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Preclinically, the taxanes appear to potentiate radiation more effectively than do the platinum compounds. In our phase I trial (LUN-17) in patients with advanced non-small-cell lung cancer, we defined the maximum tolerated

Combination treatment including chemotherapy and radiation therapy has only recently been introduced in clinical trials of lung cancer and some other malignancies. An extensive series of clinical trials[1-4] was conducted to evaluate the significance of in vitro synergy between chemotherapy, particularly cisplatin (Platinol), and radiation therapy in the treatment of lung cancer. Numerous preclinical studies[5-10] have suggested that the taxanes as a group may be more effective potentiators of radiation than are the platinum compounds, but their interactions appear to be complex, and additional preclinical studies are ongoing in hopes of increasing our understanding of the radiation-enhancing mechanisms of these agents. In this presentation we discuss clinical trials[11,12] incorporating paclitaxel (Taxol) and radiation that have been conducted to evaluate the effectiveness and the role for this combination in the treatment of lung cancer.

Radiation and Chemotherapy in the Primary Treatment of Lung Cancer

Various agents have been used either sequentially or concurrently in clinical trials of combination chemo-radiotherapy for advanced non-small-cell lung cancer (NSCLC).

**Sequential Chemoradiotherapy**

Cancer and Leukemia Group B (CALGB) 8433 was the first major randomized clinical trial to demonstrate a significant survival advantage for the combination of sequential chemotherapy and radiation for patients with inoperable stage III non-small-cell lung cancer.[13] The treatment used in that study consisted of radiation (60 Gy in 2-Gy fractions) with or without two cycles of prior cisplatin and weekly vinblastine (Velban) for 5 weeks. Response rates were 56% for patients receiving the combination therapy vs 43% for patients receiving radiation alone, with median survivals of 13.7 and 9.6 months, respectively (P = .0066).

Reanalysis of this trial at 7 years showed that the initial findings persisted, with 5-year survivals of 17% and 6%, respectively.[14] The trial results also have been confirmed independently in an Intergroup study by the Radiation Therapy Oncology Group and the Eastern Cooperative Oncology Group, with similar findings of improved 1-year and median survivals of 60% and 13.8 months for patients given the combined therapy vs a 1-year survival rate of 46% and a median survival of 11.4 months for those treated with radiation alone.[15]

In another randomized study demonstrating an improvement in 3-year survival for sequential chemoradiotherapy vs radiation alone,[16] a decreased frequency of distant relapses also was noted.[17]

**Concomitant Chemoradiotherapy**

Concomitant chemoradiotherapy offers an alternative strategy for combined treatment. Its potential advantages over sequential therapy are the immediate and simultaneous treatment of both local and distant sites of disease and the opportunity for synergy between the modalities that may enhance local control.[1] These advantages, however, must be balanced against the potential for enhancement of toxicity to normal tissues. The principle of synergy between concomitant radiation and chemotherapy has been well described in vitro,[10,18] but it is more difficult to prove in clinical practice.

In a three-arm, randomized study of patients with stage III inoperable non-small-cell lung cancer conducted by the European Organization for Research and Treatment of Cancer, patients were treated with radiation alone (split course: 55 Gy in 20 fractions, with a 3- to 4-week midcourse break), the identical radiation schedule plus cisplatin 30 mg/m²/week during radiation, or the same radiation plus cisplatin 6 mg/m²/day.[19] In both combination arms, the total dose of cisplatin given
was identical. Although overall response rates were similar for all three arms, an improvement in overall survival was noted for patients given radiation plus cisplatin vs radiation alone ($P = .04$); the difference was most apparent when radiation plus daily cisplatin was compared with radiation only ($P < .009$). Analyses of patterns of failure showed improvement was confined to regional control.

