Concurrent Paclitaxel and Radiation Therapy for Solid Tumors

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Introduction

Paclitaxel, a complex plant product extracted from the bark of the Pacific yew tree (Taxus brevifolia) has demonstrated substantial anticancer activity in solid tumors, including chemotherapy-resistant epithelial ovarian cancer, advanced breast cancer, small cell and non-small cell lung cancer, and head and neck cancer.[1-8] Preliminary data for other malignancies, such as esophageal cancer and bladder cancer, also are encouraging.[9,10] Paclitaxel interferes with mitotic spindle function by enhancing the rate and yield of microtubule assembly and preventing microtubule depolymerization.[11-13] Microtubules are polymers of tubulin in dynamic equilibrium with tubulin heterodimers that are composed of alpha and beta protein subunits.[14,15] Their principal function is thought to be formation of the mitotic spindle apparatus during the cell division that separates the duplicated sets of chromosomes. Microtubules also play a role in the performance of many vital interphase functions in the cell, including maintenance of shape, motility, anchorage, mediation of signals between surface receptors and the nucleus, and intracellular transport, especially in neural and secretory cells.[14-17]

Although the mechanism whereby paclitaxel enhances radiation toxicity is unknown, its ability to block the cell in the G2/M phase of the cell cycle may be a key mechanism of radiation enhancement. Increases in apoptosis and tumor reoxygenation also may occur.

Radiation-Enhancing Effects of Paclitaxel

Paclitaxel is an attractive agent for concurrent administration with radiation. In addition to its direct cytotoxic action on tumor cells, in vitro studies have shown that paclitaxel can potentiate the effects of radiation on malignant cells.[18-23] Paclitaxel results in arrest of cells in the G2/M phase of the cell cycle,[24] which is particularly sensitive to ionizing radiation.[25] Paclitaxel appears to affect both clonogenic growth and cytotoxicity due to radiation.[26] Clonogenic survival was <0.01% upon continuous incubation with 10 nm of paclitaxel.[23]

This concentration is most likely achieved in tumors when the plasma level is >=5 µM following a single six-hour infusion of paclitaxel (230 mg/m2) in breast cancer patients.[2] Furthermore, a 24-hour in vitro treatment with 10 nm of paclitaxel was sufficient to achieve a radiation dose modifying ratio of 1.8. The ratio approaches 2.0 in PC-3 cells. Enhancement of radiation response also was found to be a function of the duration of exposure to paclitaxel after the first eight hours. This probably is due to the observed G2/M arrest of the cell cycle by paclitaxel, although this may not be the only mechanism involved. The G2/M cell cycle block alone may not be sufficient for paclitaxel-induced radiation sensitization in other human tumor cells.[21] A good correlation between G2/M arrest and degree of radiation sensitization, however, was obtained with the other cell lines tested in this study.[18,24] In addition, our observation that a lower dose of paclitaxel is sufficient for enhancement of radiation toxicity may be clinically relevant.

Several groups have shown that mechanisms other than the paclitaxel-induced cell cycle perturbation must exist, at least in the in vivo setting, by which paclitaxel potentiates cellular radiosensitivity. Milas et al.[26] addressed a possibility that paclitaxel makes tumor cells more susceptible to radiation-induced apoptosis. There is increasing evidence that various anticancer agents, including radiation[27,28] and chemotherapeutic drugs,[29,30] induce apoptosis in tumors and that paclitaxel is capable of inducing a strong apoptotic response in murine tumors, including the MCA-4 tumor used in the present study.[26] Paclitaxel-induced apoptosis developed mainly from mitotically arrested cells.[26] Because development of apoptosis after paclitaxel treatment depended on mitotic arrest, the pattern of development of apoptosis was similar to the kinetics of mitotic arrest, with the difference being that the development of apoptosis lags several hours behind that of mitotic arrest. The apoptotic response induced by paclitaxel persists for approximately two days. In contrast to paclitaxel, radiation-induced apoptosis in MCA-4 tumors increased rapidly so that the peak in apoptotic response occurred four hours after irradiation. Radiation-induced apoptosis rapidly declined, approaching the background level by 12 hours after irradiation. The efficacy of radiation in inducing apoptosis in tumors treated with paclitaxel depended on the time when radiation was delivered after

Background: Combination radiation and chemotherapy has an intuitive appeal for improving cancer treatment. Experimental results suggest that paclitaxel plus radiation might produce additive or synergistic effects.

