Memorial Sloan-Kettering Cancer Center Experience With Paclitaxel in the Treatment of Breast Cancer

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Paclitaxel (Taxol; Bristol-Myers Squibb Company, Princeton, NJ) is the most important new cytotoxic agent to be introduced for the management of breast cancer in many years. During this decade, investigators at Memorial Sloan-Kettering Cancer Center have conducted multiple clinical and laboratory investigations aimed at optimally integrating this agent into therapeutic strategies for breast cancer. These studies address both single-agent and combination regimens in the metastatic and adjuvant settings. This report will review previous results, but focus on active studies and future avenues of research. Copyright © 1995 by W.B. Saunders Company

After the initial demonstration of the safety and important antitumor activity of paclitaxel (Taxol; Bristol-Myers Squibb Company, Princeton, NJ) against metastatic breast cancer,1 we performed a series of phase II clinical trials characterizing its potential as single-agent therapy for metastatic breast cancer. These trials used various doses and schedules in patients without prior chemotherapy for stage IV disease as well as those with moderate and extensive prior therapy.2-4 (Table 1). In heavily pretreated patients, we have performed formal, parallel investigation of quality of life parameters to better assess the impact of paclitaxel among patients receiving this agent with palliative intent.5,7 These efforts are continuing prospectively in an ongoing study that addresses economic variables (charges/costs) in addition to quality of life and standard tumor response and toxicity outcomes for patients receiving paclitaxel by various infusion schedules. Motivated by preclinical data suggesting schedule-dependent cytokinetic variability in resistance profiles to taxanes5-12 and the demonstrated activity and safety of a 96-hour infusion schedule against anthracycline-refractory breast cancer,13 we have conducted a phase II and pharmacologic trial, evaluating the efficacy and safety of this prolonged infusion schedule in patients with demonstrated disease progression during brief taxane exposure.14 Efforts to better characterize clinically relevant mechanisms of resistance to paclitaxel in studies involving human breast cancer tissue are under way.

Paclitaxel combinations with various cytotoxic agents are being actively explored and are addressed elsewhere in this supplement. At our institution, we are investigating the combination of paclitaxel and edatrexate, a dihydrofolate reductase inhibitor with preclinical advantages over methotrexate15 and documented single-agent activity against metastatic breast cancer.16,17 The trial design derives from schedule-dependent synergy observed in vitro in mammary carcinoma cells.18,19 A novel area of potentially fruitful future clinical research pertains to the observed synergy between paclitaxel and monoclonal antibodies (MoAbs) directed at various growth factor receptor antibodies in human breast carcinoma xenografts.20,21 Studies addressing possible mechanistic explanations for this effect are ongoing.

The activity of paclitaxel and the potential for non-cross-resistance with anthracycline has motivated its evaluation as a component of an adjuvant sequential chemotherapy regimen for node-positive stage II/III resectable breast cancer.22 We are presently evaluating the optimal integration of paclitaxel into doxorubicin/cyclophosphamide-based adjuvant therapy in a randomized clinical trial. This report will address the past, present, and future investigations with paclitaxel in the treatment of breast cancer at Memorial Sloan-Kettering Cancer Center (MSKCC).

SINGLE-AGENT TRIALS

Impressed by an early report from the M.D. Anderson Cancer Center (Houston, TX) of the promising antitumor activity of paclitaxel (a 56% response proportion [95% confidence interval (CI), 35% to 76%] was seen among patients with minimal prior therapy1), we performed a confirmatory
phase II trial of paclitaxel as initial chemotherapy of metastatic breast cancer. In this study, 28 patients without prior chemotherapy for metastatic disease received paclitaxel 250 mg/m² via 24-hour infusion every 3 weeks. Significant myelosuppression was observed in the first two patients we treated on this protocol and indeed was dose limiting in the previous trial. The protocol was therefore amended such that all subsequent patients received granulocyte colony-stimulating factor (G-CSF) 5 µg/kg/d subcutaneously on days 3 through 10 of each cycle. A 62% response rate (95% CI, 41% to 80%) was noted, including three complete responses (CRs). Responses were seen in 10 of 16 patients (63%) who had received prior adjuvant chemotherapy, including one CR and four partial responses (PRs) among eight patients who had received prior doxorubicin-based adjuvant chemotherapy.

Treatment was well tolerated. Adverse effects included generalized alopecia in all patients; grade ≥3 nonhematologic toxicities were uncommon. Of 178 cycles administered, there were eight admissions (4%) for febrile neutropenia, involving six of 28 patients (21%). Administration of recombinant human G-CSF resulted in a median of 2 days with an absolute neutrophil count less than 500 cells/µL, shorter than that previously reported (7 days) without concomitant growth factor support. Notably, 58% of cycles were delivered at a reduced dose, most frequently 180 or 200 mg/m². The most common reason for dose reduction was an absolute neutrophil nadir less than 250 cells/µL and/or febrile neutropenia. Because of drug supply considerations, response duration was not a valid end point of this trial; the clinical trial design specified a length of treatment to two cycles beyond the best response to a maximum of 10 cycles per patient.

After this confirmation of paclitaxel's significant antitumor activity in patients with minimal prior treatment, we next focused on patients who had received extensive prior chemotherapy for metastatic breast cancer. We enrolled 51 patients who had previously received a minimum of two prior chemotherapy regimens for metastatic disease (median; 3; range, 2 to 6; all with prior anthracycline) into our second phase II trial. The median Karnofsky performance score for these patients was 70% (range, 60% to 90%). Of these patients, 14% had received prior high-dose chemotherapy regimens sufficiently myelotoxic to require reinfusion of autologous bone marrow and/or peripheral blood progenitor cells; two thirds of these patients had received radiotherapy for metastatic disease.

Paclitaxel was administered at 200 mg/m² via 24-hour infusion every 3 weeks with G-CSF support, as previously described. (The lower starting dose was chosen in anticipation of more significant toxicity in this group of patients.) Fourteen PRs were observed (27.5%; 95% CI, 16% to 42%), with a median response duration of 7 months. Febrile neutropenia resulting in hospitalization occurred in 24 of the first 312 cycles (8%) and in none of 51 patients (18%). No patient was removed from the trial due to toxicity. Our next trial evaluated the higher, 250-mg/m² dose, again via 24-hour infusion every 3 weeks, in patients who had received just one prior chemotherapy regimen for metastatic disease (with or without prior adjuvant therapy). Nine PRs and two CRs were noted in 25 evaluable patients (44%; 95% CI, 24% to 65%). Significantly, in this and the previous trial, prior demonstrated sensitivity or resistance to anthracy-
Dosing Schedule Issues

With renewed interest in the shorter, more convenient, 3-hour infusion schedule, our next two phase II trials addressed the safety and efficacy of this schedule as “salvage” chemotherapy in heavily treated patients and as initial chemotherapy for stage IV disease. For previously treated patients (two or more prior regimens for metastatic disease, including anthracycline), paclitaxel was administered via 3-hour infusion every 3 weeks, at a starting dose of 175 mg/m². Prophylactic G-CSF was not administered, as 3-hour infusions had been shown to be associated with less significant myelosuppression than 24-hour infusions. Visceral-dominant disease was present in 64% of patients, and the median Karnofsky performance score was 70%. After delivery of the first 111 cycles (median per patient, three; range, one to eight), five PRs were observed in 24 evaluable patients (20.8%; 95% CI, 7% to 42%),4 with a median response duration of 4 months (range, 2 to 11). Treatment was well tolerated; the only grade ≥3 nonhematologic toxicities noted were myalgia (4%) and mucositis (4%). Grade ≥3 neutropenia was seen in one third of patients, grade ≥3 thrombocytopenia was noted in 8%, and grade ≥3 anemia was observed in 13%. Dose reduction was required in 21%, with dose escalation possible in only 4%.

We then evaluated a 250-mg/m² starting dose via 3-hour infusion, again without prophylactic G-CSF, as initial chemotherapy for metastatic breast cancer. One CR and seven PRs have been noted among 25 evaluable patients (32%; 95% CI, 15% to 53%).4 Myalgias, arthralgias, and neuropathy appeared to be more significant in this trial than in our prior experience with this dose delivered over 24 hours to a similar group of patients. Several patients experienced the phenomenon of photopsia26 at doses ≥250 mg/m² over 3 hours, which may represent an optic neuropathy.27 Additionally, six patients experienced intense pruritus and hyperesthesia as a manifestation of neurotoxicity; this symptom was alleviated with the administration of tricyclic antidepressants in four patients.28 This trial has provided pilot data for the design of randomized trials of the Cancer and Leukemia Group B and the National Surgical Adjuvant Breast Project.

Supported by in vitro data demonstrating less resistance to paclitaxel in p-glycoprotein overexpressing MCF-7 breast cancer cells with longer drug exposure time,8 other preclinical studies,9,12 and encouraging clinical experience in patients with anthracycline-resistant breast cancer,13 we designed a phase II clinical and pharmacologic trial to evaluate the possibility of schedule-dependent activity by administering paclitaxel via 96-hour continuous infusion, specifically to patients with disease of demonstrated clinical resistance to “short taxane exposure.”14 Twenty-seven patients who experienced disease progression while receiving either 3-hour paclitaxel (n = 24), 1-hour docetaxel (n = 2), or both (n = 1) received paclitaxel 140 mg/m² (35 mg/m²/d × 4) via 96-hour infusion with a starting dose of 120 mg/m² for patients with impaired hepatic function. As early data suggested that the omission of steroid and H₂-receptor antagonist premedication was not associated with significant hypersensitivity reactions...
with this dose and schedule, these agents were not given in our study. With 173 cycles administered, seven PRs have been noted in 25 evaluable patients (28%; 95% CI, 12% to 49%), with acceptable hematologic and nonhematologic toxicity and no significant hypersensitivity reactions.

Paclitaxel serum concentrations were assayed in 23 patients by high-performance liquid chromatography during the infusions at 24, 48, 72, and 96 hours. The median steady-state paclitaxel concentration \((C_{ss})\) was 0.047 \(\mu\text{mol/L}\) (range, 0.023 to 0.176 \(\mu\text{mol/L}\)); for 11 patients experiencing grade 4 neutropenia it was 0.068 \(\mu\text{mol/L}\) (range, 0.032 to 0.176 \(\mu\text{mol/L}\)), compared with 0.039 \(\mu\text{mol/L}\) (range, 0.023 to 0.098 \(\mu\text{mol/L}\)) in 12 patients with less severe neutropenia \((P < .05)\). Median \(C_{mm}\) and absolute neutrophil nadirs were 0.094 \(\mu\text{mol/L}\) (range, 0.074 to 0.176 \(\mu\text{mol/L}\)) and 300 cells/\(\mu\text{L}\), respectively, in four patients with baseline elevation of hepatic transaminases versus 0.041 \(\mu\text{mol/L}\) (range, 0.023 to 0.102 \(\mu\text{mol/L}\)) and 800 cells/\(\mu\text{L}\), respectively, in 19 patients with normal transaminases \((C_{mm}, P < .01);\) absolute neutrophil count, not significant. To further define the significance of duration of drug infusion for paclitaxel, we are presently randomizing patients with refractory metastatic breast cancer to receive 3- versus 96-hour infusion schedules in a multi-institution trial led by Dr F.A. Holmes at the M.D. Anderson Cancer Center. As there are greater pharmacologic differences between 3- and 96-hour schedules compared with 3- and 24-hour infusion schedules, and preclinical data suggest the importance of paclitaxel exposure duration in breast carcinoma cells, this trial should provide important information regarding the impact of paclitaxel infusion duration on efficacy and toxicity.

**Quality of Life Considerations**

As the therapeutic goals in the management of metastatic breast cancer extend beyond classic bidimensional measurement of tumor response to include relief of tumor-related symptoms and, ideally, maintenance or enhancement of quality of life, we performed a parallel prospective and comprehensive assessment of these parameters in conjunction with our clinical trials of 24-hour paclitaxel infusion with G-CSF support in previously treated patients with metastatic disease. Patients completed a series of validated instruments designed to capture the many dimensions that contribute to global quality of life prior to treatment and at 9-week (three-cycle) intervals during paclitaxel therapy. We have shown the feasibility of quality of life assessment in patients with advanced cancer receiving investigational therapy in a phase II clinical trial setting, and are encouraged by ongoing investigations addressing these important issues in parallel with randomized phase III trials of paclitaxel alone and in combination. Although limited by sample sizes, our single-institution experience suggests a potential palliative benefit for paclitaxel in patients with responsive disease (PR or minor response). Multivariate analysis and logistic regression models also have demonstrated the independent prognostic value of baseline scores of two quality of life instruments, the Global Distress Index \((a 10\text{-item subscale of the recently validated Memorial Symptom Assessment Scale})\) and the Functional Living Index—Cancer, in predicting survival.