**Combined Modalities vs Radiation Alone**

A recent meta-analysis[20] evaluating multiple clinical trials from the pretaxane era confirms an overall beneficial effect for combined therapy over radiation alone. However, local and distant failures still occurred in the majority of patients. Combined-modality therapy resulted in a mean gain in life expectancy of approximately 2 months by the end of 3 years, and a median survival improvement from 10.3 to 12 months. Clearly, incorporation of newer, more active chemotherapeutic agents and regimens is needed to improve local and distant control of disease.

**Combination Paclitaxel and Carboplatin**

Paclitaxel is among the most active single agents in the treatment of non-small-cell lung cancer.[21,22] Phase II trials evaluating paclitaxel in patients with previously untreated stage IIIA, stage IIIB, or advanced stage IV non-small-cell lung cancer indicate that paclitaxel used alone was associated with a response rate of 21% to 24% and a 1-year survival rate of 42%. Carboplatin (Paraplatin) is less neurotoxic, nephrotoxic, and ototoxic than its parent drug, cisplatin. Carboplatin is active against non-small-cell lung cancer and serves as a radiation sensitizer by potentially interfering with repair of sublethal radiation injury.[23] In a large randomized trial conducted by the Eastern Cooperative Oncology Group, single-agent carboplatin produced the highest 1-year survival rate with the least toxicity in patients with metastatic non-small-cell lung cancer.

Our recent laboratory data also suggest a possible synergistic relationship between paclitaxel and carboplatin.[24] Several studies have shown that the combination of paclitaxel and carboplatin provides an impressive response rate and survival time.[25-28] The Fox Chase Cancer Center, for example, conducted a phase II study of escalating doses of paclitaxel combined with a fixed dose of carboplatin. Their response rate was 63%, with a median survival of 53 weeks, which was better than any other combination in the management of stage IV non-small-cell lung cancer.

**Mechanisms of Radiation-Enhancing Effects of Paclitaxel**

Significant efforts have been focused on the ability of taxanes to potentiate the effects of radiation. Although support for several potential mechanisms of interaction has been demonstrated in vitro, cell synchronization appears to be the dominant factor.[5-10]

**Mitotic Arrest**

Paclitaxel, the prototype taxane, is extremely effective in arresting the activity of tumor cells in the G/M phase of the cell cycle. After only brief and low-level exposure to paclitaxel at concentrations of 30 nmol/L for 1 hour, arrest of proliferating cells in G/M can be noted. The effect has been observed to begin as early as 4 hours after initiation of treatment and approaches a maximum of 70% at 24 hours. These concentrations are routinely exceeded by 100-fold in the plasma and are achievable within the tumor in clinical practice.[29] The fraction of arrested cells increases as a function of both concentration and duration of exposure.[30]

**Increased Apoptosis**

Several groups, however, have shown that mechanisms of synergy other than the paclitaxel-induced cell-cycle perturbation must be operative, at least in the in vivo setting. Milas et al addressed the possibility that paclitaxel increases the susceptibility of tumor cells to radiation-induced apoptosis.[31] They demonstrated that paclitaxel-induced apoptosis developed mainly from mitotically arrested cells. Consequently, the pattern of apoptosis development was similar to the kinetics of mitotic arrest but lagged several hours behind, suggesting the influence of alternative mechanisms. The apoptotic response induced by paclitaxel persists for about 2 days. In contrast, radiation-induced apoptosis in MCA-4 tumors peaks in 4 hours and then rapidly declines, approaching background levels by 12 hours after irradiation.

**Timing** The efficacy of radiation-induced apoptosis in tumors treated with paclitaxel also is dependent on the timing of therapies and the phase of the cell cycle. These investigators[31] showed that radiation delivered 1 hour after paclitaxel, when only a low percentage of cells were in mitosis, was no more effective in terms of inducing apoptosis than it was in tumors that had not been treated with paclitaxel. However, when radiation was given 9 or 24 hours after paclitaxel, when many cells were in mitosis, radiation-induced apoptosis increased significantly.