Methods: A series of phase I and II trials to test tolerance and begin to evaluate effectiveness were performed on patients with non-small cell lung cancer, high-grade astrocytic brain tumors, and pancreatic and gastric cancers.

Results: Tolerance of the combined drug and radiation programs was generally good. Esophagitis was dose-limiting for the intrathoracic tumors. Hematologic toxicity was mild, but peripheral neuritis and cutaneous reactions were common.

Conclusions: These trials show that paclitaxel plus concurrent radiation is feasible at the dose levels and schedules tested. Antitumor responses have been observed.

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paclitaxel administration or whether cells were in mitosis at the time of irradiation. Radiation delivered one hour after paclitaxel administration, when only a low percentage of cells were in mitosis, was not more effective in inducing apoptosis than in tumors not treated with paclitaxel. However, when radiation was given nine or 24 hours after paclitaxel administration, when many cells were in mitosis, radiation-induced apoptosis increased significantly.

An alternative explanation is that treatment with paclitaxel results in reoxygenation of hypoxic tumor cells, a reoxygenation that increases with time. Approximately one third of the total tumor cell population becomes mitotically arrested within nine hours after paclitaxel administration, and the majority of these cells die by apoptosis or other modes of cell death.[29] The dead cells are rapidly removed from the tumor so that at 24 hours after paclitaxel administration, the MCA-4 tumor was histologically depopulated. It is logical to anticipate that this removal of dead cells should result in tumor reoxygenation, which makes tumor cells two to three times more sensitive to radiation.[31] Since approximately 30% of cells in 8-mm MCA-4 tumors are hypoxic[32] in untreated, air-breathing mice, their reoxygenation would considerably increase tumor radioresponse. The in vivo study by Milas et al.[33] showed that paclitaxel reduced radiobiological hypoxia in tumors, a major cause of tumor cell resistance to radiation, and that the induced reoxygenation increased as the time between administration of paclitaxel and tumor irradiation increased within the three-day observation period.

In summary, how paclitaxel enhances radiation toxicity is unclear, but mitotic arrest probably plays a major role, and increases in apoptosis and tumor reoxygenation may constitute additional mechanisms.

Phase I Study of Concurrent Paclitaxel and Radiation Therapy for Non-Small Cell Lung Cancer

This study was designed to determine the maximum tolerated dose and dose-limiting toxicities of paclitaxel administered weekly, with concurrent thoracic radiation, to outpatients with advanced non-small cell lung cancer (NSCLC).[34] In this Phase I trial, paclitaxel was administered as a three-hour intravenous infusion, repeated every week for six weeks with a low starting dose of 10 mg/m$^2$. Doses were escalated in increments of 10 mg/m$^2$. The dosage was escalated in successive cohorts of three new patients so long as no dose-limiting toxicity was observed, ie, grade 3 or 4 nonhematologic toxicity excluding nausea and vomiting or grade 4 hematologic toxicity.

Radiation therapy was delivered with weekly paclitaxel for six weeks. The treatment volumes consisted of original and boost volumes irradiated sequentially. Original volume included the primary disease site with a margin of 2 cm around the mass and the ipsilateral hilum. The whole width of the mediastinum was included with a margin of 2 cm around the radiographically visible involvement (pretreatment radiograph of the chest and computed tomography scan). The inferior margin was extended to 4 cm below the carina or 2 cm below the radiographically demonstrated tumor mass. The ipsilateral supraclavicular fossa was treated from the cricoid cartilage laterally to the mid-clavicular line. The boost volume included the original tumor volume with a margin of 2 cm. Elective supraclavicular field radiation treatment was not allowed. The dose to the original volume was 40 Gy in 20 fractions of 2 Gy/fraction to the prescription point over a period of four weeks. The boost volume dose was 20 Gy in 10 fractions of 2 Gy/Fraction to the prescription point over a period of two weeks.

