Paclitaxel and Carboplatin With Thoracic Radiation: Locally Advanced Non–Small-Cell Lung Cancer

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By Chandra P. Belani, MD

Combined-modality approaches integrating carboplatin (Paraplatin) and low doses of weekly paclitaxel (Taxol) with thoracic radiation therapy for prolonging survival in patients with locally advanced non–small-cell lung cancer

Introduction

Combined chemotherapy and radiation therapy have started to replace the traditional local approach of thoracic radiotherapy alone for unresectable stage III non–small-cell lung cancer. By itself, thoracic radiotherapy provides local control and effective palliation of symptoms, but has a minimal effect on survival.[1-3] Novel schemes of radiation such as hyperfractionated radiation[4] and continuous hyperfractionated accelerated radiotherapy[5,6] have been developed and tested. Saunders et al[6] demonstrated the superiority of the continuous hyperfractionated accelerated radiotherapy regimen (57.6 Gy in 36 fractions over 12 continuous days) over conventional radiotherapy in the treatment of patients with non–small-cell lung cancer, but at the expense of substantial esophagitis upon completion of treatment.

The addition of chemotherapy to thoracic radiotherapy sequentially[7-10] or concurrently[11-13] has shown an improvement in survival and quality of life of unresectable non–small-cell lung cancer stage III patients, especially those with a good performance status and < 5% weight loss,[8-10] when compared to radiation therapy alone (Table 1). The French trial[7] not only demonstrated an improvement in survival with the addition of chemotherapy, but also showed an improvement in systemic control with a reduction in distant metastasis when compared to radiotherapy alone. In Dillman’s study[7] (100 mg/m² of cisplatin [Platinol] on days 1 and 29 and 5 mg/m² of vinblastine [Velban] on days 1, 8, 15, 22, and 29, followed by radiotherapy beginning on day 50 vs radiotherapy alone), the median survival of 13.7 months in the combined-modality arm was significantly better than 9.6 months observed in the radiotherapy alone arm (P = .01), and there were twice the number of survivors at 3, 4, 5, and 7 years. This study[8,9] was duplicated by the Radiation Therapy Oncology Group (RTOG) and the Eastern Cooperative Oncology Group (ECOG),[10,11] adding a third arm consisting of hyperfractionated radiation (69.6 Gy). Results showed that 1-year and median survivals in the combined-modality arm (60% and 13.8 months, respectively) were significantly improved compared with the hyperfractionated radiation alone arm (51%, 12.3 months) and the standard thoracic radiotherapy arm (46%, 11.4 months) (P = .03). The combined-modality arm continues to show improved survival at 5-year follow-up (P = .004).[11]

Meta-analysis of randomized studies assessing the comparative efficacy of radiation therapy alone to combined chemotherapy and radiation therapy in patients with locally advanced, unresectable non–small-cell lung cancer[12] showed that the relative risk for death at 1, 2, and 3 years was reduced by 12%, 13%, and 17%, respectively, in favor of combined-modality therapy. The benefit of chemotherapy appeared to increase with time reaching the maximum at 31 to 36 months from the start of treatment. The mean gain in life expectancy was approximately 2 months at the end of 3 years, with an improvement in median survival of 1.7 months. Although chemotherapy did not impair delivery of radiation therapy, serious toxic effects, particularly febrile neutropenia and gastrointestinal disturbances, were more prevalent in patients receiving cisplatin-based chemotherapy. Thus, the addition of chemotherapy to radiotherapy offers an advantage in patients with locally advanced, unresectable stage III non–small-cell lung cancer, but the exact sequence of combined-modality therapy, the optimal and effective agents to be used in combination with radiation, and the best schedule of radiation therapy, are all subjects of continued investigation.

Concurrent Chemotherapy and Radiation

In an attempt to decrease the toxicity of cisplatin-based chemoradiation, we conducted a pilot study using weekly carboplatin (Paraplatin), the less toxic analog of cisplatin, and concurrent thoracic
radiotherapy in patients with locally advanced non-small-cell lung cancer.[13] In this study, 35 previously untreated patients with stage III non-small-cell lung cancer were given 100 mg/m² of carboplatin weekly, with concurrent thoracic radiotherapy (total dose, 60 Gy). The response rate was 34%, and median survival was 13 months. The treatment was well tolerated, with only three patients requiring treatment prolongations of > 1 week. This regimen demonstrated efficacy and feasibility with a mild toxicity profile, and appeared suitable for combination with other chemotherapeutic agents. In a subsequent study, we added paclitaxel (45 mg/m² given over 3 hours), followed by carboplatin (100 mg/m² over 30 minutes) with concurrent thoracic radiotherapy (60-65 Gy over 6 or 7 weeks).[14,15] (Table 2).