**Tumor Reoxygenation**
An alternative explanation for the ability of the taxanes to potentiate radiation is that treatment with paclitaxel results in reoxygenation of hypoxic tumor cells, and the reoxygenation increases with time. About one third of the total tumor-cell population is mitotically arrested within 9 hours after paclitaxel administration, and the majority of these cells die by paclitaxel-induced apoptosis or other modes of cell death. The dead cells are rapidly removed from the tumor. It is logical to anticipate that this removal of dead cells results in tumor reoxygenation, rendering them two to three times more sensitive to radiation.[32] Since about 30% of cells in 8-mm MCA-4 tumors are hypoxic[33] in untreated air-breathing mice, their reoxygenation would considerably increase the radioresponsiveness of the tumor.

**Multifactorial Interaction**

In summary, the taxanes interact with radiation at many levels. Cell-cycle synchronization through mitotic arrest has been consistently shown to play a major role in radiation enhancement, but increased apoptosis and tumor reoxygenation may constitute additional mechanisms. Clearly, the interaction is multifactorial and the dominant mechanism may be affected by specifics of the setting, including drug exposure and concentration, tumor type, and radiation dosimetry.

**Phase I/II Studies of Combination Paclitaxel and Radiation Therapy for NSCLC**

**Concurrent Paclitaxel and Radiation Therapy**

This phase I study (LUN-17) was conducted to determine the maximum tolerated dose and dose-limiting toxicities of paclitaxel administered weekly, with concurrent thoracic irradiation, to outpatients with advanced non-small-cell lung cancer.[11]

Paclitaxel, at a starting dose of only 10 mg/m², was administered as a 3-hour intravenous infusion and repeated every week for 6 weeks, with concurrent radiation therapy. Paclitaxel doses were escalated in increments of 10 mg/m². Radiation therapy was dosed to the original volume as 40 Gy in 20 fractions of 2 Gy/fraction to the prescription point over the 6 weeks. The boost-volume dose was 20 Gy in 10 fractions of 2 Gy/fraction to the prescription point for a period of 2 weeks. In total, 27 patients received weekly paclitaxel plus daily radiation therapy, with paclitaxel doses ranging from 10 to 70 mg/m²/week for 6 weeks.

Esophagitis was the principal dose-limiting toxicity of this combination in lung cancer patients. Severe esophagitis (grade 4) occurred in two patients at paclitaxel 70 mg/m², and a third patient developed grade 2 esophagitis. Neutropenia was mild, except in one patient who developed grade 3 toxicity at a dose of 70 mg/m².

Four of 23 assessable patients had a complete response to therapy (17%), and 13 additional patients had a partial response (57%), for an overall objective response rate of 74% (95% confidence interval, 65% to 83%). Responses were seen at each dose level, and all patients responded at a paclitaxel dose > 40 mg/m², except for one patient with stage IV disease.

This phase I study demonstrated that concurrent mediastinal radiation therapy can be safely delivered with paclitaxel 60 mg/m² as a 6-week, 3-hour infusion for patients with regionally advanced non-small-cell lung cancer. Esophagitis was defined as the dose-limiting toxicity.

**Weekly Paclitaxel and Radiation Therapy**

Previously untreated patients with histologically documented inoperable stage IIIA or stage IIIB non-small-cell lung cancer were entered into this phase II study (LUN-27).[12] Paclitaxel 60 mg/m² was administered once weekly as a 3-hour intravenous infusion for 6 weeks. Paclitaxel was given in the outpatient setting and usually at the beginning of the week, before the first weekly dose of radiation. Radiation was delivered as 2-Gy fractions 5 days/week for 6 weeks (Figure 1). The original and boost volumes were irradiated sequentially, and treatment volume and dose were the same as in the phase I study, LUN-17.

