Paclitaxel and Carboplatin for Advanced Breast Cancer

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This report evaluates the activity of paclitaxel alone (Taxol; Bristol-Myers Squibb Company, Princeton, NJ), carboplatin alone, and their combination in the treatment of patients with advanced breast cancer. The preliminary safety information of this combination in other tumor types is also discussed. Finally, the overall rationale for ongoing studies of the efficacy of paclitaxel and carboplatin, along with appropriate translational studies, as first-line chemotherapy in patients with metastatic breast cancer is examined. Both paclitaxel and carboplatin have well-established single-agent activity in the treatment of women with breast cancer. The tolerability of this combination, using the sequence paclitaxel followed by carboplatin infusion, has already been established in patients with lung cancer and ovarian cancer. In addition, this therapy has the novel attribute of a relative platelet-sparing effect. A phase II trial evaluating the efficacy of the paclitaxel/carboplatin combination, along with the evaluation of thrombopoe­titin levels and quality of life, has been initiated recently through the North Central Cancer Treatment Group. In this trial, intravenous paclitaxel 200 mg/m² infused over 3 hours is followed by carboplatin at a calculated area under the concentration-time curve dose of 6, with cycles repeated every 21 days. Results from this trial will help document the role of the paclitaxel/carboplatin combination in the treatment of women with breast cancer.

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METASTATIC breast cancer is rarely curable with standard chemotherapy. Standard chemotherapy combinations like cyclophosphamide/doxorubicin or cyclophosphamide/methotrexate/5-fluorouracil result in objective responses in approximately 30% to 50% of such patients. Since a significant portion of patients with operable breast cancer are candidates for adjuvant chemotherapy with cyclophosphamide/methotrexate/5-fluorouracil or cyclophosphamide/doxorubicin/5-fluorouracil (or similar regimens), many patients with advanced breast cancer will already have been exposed to the drugs most commonly used to treat advanced disease, rendering them less likely to respond to such therapy a second time. The identification of active new drugs or drug combinations, therefore, is urgently needed.

PACLITAXEL IN ADVANCED BREAST CANCER

Paclitaxel (Taxol; Bristol-Myers Squibb Company, Princeton, NJ) is a promising new agent in the treatment of women with advanced breast cancer. Its use leads to objective responses in approximately 50% to 60% of such patients when used as initial therapy. Paclitaxel also produces objective responses in approximately 20% to 25% of patients with advanced disease who are resistant to other chemotherapy. Clinical trials have investigated the administration of paclitaxel every 3 weeks at varying doses (135 to 250 mg/m²) and schedules (1- to 96-hour infusions). Weekly administration of paclitaxel is also being investigated, as is prolonged continuous infusion. Paclitaxel's optimal dose and administration schedule, whether used as a single agent or in a combination regimen, are a matter of extensive ongoing research. The dose-limiting toxicity of paclitaxel, a deep but brief neutropenia, is both dose and schedule dependent. A variety of combination chemotherapy trials with paclitaxel and other agents have been reported recently, demonstrating the potentially important role of this agent in combination treatment. Phase I/II studies by Gianni and colleagues and Gehl et al evaluated paclitaxel and doxorubicin in patients with metastatic breast cancer. Preliminary data are consistent with previous trials and show overall response rates greater than 85% and complete response rates between 30% and 40%; however, further follow-up will be necessary to evaluate the impact of this combination on median length of survival. The concurrent use of these two agents is associated with a somewhat greater than expected degree of cardiac toxicity, thereby limiting the total cumulative dose of doxorubicin to no greater than 360 mg/m². Recent phase II studies evaluating paclitaxel 200 mg/m² plus doxorubicin 60 mg/m² intravenously (IV) every 3 weeks, with and without hematopoietic growth factors, have been initiated through the Eastern Cooperative Oncology Group and the Southwest Oncology Group.

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The combination of paclitaxel/cisplatin has been studied by several groups using biweekly schedules for the treatment of breast cancer. Response rates are reported to be between 44% and 94%, depending on the extent of prior therapy. Cumulative neurotoxicity appears to be significant, with 91% of patients in one study presenting with some degree of neuropathy by the fifth course of treatment and 50% of patients in another study having to be withdrawn from treatment.

