, and other new agents are in progress.[36,37] No definitive results are available.

**Randomized Clinical Trials**

One very important trial compares single-agent paclitaxel, single-agent doxorubicin, and the combination of doxorubicin and paclitaxel.[16] This study has now completed accrual, although results are not available as yet.

Based on the promising results of the paclitaxel/doxorubicin combinations, the Southwest Oncology Group (SWOG) recently initiated a comparative trial in which the standard combination of doxorubicin/cyclophosphamide is being compared with doxorubicin/paclitaxel. This randomized trial will define the relative efficacy and toxicities of these two attractive combinations. This comparison is all the more important since the doxorubicin/paclitaxel combination is already being introduced into the adjuvant therapy of high-risk primary breast cancer.

**High-Dose Combination Chemotherapy**

The initial phase I studies with paclitaxel established 250 mg/m² as the maximum tolerated dose when paclitaxel was administered by a 24-hour infusion. Subsequent clinical trials have suggested that this is also the maximum tolerated dose when paclitaxel is administered over 3 hours every 21 days. More prolonged schedules of administration, such as a 96-hour infusion every 21 days, produce more intensive myelosuppressive and mucocutaneous toxicity. The maximum tolerated dose of paclitaxel when administered by this schedule is 140 mg/m² for good-risk patients (and 120 mg/m² for poor-risk patients). No formal phase I trials were conducted with paclitaxel given over 1 hour; therefore, the maximum tolerated dose of this schedule is uncertain, although it is likely to be similar to that achieved with a 3-hour infusion.

These maximum tolerated doses were defined in the absence of G-CSF or granulocyte-macrophage colony-stimulating factor (GM-CSF [Leukine, Prokine]) or other forms of hematopoietic support. Recent dose-escalation trials have demonstrated that the dose of paclitaxel can be increased substantially (more than threefold) when treatment is limited to a single cycle. At the maximum dose administered, 825 mg/m², pulmonary capillary leak, stupor, renal insufficiency, and mucositis were dose-limiting effects.[24] The authors considered that the recommended dose would be one level lower, at 750 mg/m². Even this dose results in substantial peripheral neuropathy, which appears to be slowly reversible.

Other attempts at intensifying the dose of paclitaxel concentrated on intermediate doses and the ability to deliver multiple cycles. The Memorial Sloan-Kettering Cancer Center group introduced a regimen based on high-dose alkylating agents combined with full-dose (250 mg/m²) paclitaxel over four cycles of treatment with G-CSF and peripheral stem-cell support.[38] This regimen is clearly
tolerable, and the therapeutic results are awaited with interest. The University of Texas M. D. Anderson Cancer Center Bone Marrow Transplantation Group developed a combination of high-dose carboplatin, high-dose cyclophosphamide, and full-dose paclitaxel (250 mg/m²); this regimen is also intended for multicycle administration with G-CSF and peripheral cellular support. This combination is also well tolerated and effective, although its final evaluation is incomplete. [Z. Rahman, unpublished information]

The sequential administration of doxorubicin and paclitaxel at full doses, combined with high-dose cyclophosphamide (3,000 mg/m²) and with G-CSF support to accelerate hematopoietic recovery is currently under evaluation both for metastatic and high-risk adjuvant therapy. [39,40] In addition, a regimen that incorporates the doxorubicin/paclitaxel combination described above with the addition of high-dose cyclophosphamide, G-CSF, and peripheral stem-cell support is currently under evaluation at The University of Texas M.D. Anderson Cancer Center.

To date, while there is suggestive evidence that higher doses of paclitaxel may be more effective than lower doses, the dose-response curve remains largely undefined. Many of the studies described above are exploratory in nature and will contribute some information to our understanding of the dose-response curve. More important, randomized clinical trials specifically designed to address the dose-response correlation are in progress.

**Paclitaxel for Adjuvant Chemotherapy of Breast Cancer**

The marked antitumor activity of paclitaxel as a single agent or as part of combination chemotherapy for metastatic breast cancer has led to the introduction of this agent into clinical trials of adjuvant therapy of breast cancer. In several clinical trials, paclitaxel was added at full doses to existing combinations, mostly combinations of doxorubicin and cyclophosphamide (Table 7). [11,41] This addition is made sequentially, with paclitaxel either preceding or following the administration of standard adjuvant chemotherapy with doxorubicin/cyclophosphamide.

In another study, the sequential administration of dose-dense doxorubicin followed by paclitaxel and then intermediate-dose cyclophosphamide is being compared to standard chemotherapy with doxorubicin/cyclophosphamide followed by one cycle of high-dose chemotherapy with autologous cellular support (SWOG 96-23).

Finally, a recently activated European trial will compare four cycles of doxorubicin/paclitaxel followed by eight cycles of cyclophosphamide/methotrexate/fluorouracil (CMF) to four cycles of doxorubicin alone followed by eight cycles of CMF. [L. Gianni, unpublished information] This is in an attempt to build on the efficacy of a well-established adjuvant chemotherapy program in which four cycles of doxorubicin were followed by eight cycles of CMF. [42,43]

**Conclusions**

The clinical development of paclitaxel continues at an accelerated pace. Multiple combinations based on this agent have demonstrated marked antitumor activity in metastatic breast cancer and are under evaluation in randomized trials. The dose-response correlation of paclitaxel is under active investigation, while the limits of dose-escalation are being explored.

Perhaps most important, paclitaxel as a single agent or as part of combination therapy is under evaluation in the multidisciplinary management of primary breast cancer. It may be at this juncture that new agents such as paclitaxel are expected to make their greatest contribution to the management of breast cancer.

**References:**


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