Ultimately, this study comprised 33 patients, 19 men and 14 women, ranging in age from 40 to 80 years (median age, 68 years). Twelve patients had stage IIIA disease, and 21 had stage IIIB. The most common histologic type was squamous-cell carcinoma (55%). Most patients had a CALGB performance status of 1.

Of the 33 patients enrolled, four were inevaluable. 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 refusal of any additional chemotherapy in the other, and the fourth 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. Thus, a total of 172 cycles of weekly paclitaxel were administered to 29 evaluable patients, for 99% of the planned paclitaxel doses. Twenty-seven of 29 patients received the planned total 60-Gy radiation. The radiation dosage was reduced to 48 and 50 Gy in the two patients who developed esophagitis.

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

Esophagitis, the most significant toxicity noted in this study, generally began in the final 2 weeks of treatment and resolved in all patients within 2 weeks of completing treatment. Two patients developed pulmonary toxicity presenting as pneumonitis with shortness of breath, hypoxia, and interstitial infiltrates. The pneumonitis improved rapidly with corticosteroids. The only significant hematologic toxicity was grade 3 neutropenia, which developed in two patients.

At a median follow-up of 18 months, the overall median survival time had not yet been reached in this study; the overall 1-year survival rate was 73% (95% confidence interval, 66% to 96%). Although median follow-up in this study is just 18 months, the 86% overall response rate is promising and compares favorably with 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[34] or the 45% response rate reported by Perez for locally advanced non-small-cell lung cancer.[35] The response rate is also much greater than the 20% to 25% response rate anticipated from paclitaxel as a single agent.[21,22] Thus, the substantial response rate seen with concurrent paclitaxel and radiation therapy confirms a basis for further clinical trials.

**Weekly Paclitaxel, Carboplatin, and Thoracic Radiation**

This phase II study (LUN-56) was designed to investigate the combined use of paclitaxel, carboplatin, and radiation therapy followed by two cycles of paclitaxel and carboplatin (Figure 2). Carboplatin was added as a second radiopotentiant and for its clinically demonstrated enhanced effects when used in combination with paclitaxel. The two cycles of adjuvant bolus paclitaxel and carboplatin were delivered to enhance systemic control.

Previously untreated patients with histologically documented stage IIIA and stage IIIB non-small-cell lung cancer were eligible for this study. Before treatment, all patients underwent staging studies, including chest x-ray, thoracic and brain computed tomography scan, and bone scan.

Of 23 patients entered into this study and evaluable thus far, nine (39%) had stage IIIA disease and 14 (61%) had stage IIIB. Their mean age was 66 years, with a range of 37 to 85.

The partial response rate was 61% (14 of 23). One patient had stable disease for 6 months and died at 9 months with progression of disease. Two patients showed disease progression shortly after completion of the concurrent phase of therapy and died at 4 and 5 months. Of those 23 patients, 17 completed the planned course of concurrent chemotherapy followed by adjuvant chemotherapy.

The major toxicity encountered was esophagitis, which reached grade 3 in 15% of patients and grade 4 in 30% by the National Cancer Institute toxicity table. Most of the esophagitis was of short duration and only two patients were unable to receive adjuvant chemotherapy due to weight loss and esophagitis. The only significant hematologic toxicity was grade 3 neutropenia, which occurred in 25% of patients during the adjuvant chemotherapy phase. One patient developed grade 4 pneumonitis for 2 weeks following concurrent chemotherapy and radiation therapy. She later recovered and received additional chemotherapy as planned. One patient had grade 3 peripheral neuropathy after completion of concurrent chemotherapy and radiation therapy; she did not receive adjuvant chemotherapy.

This phase II study of concurrent weekly paclitaxel, carboplatin, and radiation therapy followed by adjuvant paclitaxel and carboplatin just completed its accrual with 40 patients. Patients participating in this study were allowed poor prognostic factors; ie, there was no weight loss limitation, and patients could have supraclavicular lymph-node involvement. The overall response rate was 77% (16 complete response, 61% partial response), and median survival was 16 months. The final analyses are incomplete, but the overall toxicities appear to be acceptable. Despite the additional carboplatin given weekly during the concurrent phase of the study, the overall toxicity was also comparable to the previous phase II study (LUN-27).