Data from trials of paclitaxel combined with other agents, including ifosfamide, also have been reported recently. Murad et al, for example, evaluated paclitaxel 175 mg/m² IV over 3 hours on day 1, plus ifosfamide at a dose of 1.8 g/m² on days 2 to 4, along with mesna in 22 patients receiving third- or fourth-line chemotherapy for metastatic breast cancer, with cycles repeated every 21 days. Preliminary data are consistent with a response rate of 50% and only moderate toxicity, with one case of grade 3 neuropathy and three cases of transient grade 4 neutropenia. Further combination trials of paclitaxel and other chemotherapy agents are warranted.

**Carboplatin in Advanced Breast Cancer**

Like paclitaxel, carboplatin also has substantial activity when used as a single agent in the treatment of advanced breast cancer, yielding objective responses in approximately 25% to 37% of patients who have not received chemotherapy for advanced disease. Carboplatin is a less reactive derivative of cisplatin, but both drugs are activated to the same aquated metabolites. The major difference between carboplatin and cisplatin is that carboplatin has a lower toxicity profile. The renal, neurologic, ototoxic, and emetic toxicities of carboplatin are reduced substantially compared with those seen with cisplatin, making carboplatin a better-tolerated form of the parent compound. Furthermore, carboplatin can be administered on an outpatient basis. The most prominent toxic effect of carboplatin is myelosuppression with prominent thrombocytopenia. Several published formulas, such as the Calvert formula, can now successfully predict for a particular level of carboplatin-induced thrombocytopenia. This is based on dosage individualization based on the glomerular filtration rate (GFR) and target area under the concentration-time curve (AUC), with the total dose of carboplatin (mg) = AUC × (GFR + 25).

**Paclitaxel Plus Carboplatin**

To our knowledge, the combination of paclitaxel/carboplatin has not been studied in the treatment of patients with metastatic breast cancer. Phase I and II dose escalation studies of this combination, however, have sought an effective, well-tolerated dose for the treatment of patients with non–small cell lung cancer. Cumulative severe neurotoxicity was not found to be a significant problem when paclitaxel was infused over 3 hours and then followed by carboplatin. In a recent dose escalation study of paclitaxel and carboplatin in previously untreated patients with non–small cell lung cancer, the investigators established that the maximum tolerated dose was paclitaxel 250 mg/m² with carboplatin at an AUC of 6 given every 3 weeks. The dose-limiting toxicity consisted primarily of grade 3 osteoarthralgias or sensory neuropathy. Paclitaxel 225 mg/m² given over 3 hours and followed immediately by carboplatin at an AUC of 6 was established as the optimal dose. Grade 3 or 4 thrombocytopenia was not seen, but 10% of patients demonstrated grade 3 sensory neuropathy after the third treatment cycle. Preliminary data of this combination for advanced non–small cell lung cancer are consistent with response rates between 50% and 65% and median lengths of survival in excess of 1 year.

Based on this background information, we initiated through the North Central Cancer Treatment Group a phase II study of patients receiving first-line chemotherapy for advanced or metastatic breast cancer. Paclitaxel 200 mg/m² IV was administered over 3 hours followed by carboplatin at an AUC of 6, based on the Calvert formula, with cycles repeated every 21 days. In addition to evaluating the efficacy and toxicity of this combination, this trial includes two corollary studies, one to determine its effect on thrombopoietin (TPO) levels and the other to evaluate effect of treatment on quality of life using the Functional Assessment of Cancer Therapy—Breast (FACT-B) scale.

Our primary objective is to determine the response rate achieved by paclitaxel/carboplatin in the treatment of women with advanced breast cancer; the secondary objectives are to determine its time-to-progression and toxicity and to evaluate its effect on patients' quality of life and serum TPO levels. The study is being conducted in women who are at least 18 years of age who have histologic-
cally confirmed adenocarcinoma of the breast with manifestations of metastatic cancer and measurable disease. All women have an Eastern Cooperative Oncology Group performance status of 0, 1, or 2, a life expectancy of \( \geq 3 \) months, and adequate hematologic, renal, and hepatic functions.

Premedication for paclitaxel is required and consists of dexamethasone 20 mg orally 6 and 12 hours before paclitaxel plus dexamethasone 20 mg IV in combination with diphenhydramine 50 mg and cimetidine 300 mg IV administered 30 to 60 minutes before paclitaxel. (Omitting the oral dexamethasone premedication at 6 and 12 hours prior to paclitaxel infusion is permitted.) Paclitaxel is then administered as a 3-hour infusion in 500 mL of D5W. Carboplatin is infused immediately after paclitaxel, over 30 minutes in 250 mL of D5W. The dose of carboplatin administered is calculated by the Calvert formula: carboplatin dose \( (\text{mg}) = \text{target AUC} \times (\text{GFR} + 25) \). The treatment cycles are repeated every 21 days. Preliminary results from this trial should be available in the next several months.

**Paclitaxel, Carboplatin, and Platelets**

In addition to the above tolerability and response data, Kearns et al have observed that paclitaxel has a modulating effect on the thrombocytopenia caused by carboplatin.\(^{31}\) This effect was measured in two other separate studies as well. Each study demonstrated that platelet nadirs increased as the doses of paclitaxel increased.\(^{30,32}\)

Bolis et al\(^{19}\) reported that as the dose of paclitaxel increased, while the dose of carboplatin remained at 300 mg/m\(^2\), both the median platelet nadir and the median white blood cell nadir increased. This finding suggests a modulatory effect of paclitaxel on carboplatin-induced myelosuppression. In addition, significant dose-limiting nonhematologic toxicity was not observed using the combination of paclitaxel 150 to 250 mg/m\(^2\) administered over 3 hours and carboplatin at 300 mg/m\(^2\) in this study.

A study by Siddiqui et al\(^{33}\) demonstrated that the incidence of thrombocytopenia decreased as the dose of paclitaxel increased from 150 to 175 mg/m\(^2\) administered over 3 hours in combination with carboplatin. The investigators concluded that paclitaxel has a protective effect on the thrombocytopenia caused by carboplatin. They further concluded that the pharmacokinetics of carboplatin are not altered by concurrent use of paclitaxel. The pathophysiology of this interaction has not been elucidated, but potential inhibition of platelet microtubules, modulation of cytokines such as TPO, or interference with megakaryocyte ploidy/blebbing are hypotheses worthy of exploration.

Platelets are released from long pseudopods extending from megakaryocytes, either directly or from proplatelets, which are fragments of pseudopods containing multiple platelet domain. Intracellular cytoskeletal proteins, such as tubulin, participate in pseudopod formation.\(^{34}\) Paclitaxel binds to tubulin subunits and thus may alter platelet release processes.\(^{35}\)

The primary hormone-regulating platelet production is TPO.\(^{34,36,37}\) Thrombopoietin, also referred to as c-Mpl ligand or megakaryocyte growth and development factor, is a mature polypeptide of 332 amino acids. Recombinant TPO stimulates the proliferation and maturation of megakaryocytic stem cells and megakaryocytes in vitro.\(^{34}\) It also influences characteristics of megakaryocytic maturation, such as cell size, ploidy, and the tendency to form pseudopods. Thrombopoietin can enhance the recognition of multilineage colonies that have a megakaryocytic component and thus may stimulate multipotential cells to some extent. Thrombopoietin blood levels change reciprocally to the circulating platelet count in both animals and humans,\(^{34,38}\) but the effect of chemotherapeutic drugs on circulating TPO levels or the relationship of TPO levels to platelet nadirs seen after the administration of chemotherapy have not been explored.

In this ongoing North Central Cancer Treatment Group study we propose to test the hypothesis that TPO blood levels are higher during periods of thrombocytopenia when paclitaxel is given just prior to carboplatin, compared with what would be expected with similar levels of thrombocytopenia in patients with primary bone marrow disorders.

**CONCLUSION**

Both paclitaxel and carboplatin have significant single-agent activity in the treatment of breast cancer. The combination appears to be tolerable, with less hematopoietic toxicity than was expected based on the potential additive toxicities of each agent. The antitumor activity of this combination is being established in a variety of tumor types.
Our ongoing trial of paclitaxel 200 mg IV over 3 hours followed by carboplatin AUC = 6 will help answer the question of the potential role of this combination in the treatment of advanced breast cancer.

REFERENCES


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