**Paclitaxel Plus Carboplatin**

The rationale for including paclitaxel was based on its known clinical activity and its radiosensitizing potential in preclinical and clinical studies.[16-18] In advanced and metastatic non-small-cell lung cancer, it has shown impressive activity both as a single agent[19-20] and in combination with carboplatin.[21-24] When used in combination with thoracic radiation therapy as a single agent, the recommended dose of paclitaxel is 60 mg/m² administered as a short infusion (1 or 3 h).[25] In our study, we used a lower paclitaxel dose of 45 mg/m² to account for the toxicity related to the addition of carboplatin in this combined-modality regimen. Only nine of the 38 patients treated who had one or more weekly doses of chemotherapy interrupted treatment for more than 1 week due to grade 3 neutropenia; the incidence of severe esophagitis was 6%. The survival of patients treated with our regimen for locally advanced non-small-cell lung cancer at 1, 2, and 3 years was 61%, 39%, and 39%, respectively.

Choy and colleagues have also reported the results of their combined chemoradiotherapy utilizing paclitaxel and carboplatin.[26,27] Their regimen consisted of paclitaxel (50 mg/m² 1-hour infusion weekly), carboplatin weekly (with a dose targeted to achieve an area under the concentration-time curve of 2 [AUC in mg/mL · min]), and concurrent thoracic radiation therapy (total dose, 66 Gy) (Table 3). Patients then went on to receive two additional cycles of full-dose chemotheraphy with the same combination of paclitaxel and carboplatin.

Among the 37 evaluable patients, the overall response rate was 75% and the 1- and 2-year survival rates were 54% and 40%, respectively. The incidence of esophagitis (National Cancer Institute Common Toxicity Criteria grades 3 and 4) observed was 49%, but was of short duration. Other rare toxicities included nausea, vomiting, neuropathy, weight loss, and pulmonary complications. Choy et al.[28] recently presented the results of another phase II study of 43 patients with locally advanced non-small-cell lung cancer who received concurrent weekly low-dose paclitaxel (50 mg/m²) and carboplatin (AUC of 2) with hyperfractionated radiation (69.6 Gy administered twice daily) instead of standard fractionation utilized in the previous trial, followed by two cycles of full-dose chemotheraphy with the same agents. The incidence of grades 3 and 4 esophagitis, as measured by the RTOG scale, was 26%; 16.5% of patients had grades 3 and 4 pulmonary toxicity. One-year survival was 63%, and the median survival has not been reached. If this trial utilizing hyperfractionated radiation is put into perspective with the data previously reported by Belani et al,[14,15] and combined with data from Choy’s group utilizing the same chemotherapeutic agents with standard daily radiotherapy, there appears to be no advantage to giving concurrent twice-daily hyperfractionated radiation.

**Hyperfractionated Accelerated Radiation**

Hyperfractionated accelerated radiation therapy with no treatment on weekends has also been combined with chemotherapy in a sequential fashion. Two cycles of carboplatin (AUC of 6) and paclitaxel (175 to 225 mg/m²), followed by hyperfractionated accelerated radiation therapy to the postchemotherapy tumor volume (given in three divided daily fractions to a dose of 57.6 Gy in 12 treatment days), was used by Wagner et al at the H. Lee Moffitt Cancer Center in patients with stage III non-small-cell lung cancer.[29] Induction chemotherapy was well tolerated and all 21 patients completed hyperfractionated accelerated radiation therapy as scheduled. Two weeks after hyperfractionated accelerated radiation therapy, grade 3 or 4 esophagitis occurred in 11 patients, and 10 of these required hospitalization for toxicity. The median survival for all patients was 12 months; survival at 18 months was 30%. This same schedule is now being tested in a randomized setting by the ECOG (with study chairs Chandra P. Belani and Henry Wagner) to determine the effect of hyperfractionated accelerated radiation therapy compared with standard daily radiotherapy after induction with carboplatin and paclitaxel for patients with locally advanced, unresectable non-small-cell lung cancer (Figure 1).