In this study, the combination of radiation therapy, paclitaxel, and carboplatin was safely administered on an outpatient basis. The toxicity was acceptable and compared favorably with other regimens currently used. Based on this response and toxicity profile, we believe concurrent paclitaxel, carboplatin, and radiation therapy offers an alternative clinical option for control of both local and distant spread.
Paclitaxel, Carboplatin, and Hyperfractionated Radiation Therapy

In this current phase II study (LUN-63), patients undergo hyperfractionated radiation treatment while receiving concurrent paclitaxel/carboplatin, in an attempt to improve local control and overall survival (Figure 3). Compared with standard fractionated radiation therapy, hyperfractionated radiation therapy has been shown to improve survival without increasing late toxicity, [36] although the 2-year survival remains low. Several other studies have supported the suggestion that concurrent chemotherapy with hyperfractionated radiation therapy may improve survival of patients with non-small-cell lung cancer.[15,38,39] Jeremic and his colleagues reported significantly longer survival time in groups of patients who received hyperfractionated radiation therapy with concurrent low-dose daily carboplatin and etoposide (VePesid) compared with patients who received hyperfractionated radiation therapy only (22-month vs 4-month median survival; 23% vs 9% 4-year survival).[38,39]

LUN-63 is the third prospective phase II study designed to determine the response rate, toxicity, and survival of patients treated with concurrent weekly paclitaxel, carboplatin, and hyperfractionated radiation therapy followed by two cycles of adjuvant paclitaxel and carboplatin for locally advanced unresectable non-small-cell lung cancer (Figure 3). The goal of this ongoing study is to improve overall survival and augment local control with hyperfractionated radiation therapy.

Thirty-two patients with unresectable stage IIIA or stage IIIB non-small-cell lung cancer from Vanderbilt Cancer Center Affiliate Network institutions entered this study between June 1996 and February 1997. Weekly intravenous paclitaxel (50 mg/m² by 3-hour infusion) and weekly carbo-platin (dosed to an area under the concentration-time curve [AUC] of 2) plus concurrent hyperfractionated chest irradiation (1.2 Gy twice daily for a total dose of 69.6 Gy) were delivered for 6 weeks followed by two cycles of paclitaxel (200 mg/m²) and carboplatin (AUC 6). Among the 22 patients evaluable for response, one patient achieved a complete response (4.5%) and 16 patients achieved a partial response (72.7%), for an overall response rate of 77.2%. Thus far, among 23 patients evaluable for toxicity, the principal toxic effect was esophagitis, which was grade 3 or grade 4 in eight patients (35%). In addition, 13% of patients experienced grade 3 and 13% grade 4 pulmonary toxicities.

Weekly paclitaxel and carboplatin plus concurrent hyperfractionated radiation therapy was well tolerated as an outpatient regimen. The response rate from this regimen is encouraging and appears to be at least equivalent to the response reported in trials of more toxic chemoradiation therapy.

Conclusions

Paclitaxel, with or without carboplatin, plus radiation therapy given on a unique weekly schedule designed to enhance radiation effect, can be delivered safely in the outpatient setting. The associated toxicity compares favorably and does not exceed that of combined-modality therapy incorporating cisplatin. Response and survival rates appear to improve when compared with those attained by radiation therapy alone. We believe the combination of concurrent radiation therapy, paclitaxel, and carboplatin offers significant clinical utility for control of both local and distant spread of non-small-cell lung cancer, but our conclusions require verification by a randomized trial to determine the most effective sequence.

We are currently extending the investigation of concurrent weekly paclitaxel plus radiation therapy in a large scale, three-arm randomized phase II trial (Figure 4).

References:


