Paclitaxel for Breast Cancer: The Memorial Sloan-Kettering Cancer Center Experience

By Andrew D. Seidman, MD [2], Clifford A. Hudis, MD [3], George Raptis, MD [4], José Baselga, MD [5], David Fennelly, MD, MRCPI [6], and Larry Norton, MD [7]

The proven safety profile and antitumor activity of paclitaxel (Taxol) in the treatment of metastatic breast cancer led investigators at Memorial Sloan-Kettering Cancer Center (MSKCC) to further examine the agent's potential in the treatment of advanced breast cancer. Efficacy and tolerability studies of paclitaxel as single-agent therapy were undertaken, along with parallel investigations of quality-of-life parameters. The studies examined the effects of 96-hour infusion schedules of paclitaxel and are currently assessing the feasibility of a weekly 1-hour infusion schedule. Researchers at MSKCC also compared the results of a variety of two- and three-drug paclitaxel-containing regimens to determine possible synergism and better define safety profiles. They examined the combination of paclitaxel and edatrexate, as well as a promising combination of paclitaxel and a monoclonal antibody directed at growth factor receptors. The latter ongoing trial will include both laboratory studies that examine possible cellular mechanisms for the combination's observed synergy and a clinical trial that combines paclitaxel with a monoclonal antibody directed against the epidermal growth factor. In conclusion, the investigators discuss the optimal integration of paclitaxel into doxorubicin/cyclophosphamide (Cytoxan, Neosar)-based adjuvant therapy for node-positive stage II-III resectable breast cancer. [ONCOLOGY 11(Suppl):20-28, 1997]

Introduction

In the management of patients with metastatic breast cancer, paclitaxel (Taxol) has demonstrated safety and significant antitumor activity.[1-5] To fully characterize the drug's potential in the treatment of advanced breast cancer, we have conducted a series of phase II clinical trials evaluating its efficacy and tolerability as single-agent therapy (Table 1).

Paclitaxel has been studied in various doses and schedules among patients with metastases who have not received previous chemotherapy for advanced disease, as well as among those who have had moderate and extensive prior therapy.[1,3-5] In heavily pretreated patients, we have conducted a formal parallel investigation of quality-of-life (QOL) parameters to better assess the palliative potential of paclitaxel among patients who receive this agent with the primary intent of symptom control.[6] We are presently incorporating these variables into a prospective study that addresses economic (charges/costs) and QOL outcomes, in addition to classic tumor response and toxicity assessments, in patients receiving single-agent paclitaxel.[7]

Our studies were influenced by preclinical data demonstrating schedule-dependent cytokinetic variability in resistance profiles to the taxanes,[8-10] as well as clinical documentation of the efficacy and safety of a 96-hour infusion schedule against anthracycline-refractory breast cancer.[11] These investigations led us to perform a phase II and pharmacologic trial assessing the activity and toxicity profile of this prolonged infusion schedule in patients with documented progression of disease during shorter taxane exposure.[12]

Data supporting the feasibility and efficacy of more frequent, shorter-duration taxane infusions[13] has motivated our ongoing trial, which is evaluating a weekly 1-hour infusion paclitaxel schedule in patients who have received one or two prior regimens for breast cancer (including adjuvant therapy).[14] Collaborative laboratory investigations aimed at characterizing clinically relevant mechanisms of resistance to paclitaxel are well underway in studies involving biopsied human breast cancer tissue.

Combinations of paclitaxel and other cytotoxic agents are being studied. A variety of two- and three-drug paclitaxel-containing regimens are in clinical trials to define possible synergism, as well as to illuminate safety profiles. At Memorial Sloan-Kettering Cancer Center (MSKCC), we have investigated the combination of paclitaxel and edatrexate, a dihydrofolate reductase inhibitor with
preclinical advantages over methotrexate[15] and proven 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 promising avenue of translational research pertains to the observed synergy between paclitaxel and monoclonal antibodies (MoAbs) directed at various growth factor receptors in human breast carcinoma xenografts.[20,21] While laboratory studies addressing possible cellular mechanisms for this effect are ongoing, we are conducting a clinical trial combining paclitaxel with a MoAb directed against the epidermal growth factor.

The preserved activity of paclitaxel after anthracycline therapy has stimulated its evaluation as a component of an adjuvant sequential chemotherapy regimen for node-positive stage II-III resectable breast cancer.[22] We recently evaluated the optimal integration of paclitaxel into doxorubicin/cyclophosphamide (Cytoxan, Neosar)-based adjuvant therapy in a randomized clinical trial.[23] This article will review 6 years of experience with paclitaxel in the treatment of breast cancer at MSKCC and describe ongoing and planned studies.

**Single-Agent Paclitaxel**

*First-Line Therapy*

Subsequent to the M. D. Anderson Cancer Center report of the promising antitumor activity of paclitaxel against metastatic breast cancer,[2] we performed a confirmatory phase II trial of the agent as first-line chemotherapy for stage IV disease.[3] In this study, 28 patients who had not received prior chemotherapy for metastatic disease were treated with paclitaxel, 250 mg/m² via a 24-hour infusion every 3 weeks. Because the first two patients we treated on this protocol experienced significant myelosuppression (which was dose-limiting in the previous trial[2]), the protocol was amended so that all subsequent patients received prophylactic granulocyte colony-stimulating factor (G-CSF [Neupogen]), 5 µg/kg/d subcutaneously, on days 3 to 10 of each cycle.

A 62% response rate (95% confidence interval [CI], 41% to 80%) was noted, including three complete responses.[3] Responses were as common among women who had received prior adjuvant therapy, including doxorubicin-containing regimens, as among those who had not. Treatment was well tolerated; adverse effects included generalized alopecia in all patients, and grade 3 or 4 nonhematologic toxicities were uncommon. Of 178 cycles administered, there were 8 admissions (4%) for febrile neutropenia, involving 6 (21%) of 28 patients.

Administration of recombinant human granulocyte colony stimulating factor (rh-G-CSF) resulted in a median duration with an absolute neutrophil count less than 500 cells/µL of 2 days, which was shorter than that previously reported (7 days)[1] without concomitant growth factor support. Fifty-eight percent of cycles were delivered at modestly reduced doses, primarily due to significant neutropenia or febrile neutropenia. Because drug supply was a consideration at this time in the agent's development, the clinical trial design specified the length of treatment to be two cycles beyond the best response, with a maximum of 10 cycles per patient. Thus, response duration was not a valid end point of this trial.

*After Prior Chemotherapy*

Following this confirmation of paclitaxel's marked antitumor activity in patients with minimal prior therapy, we evaluated patients who had received extensive prior chemotherapy for metastatic breast cancer.[4] Fifty-one patients who had previously received two or more prior chemotherapy regimens for metastatic disease (median number of regimens, three; range, two to six; all with prior anthracycline therapy) entered our second phase II trial.

The median Karnofsky performance score (KPS) for these patients was 70% (range, 60% to 90%). Fourteen percent had received prior high-dose chemotherapy regimens sufficiently myelotoxic as to require the 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 (a lower starting dose was chosen in anticipation of significant toxicity in these more heavily pretreated patients) via a 24-hour infusion every 3 weeks with G-CSF, as previously described.

Partial responses were observed in 14 patients (27.5%; 95% CI, 16% to 42%), with a median response duration of 7 months. Hospitalization for febrile neutropenia occurred in 24 (8%) of the first 312 cycles and in 9 (18%) of 51 patients. No patient was removed from the trial due to toxicity. Our next trial evaluated the higher 250-mg/m² dose, again via a 24 hour infusion every 3 weeks, in
patients who had received only one prior chemotherapy regimen for metastatic disease (with or without prior adjuvant therapy).[4] Nine partial and two complete responses were noted among 25 evaluable patients (44%; 95% CI, 24% to 65%). Significantly, in this and the previous trial, prior demonstrated sensitivity or resistance to an anthracycline did not predict the likelihood of subsequent response to paclitaxel. This lack of significant clinical cross-resistance between paclitaxel and doxorubicin, an observation corroborated by others, was particularly gratifying because preclinical data suggest significant in vitro cross-resistance between paclitaxel and other agents for which p-glycoprotein-mediated multidrug resistance is considered relevant.[24,25] These observations have motivated our ongoing studies characterizing pre- and post-paclitaxel human tumor tissue biopsies for mdr expression, tubulin alterations, and genomic changes. It is hoped that such studies will expand the understanding of clinically relevant mechanisms of taxane resistance, which may then guide the development of efficient strategies to overcome resistance and, potentially, the development of superior analogs.

**Shorter Infusion Schedule**

Renewed interest in the shorter, more convenient 3-hour infusion schedule coincided with our next two phase II trials, which addressed the safety and efficacy of this schedule as salvage chemotherapy in heavily treated patients and as initial chemotherapy for stage IV disease. In the previously treated patients (two or more prior regimens for metastatic disease, including an anthracycline), paclitaxel was administered at a starting dose of 175 mg/m² via a 3-hour infusion every 3 weeks. Since 3-hour infusions are associated with less significant myelosuppression than 24-hour infusions, G-CSF was not administered prophylactically.

Sixty-four percent of the patients had predominantly visceral disease, and the median KPS was 70%. After the 111 cycles were delivered (median, 3; range, 1 to 8), five partial responses were observed in 24 evaluable patients (20.8%; 95% CI, 7% to 42%),[5] with a median response duration of 4 months (range, 2 to 11 months).

Paclitaxel treatment was well tolerated; the only grade 3 or 4 nonhematologic toxicities noted were myalgia (4%) and mucositis (4%). Grade 3 or 4 neutropenia was seen in one-third of patients, grade 3 or 4 thrombocytopenia in 8%, and grade 3 or 4 anemia in 13%. Dose reduction was required in 21% of patients, and dose escalation was possible in only 4%.

We then evaluated a 250-mg/m² dose administered via a 3-hour infusion, again without prophylactic G-CSF, as first-line chemotherapy for metastatic breast cancer. Among 25 evaluable patients, 1 complete and 7 partial responses were noted (32%; 95% CI, 15% to 53%).[5] Myalgias, arthralgias, and neuropathy appeared to be more significant than in our prior experience with this dose delivered over 24 hours to a similar group of patients. Several patients experienced photopsia[26] at paclitaxel doses of 250 mg/m² or more over 3 hours, a phenomenon that may represent an optic neuropathy.[27] These trials provided pilot data for the design of ongoing randomized trials by the Cancer and Leukemia Group B (CALGB) and National Surgical Adjuvant Breast and Bowel Project (NSABP).

**Additional Effects of Prolonged Treatment**

In the course of these trials, it became obvious to us that many patients experiencing symptomatic relief of bone pain and radiographic healing of osteolytic metastases on plain x-rays, CT, or MRI had transient worsening on nuclear scintigraphic evaluation of the skeleton.[28] This radiographic "flare" on bone scan was followed by further clinical improvement in skeletal pain and recalcification of destructive bone lesions in one-third of patients. Another phenomenon became apparent with prolonged paclitaxel treatment (in some cases, beyond 20 courses). Among a series of 52 patients experiencing continued response of visceral, osseous, and soft-tissue metastases during paclitaxel treatment, 6 experienced disease progression in the central nervous system in the absence of other evidence of treatment failure. This manifested as both parenchymal brain metastases and leptomeningeal disease. Thus, the central nervous system does appear to be a sanctuary site in many women receiving paclitaxel for the management of metastatic breast cancer.[29]

**Schedule-Dependent Activity**

Our next phase II clinical and pharmacologic trial was motivated by in vitro data showing less resistance to paclitaxel in p-glycoprotein-overexpressing MCF-7 breast cancer cells with longer drug exposure time.[8] Further support of this phenomenon came from other preclinical studies[9,10,30,31] and encouraging clinical experience with prolonged paclitaxel infusion in patients with anthracycline-resistant breast cancer.[11]