**Dose-Escalation Trial**

The Fox Chase Cancer Center study[30] in patients with stage III non-small-cell lung cancer was
designed to test induction full-dose paclitaxel and carboplatin with growth factor support followed by concurrent carboplatin and paclitaxel administered in escalating doses for two cycles (days 43 and 64) with thoracic radiation therapy. The response to induction therapy has been 38%, but the overall response rate with both phases is 59%. The dose level of paclitaxel (175 mg/m²) has been well tolerated at a carboplatin dose targeted to achieve an AUC of 3.75 during the concurrent phase (Table 4). Inferences regarding toxicity, especially esophagitis, cannot be made from this study because this is a dose-escalation trial. Nevertheless, these investigators have shown that the length of exposure of the esophagus in the radiation field is an important factor responsible for occurrence of esophagitis, especially with combined-modality regimens.[31]

Discussion

Carboplatin and paclitaxel have been successfully integrated with thoracic radiation therapy for patients with locally advanced unresectable non–small-cell lung cancer. Early results have shown an improved outcome compared to historical controls. Both sequential and concurrent regimens are feasible and the toxicity profiles are acceptable. Concurrent chemoradiotherapy incorporating low doses of weekly paclitaxel and carboplatin is not only feasible, but also effective in prolonging survival of patients with locally advanced non–small-cell lung cancer. The dose and schedule of administration for paclitaxel in the combined-modality programs continues to be a subject of controversy. Based on preliminary results, the doses of paclitaxel at 45 to 50 mg/m²/week with 1- or 3-hour infusion, and carboplatin at 100 mg/m² (or an AUC of 2), can be combined with concurrent radiation therapy for the treatment of locally advanced non–small-cell lung cancer. There appears to be no advantage to administering paclitaxel on a prolonged schedule of 24-hour infusion or daily bolus during radiation therapy.[32,33] When cisplatin (75 mg/m²) and full-dose paclitaxel (135 mg/m²) were combined with concurrent thoracic radiation to 64.8 Gy (34 fractions over 7 weeks) for patients with unresectable stages IIIA and IIIB non–small-cell lung cancer to assess treatment tolerability, efficacy, and survival,[32] the major toxicities encountered were esophagitis and leukopenia. The investigators concluded that administration of larger/full doses of paclitaxel every 4 weeks with concurrent radiation therapy could not be recommended for use because of prohibitive toxicity. Administration of a larger dose of paclitaxel on a 3- to 4-week schedule in the concurrent chemoradiotherapy programs provides the same dose intensity but is associated with increased toxicity. The length of the esophagus included in the radiation field also should be minimized so as to avoid excessive toxicity.[31]

The systemic patterns of failure in the patients treated with concurrent paclitaxel, carboplatin, and thoracic radiation therapy suggest the need for additional chemotherapy either at the front end or after the completion of the concurrent regimen. A large multicenter randomized study conducted by the American College of Radiology (Locally Advanced Multimodality Protocol [LAMP]) (Figure 2) has been initiated to address these issues of improvement in distant control and to further refine the combined-modality approach for patients with locally advanced non–small-cell lung cancer. The dose of paclitaxel was kept at 45 mg/m² during the concurrent phase with radiation therapy so as to decrease the incidence of mucosal and pulmonary toxicity. The hope for the immediate future is to define an effective and optimal regimen that can be given simultaneously with radiation therapy and which can result in improved local and systemic control in patients with regionally advanced non–small-cell lung cancer. Other agents, such as docetaxel (Taxotere), vinorelbine (Navelbine), and gemcitabine (Gemzar) have also been used with radiation therapy, but reports are still preliminary. Results of the CALGB study presented by Vokes et al[34] suggested the need for dosage reduction of gemcitabine, paclitaxel, and vinorelbine when combined with radiation therapy. Physicians need to exercise caution in combining these novel agents with radiotherapy because of the possibility of excessive mucosal and marrow toxicities. The doses of chemotherapeutic agents in concurrent chemotherapy regimens need to be carefully chosen, based on available data. The use of slightly higher doses may result in significant adverse effects and overall reduction in quality of life. The addition of selective approaches, for example, gene therapy, antiangiogenic agents, and monoclonal antibodies (Herceptin), in combined-modality regimens may further enhance the overall outcome of patients with locally advanced non–small-cell lung cancer.


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