Twenty-seven patients received weekly paclitaxel plus daily radiation therapy with doses ranging from 10 to 70 mg/m$^2$ per week for six weeks. Esophagitis was the principal dose-limiting toxicity of the paclitaxel-radiation combination in lung cancer patients. Severe esophagitis (grade 4) occurred in two patients at 70 mg/m$^2$, and a third patient developed grade 2 esophagitis. In the expanded 60 mg/m$^2$ level, one of eight patients developed grade 3 esophagitis and three of eight patients developed grade 2 esophagitis. Two patients receiving 70 mg/m$^2$ of paclitaxel required short hospitalizations for intravenous hydration and analgesic administration, and a third voluntarily discontinued after five cycles of paclitaxel due to grade 2 esophagitis. All patients developed skin reactions due to the radiation. Most of the skin reactions were mild except for two patients with grade 3 esophagitis and three of eight patients developed grade 3 esophagitis. Only four patients developed partial alopecia. Diarrhea, nausea, or vomiting did not occur. Seven patients developed mild joint discomfort and myalgias (grade 1). These symptoms did not appear to be dose dependent, and their symptoms usually subsided with nonsteroidal, anti-inflammatory medications. No cardiac toxicities were apparent, and no abnormalities were noted on neurologic examination. Added pulmonary toxicity from paclitaxel was not apparent. Neutropenia was mild except in one patient who developed grade 3 toxicity at a dose of 70 mg/m$^2$.

Of 23 assessable patients, four (17%) had a complete response to therapy and 13 (56%) had a partial response, for an overall objective response rate of 73% (95% confidence interval, 65% to 83%). Responses were seen at each level and in all patients at paclitaxel doses greater than 40 mg/m$^2$ (except one patient with stage IV disease).

This phase I study demonstrated that concurrent mediastinal radiation therapy can be safely delivered with paclitaxel as a three-hour infusion at 60 mg/m$^2$ given weekly for six weeks in patients with regionally advanced NSCLC. Esophagitis was defined as the dose-limiting toxicity.

Paclitaxel and Concurrent Cranial Irradiation for Adults With Primary Brain Tumors

This phase I study investigated paclitaxel administered weekly by three-hour infusion concurrent with daily cranial irradiation as the initial treatment for patients who were newly diagnosed with astrocytic high-grade glioma brain tumors. The treatment protocol was designed to increase the opportunity for radiosensitizing interaction, to take advantage of the phase-specific properties of paclitaxel, and to permit treatment to proceed entirely on an outpatient basis. The objectives of this study were to establish the maximum tolerated dose of paclitaxel administered in this setting and to identify the toxicities associated with this treatment regimen.[35]

Cranial irradiation and intravenous paclitaxel were given concurrently as a three-hour infusion once weekly for six consecutive weeks in the outpatient setting. The initial weekly dose of paclitaxel (20 mg/m$^2$) was escalated in cohorts of three patients until dose-limiting toxicity was observed. Cranial irradiation (using a linear accelerator with an energy of at least 6 MeV) was administered in 2 Gy fractions, one fraction per day for five consecutive days per week to a total dose of 60 Gy. The initial 40 Gy was given to the area of contrast enhancement on the preoperative magnetic resonance imaging scan, plus a 4-cm margin. The final 20 Gy was given to the enhancing lesion plus a 2-cm margin.

Sixty patients were entered into this study and received at least one course of therapy. The weekly dose of paclitaxel ranged from 20 mg/m$^2$ to 275 mg/m$^2$. Four patients discontinued treatment after one (three patients) or two (one patient) treatments, and 56 patients completed the prescribed course of therapy. Four of the 60 patients entered into this study died after receiving two or fewer courses of treatment. Death was due solely to disease progression in three patients. Hematologic toxicity was minimal and never required a dose reduction or treatment delay. No patient experienced greater than grade 2 anemia or grade 1 thrombocytopenia. One patient developed grade 3 neutropenia two days after her sixth course of paclitaxel at 175 mg/m$^2$. Aspiration pneumonia (secondary to a recent stroke) and subsequent sepsis preceded the development of neutropenia in this patient and were the causes of death. Grade 2 neutropenia was seen in four patients. Most patients (27, 48%) experienced their lowest absolute neutrophil count during the third week of treatment. The timing of platelet nadirs during therapy was similar. Anemia, although mild, was most common during the last three weeks of treatment. Peripheral neuropathy was the dose-limiting toxicity in this study. Of the 56 evaluable patients, 14 (25%) developed some degree of neuropathy (grade 1 in four patients, grade 2 in eight, and grade 3 in two). All patients with grade 3 neuropathy received 275 mg/m$^2$ of paclitaxel. The neuropathy developed during the second (one patient), third (four patients) fourth (seven patients), or fifth (two patients) weeks of treatment, progressed...
During the remainder of therapy, and continued to progress for one to three weeks after treatment had ended. Symptoms included tingling, loss of sensation, and rarely, mildly painful dysesthesias in the fingertips and toes and progressing proximally. Fine finger movement (eg, buttoning, tying shoes, manipulating keys) and gait were impaired in both patients with grade 3 neuropathy. In four patients (receiving paclitaxel doses of 225, 250, and 275 mg/m²), the neuropathy also was accompanied by severe and, at times, continuous pruritus that was undiminished by oral, parenteral, or topical diphenhydramine, dexchlorpheniramine, codeine, morphine, emollients, or soaking.