In this study, we evaluated the possibility of schedule-dependent activity by administering paclitaxel...
via a 96-hour continuous infusion specifically to patients with disease that had demonstrated clinical resistance to short taxane exposure.[12] A total of 27 such patients with disease progression had recently received 3-hour paclitaxel (N = 24), 1-hour docetaxel (Taxotere; N = 2), or both (N = 1). Per protocol, all patients received paclitaxel via a 96-hour infusion at 140 mg/m² (35 mg/m²/d ×4), with a starting dose of 120 mg/m²/d for patients with impaired hepatic function. Because early data had suggested that the omission of steroid and H1- and H2-receptor antagonist premedication was not associated with significant hypersensitivity-like reactions with this dose and schedule,[11] these drugs were not given in our study.

With 195 cycles administered, seven partial responses were noted in 26 evaluable patients (26.9%; 95% CI, 11.6% to 47.8%), with acceptable hematologic and nonhematologic toxicity. Despite the omission of standard premedication, no cases of hypersensitivity-like reactions occurred. This suggests that the slower rate of exposure to paclitaxel—and possibly to the polyoxyethylated castor oil (Cremophor EL) formulation—may not precipitate mast-cell degranulation and other cellular phenomena associated with hypersensitivity reactions.

Serum paclitaxel concentrations were assayed in 23 patients by high-performance liquid chromatography at 24, 48, 72, and 96 hours of the infusion. The median steady-state paclitaxel concentration (Css) was .047 µM (range, .023 to .176 µM). For 11 patients experiencing grade 4 neutropenia, median Css was .068 µM (range, .032 to .176 µM), as compared with .039 µM (.023 to .098 µM) in 12 patients with less severe neutropenia (P less than .05). Median Css and absolute neutrophil count (ANC) nadirs were .094 µM (range, .074 to .176 µM) and 300 cells/mm³, respectively, in four patients with baseline elevation of hepatic transaminases vs .041 µM (.023 to .102 µM) and 800 cells/mm³ in 19 patients with normal transaminases (Css, P less than .01; ANC, not significant).[12]

No relationship between steady-state level and tumor response was noted with this limited sample size. To further define the significance of infusion duration for paclitaxel, a recently completed multi-institution trial led by the M. D. Anderson Cancer Center randomized patients with refractory metastatic breast cancer to receive paclitaxel via either a 3- or 96-hour infusion schedule. It is noteworthy that there are greater pharmacologic differences between the 3- and 96-hour infusion schedules than between the 3- and 24-hour schedules, and many preclinical data suggest the importance of paclitaxel exposure duration in breast carcinoma cells. Thus, this trial should provide the most definitive information about the impact of paclitaxel infusion duration on efficacy and toxicity.

**Weekly 1-Hour Paclitaxel in Metastatic Breast Cancer**

**Experience With Shorter Infusions**

Although paclitaxel exposure duration seems to be an important determinant of cell kill, many oncologists perceive prolonged continuous infusions to be cumbersome and inconvenient. Theoretically, one might approximate the pharmacokinetics of prolonged paclitaxel infusion by more frequent administration of the agent, which can also increase the delivered dose density. Pharmacodynamic studies have linked pharmacologic parameters, such as time above a specific threshold plasma paclitaxel concentration and neutropenia, with toxicity. However, little is known about pharmacologic correlates of antitumor activity.

Recently, several investigators have begun to explore short 1-hour infusions of paclitaxel. Hainsworth et al[32] compared a triweekly 1-hour infusion vs split-dose paclitaxel for three consecutive daily 1-hour infusions every 3 weeks in 164 patients with advanced refractory cancers. In this study, no serious hypersensitivity reactions occurred, and activity in various solid tumor types was noted.