**COMBINATIONS: PRESENT AND FUTURE**

Paclitaxel combinations with doxorubicin and cisplatin have been reported. Not surprisingly, these combinations show impressive antitumor activity against metastatic breast cancer, but not without appreciable toxicity. Randomized trials such as the Eastern Cooperative Oncology Group study of paclitaxel (P) versus doxorubicin (D) versus P + D (+ G-CSF) are important to gauge the relative worth of such combinations over single-agent therapy with paclitaxel alone.

Edatrexate (E) is a methotrexate analogue that competes avidly for the folate binding site of the enzyme dihydrofolate reductase. It thus indirectly blocks nucleotide synthesis. Edatrexate possesses potential preclinical advantages over methotrexate in that it demonstrates greater selective entry and intracellular conversion to polyglutamate forms in neoplastic cells compared with other antifolates. Additionally, it has shown promising single-agent activity against metastatic breast cancer in previous clinical trials. In vitro data from our center have demonstrated that the sequence of edatrexate followed by paclitaxel (24 to 27 hours later) showed marked synergism in inhibiting the growth of SKBR-3 human breast adenocarcinoma cells. The reverse schedule showed antagonism. We are presently evaluating the sequential combination of "E \(\rightarrow\) P" in a phase I/II clinical trial in patients with stage IV breast cancer. Thus far,
edatrexate doses of up to 300 mg/m² have been well tolerated in combination with paclitaxel at 175 mg/m² via 3-hour infusion without hematopoietic growth factor support, with both agents recycled every 21 days. At this early juncture, eight responses (three CRs and five PRs) have been noted among the first 12 evaluable patients (edatrexate dose range, 180 to 270 mg/m²). As only one patient has experienced grade 3 mucositis, dose escalation of edatrexate continues.

In patients with responding metastatic breast cancer, single-cycle, conventional high-dose chemotherapy regimens with autologous stem cell support have produced CRs in approximately 50% of patients, yet disease recurs in the majority of these patients. Applying the concepts of the Norton-Simon hypothesis and the Gompertzian model of breast cancer kinetics,40 and motivated by the apparent failure of a single high-dose application of chemotherapy to eradicate all viable malignant cells in prior clinical trials, we have performed a series of studies evaluating the delivery of multiple courses of high-dose alkylating agents at short intertreatment intervals in patients with responsive metastatic breast cancer.41,42 Notably, our group has demonstrated that the addition of paclitaxel (250 mg/m²) to high-dose cyclophosphamide (3 g/m²) does not compromise the mobilization of CD34+ peripheral blood progenitor cells (median, 16.22 E/7/kg/leukapheresis) compared with 3 g/m² cyclophosphamide alone (2.64 E/7/kg/leukapheresis).43 Hence, we are presently evaluating the incorporation of paclitaxel into our present high-dose sequential regimen in responsive metastatic breast cancer, consisting of tandem cycles of high-dose cyclophosphamide plus paclitaxel followed by tandem cycles of high-dose thiotepa plus paclitaxel with peripheral blood progenitor cells for hematologic rescue, with 14-day treatment intervals (Fig 2).

Growth Factor Studies
A greater appreciation of autocrine and paracrine growth factor regulation of breast cancer cell growth has led to new avenues of investigation. Major advances have been made since the mid-1980s in the understanding of the role that certain oncopenes, growth factors, and growth factor receptors play in breast cancer.44,45 Among the best-studied growth factor receptor systems in breast cancer has been the one constituted by the epidermal growth factor receptor (EGFR) and the closely related HER-2/neu receptor. Monoclonal antibodies directed against both these receptors inhibit the growth of breast cancer cells.45 Since 1992, we and others have developed strong experimental data suggesting that combining maximally tolerated doses of chemotherapeutic agents with MoAb-mediated blockade of either EGFR or HER-2/neu receptors can eradicate well-established human tumor xenografts that were resistant to either treatment given singly.20,46,47 Striking antitumor effects are observed when paclitaxel is given in human breast cancer xenografts in combination with either anti-EGFR or anti-HER-2 MoAbs. This strong synergy is achieved with no increased toxicity in the animal model. Clinical trials with a chimeric anti-EGFR MoAb and with a humanized anti-HER-2/neu MoAb (rhMoAb HER-2) are currently under way at MSKCC. In a recently completed phase II study, significant responses with rhMoAb HER-2 were observed in patients who had been heavily pretreated.48 While mechanisms for the apparent synergy are being explored,47 these data provide a lead for translation into the clinic. Indeed, future clinical trials combining paclitaxel with anti-growth factor receptor MoAbs are being planned.

ADJUVANT THERAPY
Motivated by the significant activity and safety of paclitaxel noted in our own and others' trials in patients with advanced disease, we have incorporated paclitaxel into a postoperative adjuvant chemotherapy regimen for patients with node-positive resectable stage II/III breast cancer. The superiority of sequential versus alternating scheduling

![Fig 2. Sequential high-dose regimen. Cycles are at 14-day intervals; dose in milligrams per square meter. PBPC, peripheral blood progenitor cells.](image-url)
of active therapeutic components in the adjuvant setting has been suggested by mathematical models of tumor kinetics and substantiated by clinical trial. We have previously demonstrated the feasibility of sequential administration of doxorubicin and high-dose cyclophosphamide as adjuvant therapy for patients with resectable stage II/III breast cancer with four or more involved axillary lymph nodes. The recurrence-free survival curve noted thus far is encouraging; with a median follow-up time of 36 months, 62% recurrence-free survival proportion has been noted among 71 patients with a median of nine involved axillary nodes. This experience, combined with paclitaxel's activity and partial non-cross-resistance with doxorubicin, led us to incorporate it into an adjuvant chemotherapy regimen for women of the same risk category.

Forty-two patients with four or more positive axillary lymph nodes (median, eight; range, four to 25) have received the regimen of rapidly sequenced doxorubicin (90 mg/m²), paclitaxel (250 mg/m², 24 hours), and high-dose cyclophosphamide (C) (3 g/m²), all administered with G-CSF support, as shown in Fig 3. Two patients did not complete the regimen due to nonhematologic toxicity experienced after the second cycle of high-dose cyclophosphamide. The median delivered dose intensity for each component of this regimen (D → P → C) has been 100% of planned. Hematologic toxicities are shown in Table 2. The more frequent grade 3 nonhematologic toxicities included fatigue (24%), bone pain (24%), stomatitis (17%), dermatologic (17%); grade 4, 2%, neurosensory (15%), nausea (12%), and diarrhea (7%). Serial radionuclide gated heart scans showed no decline in cardiac ejection fraction, and no clinical cardiotoxicity was noted. At a median follow-up of 448 days after surgery (range, 82 to 632 days), 7% of patients have relapsed.

In an effort to optimally integrate paclitaxel into adjuvant systemic therapy, we are presently randomizing patients to receive a slightly modified version of the sequential regimen described above.

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<th>Table 2. Hematologic Toxicity: Doxorubicin/Paclitaxel/Cyclophosphamide Adjuvant Regimen</th>
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Abbreviations: WBC, white blood cell count; ANC, absolute neutrophil count; Hgb, hemoglobin; RBC, red blood cell.
(Fig 3) versus single-agent doxorubicin × 3, followed by concomitant paclitaxel and high-dose cyclophosphamide (Fig 4). In a different approach, an Intergroup trial will evaluate the efficacy of four cycles of paclitaxel administered via 3-hour infusion after delivery of one of three dose levels of doxorubicin/cyclophosphamide (60/600, 75/600, or 90/600 mg/m²) as adjuvant chemotherapy for node-positive early stage breast cancer.

SUMMARY

In this decade many large multicenter trials will answer important questions regarding the optimal application of single-agent paclitaxel (dose and schedule), its role in relation to other active agents and regimens, its comparative impact on quality of life, and the potential of combination regimens containing paclitaxel. Studies at MSKCC and elsewhere are attempting to characterize in vivo resistance mechanisms to this class of agents. These efforts may result in mechanism-directed strategies to overcome resistance; they may also guide analogue development. Translational research involving growth factors and their receptors promises to capitalize on an expanding knowledge of autocrine and paracrine pathways and the ability to perturb them. In the clinic and the laboratory, there are many reasons for optimism in the future application of paclitaxel against breast cancer.53

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