Reinstitution or increase in daily doses of dexamethasone provided modest relief in two patients, and complete resolution was seen in all patients within four weeks of the end of therapy. Neuropathic symptoms improved in all patients within two to four months of completing treatment and disappeared in all but four patients. Those four continue to report mild numbness in the toes of both feet. Decreased vibratory sensation has persisted in all patients with grade 2 or 3 neuropathy.

Cutaneous toxicity developed in eight patients and first appeared during week 2 (one patient), 3 (three patients), 4 (one patient), 5 (two patients), or 6 (one patient). The cutaneous toxicity was grade 1 in two patients, grade 2 in three, grade 3 in two, and grade 4 in one. Early skin changes consisted of prominent erythema (face, hands, and feet) and scattered, painless erythematous, macular lesions (hands, arms, feet, distal legs, and buttocks). These lesions coalesced and became vesicular in three patients and led to ulceration and desquamation in one patient. The skin lesions resolved in all patients within two to four weeks of discontinuing paclitaxel. No nausea, vomiting, diarrhea, stomatitis, myalgias, or seizures were seen in any patients.

The median survival for patients with glioblastoma multiformes was 9.2 months and has not been reached for patients with anaplastic astrocytomas or astrocytomas. Survival durations for these three groups differ significantly (P = .002, log-rank test). Within the glioblastoma multiforme group, a Cox proportional hazards regression analysis revealed that Karnofsky performance status and age were significant predictors of survival time (P = .03 and P = .004, respectively).

Paclitaxel dose did not appear to be a significant predictor of survival (P = .66).

Plasma pharmacokinetic studies were performed on 10 patients receiving paclitaxel doses of 100 mg/m² (one patient), 175 mg/m² (five patients), 200 mg/m² (one patient), 225 mg/m² (one patient), and 250 mg/m² (two patients). Calculated pharmacokinetic parameters for these patients resemble those previously described for women with breast or ovarian cancer receiving three-hour infusions of paclitaxel. Pharmacokinetic parameters for individual patients were used to calculate AUC and the duration that the plasma paclitaxel concentration exceeded 0.05 µmol/L (the threshold closely correlated with percentage reduction in granulocytes). The resulting AUCs and durations above 0.05 µmol/L are similar to those observed in patients receiving three-hour infusions of paclitaxel for other malignancies. The simulations during which plasma concentration of paclitaxel exceeded 0.05 µmol/L also allowed calculation of expected percent reductions in absolute neutrophil counts. The reductions expected from just the first week's dose of paclitaxel are much greater than those actually observed after all six doses administered in this study.

There are several possible explanations for this finding: (1) patients in this study received no prior chemotherapy, (2) bone marrow or other extraneural tumor involvement is extremely rare in patients with primary brain tumors and was not a factor in reducing tolerance to chemotherapy, (3) the high-dose weekly steroids administered to all patients as part of their premedication regimen may have produced chronic bone marrow stimulation and hastened recovery of white blood cells, and/or (4) the weekly schedule of paclitaxel administration may have produced changes in the bone marrow in some way that rendered the bone marrow less sensitive to the effects of subsequent doses or may have stimulated increasingly rapid recovery of the marrow. The current study does not provide enough data to evaluate these hypotheses directly. Further studies are underway.

A final obvious but incorrect hypothesis would be that a concurrent medication altered the metabolism of paclitaxel. Most patients with brain tumors also receive daily corticosteroids and anticonvulsants, which may induce the P450 enzyme systems primarily responsible for paclitaxel clearance. However, data from the 10 patients studied in this trial do not support altered pharmacokinetics as the major explanation for the unexpectedly mild neuropenia we observed. All pharmacokinetic parameters (particularly AUC and the length of time plasma paclitaxel concentrations remained above 0.05 µmol/L) in the 10 study patients are nearly identical to those observed in women with other solid tumors who received three-hour paclitaxel infusions at similar doses. Thus, the unexpectedly mild myelosuppression observed in the current trial cannot be explained primarily on the basis of altered pharmacokinetics.

Two significant and previously unreported toxicities were seen in our patients. Eight patients developed patchy, erythematous skin changes on the face and distal extremities and sometimes progressing to the proximal arms and legs and, in some cases, the body. In three patients, these lesions progressed to a painful vesicular exfoliate dermatitis. Skin biopsies in two patients demonstrated changes consistent with a drug reaction. This drug-related side effect developed in one patient receiving a paclitaxel dose of 175 mg/m².

A second unprecedented, but self-limited, paclitaxel-related side effect was severe pruritus. This developed only in patients who also were experiencing some degree of peripheral neuropathy, and we believe the pruritus to be manifestation of small fiber peripheral neuropathy. Electrophysiologic studies are underway to better characterize this form of paclitaxel-related neuropathy.

**Paclitaxel and Concurrent Irradiation for Pancreatic and Gastric Cancer**

A phase I study of paclitaxel and concurrent irradiation for patients with gastric and pancreatic cancer was initiated by the Clinical Oncology Group of Rhode Island (COGRI).[37] Eligible patients included those with residual postoperative disease, involved or close margins, recurrent disease after resection, or unresectable disease. Paclitaxel was given weekly by three-hour intravenous infusion for six weeks with 30 Gy to 50 Gy of radiation (Table 5). Patients with pancreatic cancer received a boost to a maximum of 62 Gy with two additional courses of paclitaxel.

Of the 21 patients entered in this study, 18 have completed treatment. One patient had a hypersensitivity reaction, one had grade 4 neutropenia, and two had abdominal pain. Dose-limiting toxicity has not yet been reached. Three (27%) of 11 patients with measurable disease have had partial responses; five (83%) of six patients without measurable disease remain progression-free at a median follow-up of nine months. Only three (23%) of 13 tumors had p53 mutations by single-stranded conformational polymorphism analysis. Since p53 gene mutations do not predict response to concurrent paclitaxel and radiation therapy in NSCLC, we evaluated the p16 cell cycle control gene in these neoplasms. Seven (54%) of 13 tumors had deletions or mutations of the p16 gene. Alterations of p16 were associated with highly aggressive tumors, including both cases of limits plastic. Six (86%) of seven patients with p16 alterations had rapid tumor progression. Concurrent paclitaxel and radiation therapy is a promising new regimen for locally advanced gastric and pancreatic carcinoma.

**Phase II Study of Weekly Concurrent Paclitaxel and Radiation Therapy for Non-Small Cell Lung Cancer**

Previously untreated patients with histologically documented inoperable stage IIIA or stage IIIB NSCLC were entered in this study.[37] Patients with direct vertebral body invasion or a malignant or exudative pleural effusion were ineligible. All patients had measurable or assessable disease. Weekly doses of 60 mg/m² of paclitaxel were administered as three-hour intravenous infusions in the outpatient setting for six weeks. Paclitaxel was usually given at the beginning of the week, prior to the first weekly dose of radiation treatment. Radiation was delivered as 2 Gy fractions for five days weekly for six weeks. The original and boost volumes were irradiated...
Thirty-three patients (19 men and 14 women) entered this study. The age range was 40 to 80 years, and the median age was 68 years. Twelve patients had stage IIIA disease, and 21 had stage IIIB. The most common histologic type was squamous carcinoma (55%). Most patients had a Cancer and Leukemia Group B (CALGB) performance status of 1.

Of the thirty-three patients enrolled, four were not evaluable. One patient was removed from the study after the discovery of subcutaneous metastatic disease during the first week of treatment. Two patients withdrew from the study during the second week of treatment due to disease progression in one patient and the refusal by the other patient to receive any additional chemotherapy. One patient developed a hypersensitivity reaction to her first dose of paclitaxel and was not rechallenged. Of the remaining 29 patients, 27 received all six paclitaxel treatments. Two patients received only five treatments due to esophagitis. A total of 172 cycles of weekly paclitaxel were administered for the 29 evaluable patients (99% of the planned paclitaxel doses), and 27 received the planned 60 Gy radiation. Radiation dosage was reduced to 48 Gy and 50 Gy in two patients due to esophagitis.

The complete response rate was 7% (2/29) and the partial response rate was 79% (23/29) for an overall response rate of 86% (95% confidence interval, 68% to 95%). Three patients had stable disease (10%). One patient had local tumor progression on computed tomography scan of the chest at the completion of treatment.

All subgroups responded favorably, and no statistically significant differences were noted with regard to performance status, histology, or stage. The response rate was 100% for women and 78% for men. The most frequent histologic subtype in this trial was squamous cell carcinoma. Fourteen (82%) of 17 patients with squamous cell carcinomas responded. All seven patients with adenocarcinoma had at least partial responses (100%). Patients with stage IIIA disease and those with IIIB disease responded equally well.

Esophagitis was the most significant toxicity noted in this study. Six patients (20%) had grade 3 esophagitis and required narcotics in order to eat solid food. Five patients (17%) had grade 4 esophagitis defined as the requirement for parenteral or enteral support or the need for hospitalization for intravenous hydration. Only one patient required a jejunostomy tube for enteral nutrition to complete therapy, and no patient required total parenteral nutrition. Esophagitis generally began in the final two weeks of treatment and resolved within two weeks of completing treatment in all patients. Two patients had grade 2 peripheral neuropathy, characterized by numbness and paresthesia of the hands and feet, which resolved within a few weeks of completing treatment. Two patients had significant pulmonary toxicity. These patients had pneumonitis with shortness of breath, hypoxia, and interstitial infiltrates. The pneumonitis improved rapidly with corticosteroids. The only significant hematologic toxicity was grade 3 neutropenia in two patients. One patient had a fever that persisted for four weeks during treatment as an outpatient without an identified source of infection. One patient had a grade 3 supraventricular tachycardia with a near syncopal episode. No other cardiac toxicity was observed. One patient had a grade 3 hypersensitivity reaction during her first cycle of paclitaxel with hypotension and rash, and she was not retreated. No patient had grade 3 or grade 4 nausea, vomiting, or complete alopecia.

The overall median survival time has not yet been reached in this study. At a median follow-up of 12 months, the overall survival rate was 73% (95% confidence interval, 66% to 96%). This phase II study of concurrent paclitaxel and radiation therapy for patients with stage III NSCLC demonstrated an 86% overall response rate. Responses were noted in all subgroups. There was no statistically significant difference in response rates according to gender, histology, or stage.

Although the mean follow-up in this study is just 12 months, our overall response rate is comparable to the most active chemoradiation combinations recently reported, including the 38% response rate observed with radiation alone in the control arm of the Hoosier Oncology Group study[38] and the 45% response rate reported by Perez et al.[39] for locally advanced NSCLC. Our current response rate is also greater than the 20% to 25% response rate anticipated from paclitaxel as a single agent. [6,7] Thus, the substantial response rate seen with concurrent paclitaxel and radiation therapy appears to justify the clinical use of concurrent paclitaxel and radiation therapy and is suggestive, though not conclusive, for a radiation-enhancement effect.

**Conclusions**

Concurrent paclitaxel and radiation therapy was safely administered on an outpatient basis. The toxicity is acceptable and compares favorably with other regimens currently used. Based on this response and toxicity profile, we believe concurrent radiation therapy and paclitaxel may be beneficial for control of both local and distant spread.

Several new studies using a weekly schedule of paclitaxel administration are underway. A phase II trial of concurrent cranial irradiation and weekly paclitaxel (225 mg/m²) in patients with anaplastic gliomas is nearing completion. No unanticipated toxicities have been seen, and response data will be available soon. A multicenter, phase II trial of weekly paclitaxel (250 mg/m² x 3) and cranial irradiation (3 Gy x 12) for patients with multiple brain metastases recently has been opened and is accruing patients rapidly. Survival, brain, and systemic tumor response and quality of life data are being collected. Phase II trials of weekly paclitaxel and carboplatin and radiation therapy also are underway in multiple tumor sites.

We now are extending our investigation of concurrent weekly paclitaxel and radiation therapy to the neoadjuvant setting for patients with potentially resectable, minimal N2 disease. We believe that the early institution of effective local and systemic therapy eventually will translate into improvements in survival.

**References**