Loeffler et al [33] studied a weekly paclitaxel 1-hour infusion in 50 patients, all of whom had previously received chemotherapy. Initial doses of 40 mg/m² weekly for six cycles, followed by a 3-week off-treatment interval, were escalated up to 90 mg/m² weekly, without grade 3 or 4 neutropenia. Responses were seen in 20 (40%) of the 50 patients, including partial responses in 3 of 6 patients with breast cancer.

The tolerability of a weekly 1-hour schedule has been confirmed in further studies by Klaassen et al[13] and in ovarian cancer at our institution.[34]

**An Active, Tolerable Regimen**

Motivated by these experiences, in addition to preclinical data demonstrating that paclitaxel can inhibit basic fibroblast growth factor and vascular endothelial growth factor-induced angiogenesis,[35] we recently initiated a phase II and pharmacologic study of paclitaxel, 100 mg/m²
Paclitaxel for Breast Cancer: The Memorial Sloan-Kettering Cancer Center Experience

Published on Physicians Practice (http://www.physicianspractice.com)

via a 1-hour weekly infusion, in patients with metastatic breast cancer. Patients who have not received extensive prior therapy (one or two prior regimens that may include anthracyclines in the metastatic or adjuvant setting) are eligible for inclusion. Intrapatient dose escalation or reduction according to tolerance is addressed in the trial design.

To date, 16 patients have received 215 weekly infusions of paclitaxel (median, 13 per patient; range, 7 to 22). The initial dose was 100 mg/m²; actual median delivered dose intensity is 95 mg/m²/wk thus far. Granulocyte colony-stimulating factor was not given prophylactically, nor was its administration necessary to maintain weekly dosing.

Preliminary data suggest that this is both an active and tolerable regimen. No episodes of febrile neutropenia have been encountered. In the absence of dose-limiting or cumulative myelosuppression, paclitaxel doses were increased to 110 to 120 mg/m²wk in the first nine patients. Unfortunately, this strategy resulted in grade 3 neurosensory and neuromotor toxicity in five of nine patients; hence subsequent escalation above 100 mg/m² was abandoned. Other grade 3 or 4 toxicities that have been observed are neutropenia (14%) and headache (7%).

Thus far, responses have been noted in 6 of 15 evaluable patients (40%; 95% CI, 16% to 68%), including one complete response (cutaneous chest wall disease) and five partial responses (liver, lung, lymph nodes, and skin). Plasma paclitaxel concentration assayed by high-performance liquid chromatography in 14 patients reveal a median peak concentration (Cmax) of 4.75 µM (range, 2.73 to 6.76 µM), median area under the curve of 17.23 µM-h (9.34 to 22.35 µM-h), and t½beta of 12.35 h (8.3 to 25.0 h).

Patient accrual continues to better estimate the proportion of responses to this promising schedule of paclitaxel administration.

QOL and Outcome Assessment

The therapeutic goals in the management of metastatic breast cancer are being extended beyond classic bidimensional measurement of tumor response to include relief of tumor-related symptoms and maintenance or enhancement of QOL. With this in mind, we performed a parallel prospective and comprehensive assessment of these parameters in conjunction with our clinical trials of the 24-hour paclitaxel infusion with G-CSF in previously treated patients.

Patients completed a series of validated instruments designed to capture the many dimensions that contribute to global QOL. Questionnaires were completed prior to paclitaxel therapy and at 9-week (three-cycle) intervals during therapy. We found QOL assessment to be feasible in patients with advanced cancer receiving investigational therapy in a phase II clinical trial setting. Although limited by sample sizes, our single-institution experience suggests a potential palliative benefit afforded by paclitaxel in patients with responsive disease (complete or partial response) or minor response. Multivariate analysis, using logistic regression models, also demonstrates the independent prognostic value of baseline scores of two QOL instruments in predicting survival.

These instruments are the Global Distress Index, a 10-item subscale of the recently validated Memorial Symptom Assessment Scale (MSAS), and the Functional Living Index-Cancer (FLIC). Since chemotherapy-related symptoms (eg, myalgia and arthralgia) are often transient, we have obtained frequent prospective measurements of pain in parallel with paclitaxel/G-CSF therapy of metastatic breast cancer. This exploratory analysis demonstrated the ability to capture short-lived episodic symptoms—in this case, attributable to paclitaxel and/or G-CSF—that would not have been captured with less frequent assessment. We are encouraged by ongoing investigations addressing these important issues in parallel with ongoing randomized phase III trials of paclitaxel alone and in combination (eg, Eastern Cooperative Oncology Group [ECOG] protocol 1193). We are presently addressing the issue of cost/charges of medical care relative to the standard outcome measurements of response, survival, toxicity, and QOL. Consent patients receiving single-agent paclitaxel for metastatic breast cancer are followed prospectively, with classic assessment of tumor response and toxicity. In addition, patients complete the MSAS and Functional Assessment of Cancer Therapy-Breast (FACT-B) instruments at regular intervals to capture parallel longitudinal QOL changes. Health-care expenditures incurred during the treatment period are evaluated prospectively by administrative collaborators within our institution, using existing computerized data systems. This nonrandomized effort is designed to examine the relationship between tumor response, palliation, and costs in the treatment of advanced breast cancer.

Combination Therapy

Doxorubicin/Cisplatin

Several studies have shown impressive antitumor activity of combinations of paclitaxel with...
doxorubicin[40-45] and cisplatin (Platinol)[46,47] against metastatic breast cancer and have begun to elucidate the potential toxicities of these combinations. It has become apparent in these trials that dose, duration of infusion, and sequence of administration are all important determinants of toxicity. Randomized trials, such as the intergroup study of paclitaxel vs doxorubicin vs the combination of the two agents with G-CSF support, are critical to gauge the relative value of such combinations over single-agent paclitaxel.

**Edatrexate**

Edatrexate is an analog of methotrexate that competes for the folate-binding site of the enzyme dihydrofolate reductase, and thus, indirectly blocks the synthesis of nucleotides. It possesses potential preclinical advantages over methotrexate in that it demonstrates greater selective entry and intracellular conversion to polyglutamate forms in neoplastic cells compared to other antifolates.[15] In addition, edatrexate has shown promising single-agent activity against metastatic breast cancer in previous clinical trials.[15-17]

In vitro data from our center have demonstrated that the sequence of edatrexate followed by paclitaxel showed marked synergism in inhibiting the growth of SKBR-3 human breast adenocarcinoma cells.[18,19] while the reverse schedule showed antagonism. We therefore evaluated the sequential combination of edatrexate and paclitaxel in a phase I-II clinical trial in patients with stage IV breast cancer.[48] Edatrexate doses of up to 350 mg/m² were well tolerated in combination with paclitaxel at 175 mg/m² via a 3-hour infusion without hematopoietic growth factor support, with both agents recycled every 21 days. Preliminary data show eight responses (three complete, five partial) among the first 12 evaluable patients (edatrexate dose range, 180 to 270 mg/m²).

**Cyclophosphamide**

For chemoresponsive metastatic breast cancer, single-cycle, conventional high-dose chemotherapy regimens requiring autologous stem-cell support have produced complete responses in up to 50% of patients, and yet the majority of these patients ultimately develop recurrent disease. Motivated by the apparent failure of a single high-dose application of chemotherapy to eradicate all viable malignant cells in prior clinical trials, we applied the concepts of the Norton-Simon hypothesis and the Gompertzian model of breast cancer kinetics[49] in a series of studies. We evaluated the delivery of multiple courses of high-dose alkylating agents at short intertreatment intervals in patients with responsive metastatic breast cancer.[50]

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 E⁶/kg/leukapheresis), as compared with 3 g/m² of cyclophosphamide alone (2.64 E⁶/kg/leukapheresis).[51] Hence, we are presently evaluating the incorporation of paclitaxel into a high-dose sequential regimen in chemosensitive metastatic breast cancer. This regimen consists 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 (MSKCC IRB protocol 94-77).

**Monoclonal Antibodies**

There has recently been an expansion of knowledge about the role that certain oncogenes, growth factors, and growth factor receptors play in breast cancer.[52] One of the best-studied growth factor receptor systems in breast cancer includes the epidermal growth factor receptor (EGFR) and the closely related HER-2/neu receptor, both of which possess intrinsic tyrosine kinase activity. When directed against both these receptors, MoAbs inhibit the growth of breast cancer cells overexpressing the target receptor.[52,53] Over the past several years, compelling experimental data have suggested that combining certain chemotherapeutic agents with MoAb-mediated blockade of either EGFR or HER-2/neu receptors can eradicate well-established human tumor xenografts resistant to either treatment given singly.[20,21,54]

Significant antineoplastic effects are observed when human breast cancer xenografts are exposed to paclitaxel in combination with either anti-EGFR or anti-HER-2/neu MoAb.[21] This strong synergy is achieved with no increased toxicity in the animal model. Although the mechanisms for the apparent supra-additive effects of certain chemotherapeutic agents and MoAbs are still being investigated,[55] these data provide a lead for translation into the clinic. Recent data indicate that downstream events in the signal transduction pathway may be involved in paclitaxel-induced apoptotic cell death.[56] We are presently evaluating the human-murine chimeric anti-EGFR MoAb C225 in combination with paclitaxel in a phase I trial in patients with metastatic breast cancer.

**Growth Factor Receptors and Clinical Paclitaxel Sensitivity**

There is a growing body of predominantly preclinical information suggesting a relationship between...
growth factor receptor expression and chemosensitivity or resistance.[57] Among patients receiving higher doses of anthracycline-based adjuvant therapy, those with primary breast cancers overexpressing the HER-2/neu receptor had improved disease-free and overall survival compared with those that lacked overexpression.[58] To better define this relationship for paclitaxel, we conducted a multivariate analysis of immunohistochem- ical HER-2/neu expression and clinical taxane sensitivity in patients receiving single-agent paclitaxel (and docetaxel) in clinical trials over the last 5 years at MSKCC.[59]

Preliminary analysis showed that 51 (40.5%) of 126 patients treated with either single-agent paclitaxel or docetaxel had tumor overexpression of HER-2. The overall response rate for all patients was 46.8% (59/126). The response proportion was 58.8% (30/51) if HER-2 was overexpressed, compared with 38.7% (29/75) if HER-2 was negative (Mantel-Haenszel test, P = .027).

Among the factors assessed in conjunction with tumor response, visceral-dominant disease, low KPS, and extensive prior therapy correlated with a poor clinical response. Among these, HER-2 overexpression was positively correlated with a low KPS, and a low KPS with extensive prior therapy. It appears, therefore, that HER-2 overexpression in metastatic breast cancer seems to confer sensitivity rather than resistance to taxanes, despite a positive correlation of HER-2 positivity with poor prognostic features. We are presently expanding our analysis to address other relevant oncogene modulators of paclitaxel cytotoxicity, including regulators of apoptotic cell death.[56,60]

**Adjuvant Therapy of Early-Stage Breast Cancer**

The significant activity and safety of paclitaxel noted among patients with advanced disease has motivated us to incorporate the agent into a postoperative adjuvant chemotherapy regimen. We sequence the scheduling of active therapeutic components in the adjuvant setting, as suggested by mathematical models of tumor kinetics[49] and substantiated by a clinical trial.[61] 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.[62] The recurrence-free survival curve noted thus far is encouraging; with a median follow-up time of 895 days, a 65% recurrence-free survival rate has been noted among 60 patients with a median of nine involved axillary nodes.

This experience, coupled 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.[23] Forty-two patients with 4 or more positive axillary lymph nodes (median, 8 nodes; range, 4 to 25) have received the regimen of rapidly sequenced doxorubicin (90 mg/m²), paclitaxel (250 mg/m², 24-hour schedule), and high-dose cyclophosphamide (3,000 mg/m²), all administered with G-CSF support, as shown in Figure 1.[22] The median delivered dose intensity for each component of this regimen has been 100% of planned intensity.

Approximately two-thirds of patients had to be hospitalized at least once during the regimen, most commonly for febrile neutropenia. A similar proportion of patients required red blood cell transfusion, and 10% required platelet transfusion. The more frequent grade 3 nonhematologic toxicities included fatigue (24%), bone pain (24%), stomatitis (17%), dermatologic reactions (17%) neurosensory effects (15%), nausea (12%), and diarrhea (7%). Serial gated radionuclide heart scans showed no decline in cardiac ejection fraction, and no clinical cardiotoxicity was noted.

At a median follow-up of 448 days from surgery (range, 82 to 632 days), 7% of patients have relapsed (Figure 2). In an effort to optimally integrate paclitaxel into adjuvant systemic therapy, we performed a study randomizing patients to receive either a slightly modified version of the above sequential regimen or single-agent doxorubicin ×3 followed by concomitant paclitaxel and high-dose cyclophosphamide.[23] The median number of positive lymph nodes was 8 (range, 1 to 35), and the median tumor size was 2.3 cm (range, 0.4 to 8.0 cm). All patients received G-CSF. A total of 41 patients were enrolled; 21 were randomized to receive sequential paclitaxel and cyclophosphamide (arm A) after dose-dense doxorubicin, and 20 patients received paclitaxel and cyclophosphamide concomitantly (arm B).

At a median follow-up of 10 months (range, 6 to 15 months), there have been no relapses, deaths, or instances of cardiac toxicity. The concomitant administration of paclitaxel and cyclophosphamide was associated with greater toxicity, with 16 of 20 patients (89%) hospitalized for toxicity compared with 4 (19%) of 21 patients on the sequential arm. The concomitant regimen required greater dose-reduction and delay after doxorubicin, while offering no known advantage over sequential administration.

Therefore, the appropriate regimen for phase III testing is sequential doxorubicin, paclitaxel, and cyclophosphamide, and a trial testing this regimen is ongoing (Figure 3). This trial compares sequential dose-dense chemotherapy with doxorubicin, paclitaxel, and high-dose cyclophosphamide...
with G-CSF support to a more standard doxorubicin/cyclophosphamide doublet followed by high-dose chemotherapy (STAMP I or V) requiring peripheral blood progenitor cell (and G-CSF) support. This study should complement the information being obtained from the important intergroup randomized trial (Figure 4), which is evaluating the value of four cycles of paclitaxel, administered via a 3-hour infusion, after delivery of one of three dose levels of doxorubicin/cyclophosphamide (60/600, 75/600, or 90/600 mg/m², respectively) for four courses as adjuvant chemotherapy for node-positive early-stage breast cancer. It is hoped that these results will be further augmented by those of the NSABP B-28 trial, which is using four courses of paclitaxel or no further therapy after four courses of standard doxorubicin/cyclophosphamide adjuvant therapy.

Conclusions

By the end of the 1990s, a number of large multicenter trials will have provided the answers to 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 QOL (ie, therapeutic index), and the potential benefits of combination regimens. Importantly, the potential contribution of paclitaxel to improving our ability to cure early-stage breast cancer will begin to be appreciated when survival curves from ongoing and soon-to-be-completed adjuvant trials mature. Studies at MSKCC and elsewhere are attempting to characterize in vivo resistance mechanisms to taxanes--efforts that may result in mechanism-directed strategies to overcome resistance and/or to guide the development of analogs. Translational research involving growth factors and their receptors promises to exploit an expanding knowledge of autocrine and paracrine pathways. In both the laboratory and the clinic, there are numerous reasons for optimism regarding the future contribution of paclitaxel to the fight against breast cancer.

References:


Source URL:
http://www.physicianspractice.com/review-article/paclitaxel-breast-cancer-memorial-sloan-kettering-cancer-center-experience

Links: