The Emerging Role of Paclitaxel Plus Carboplatin in Non–Small-Cell Lung Cancer

By Paul A. Bunn, Jr, MD

The activity and toxicity profiles of carboplatin (Paraplatin) and paclitaxel (Taxol) used as single agents in non–small-cell lung cancer made them logical agents for study in combination therapy. Once preliminary trials showed that both agents could be combined safely in full doses, this led to phase II and III trials of the combination in advanced non–small-cell lung cancer, to combination with chest radiotherapy in stage III disease, and to neoadjuvant therapy in stage I and II non–small-cell lung cancer.

Introduction

Lung cancer is the leading cause of cancer death in both men and women in the United States.[1] The 160,100 deaths predicted for 1998 represent 28% of all cancer deaths.[1] The cure rate is extremely low (14%) because most patients have metastatic disease at the time of presentation, and because systemic therapies are unable to cure advanced metastatic disease. Attitudes toward lung cancer therapy began to change when cisplatin-based therapies were shown to prolong survival,[2,3] relieve symptoms,[4] and improve quality of life[5] at acceptable medical costs in advanced non–small-cell lung cancer.[6]

Although cisplatin-based therapy accomplished the results described above, there was debate regarding its general utility because of its toxicity profile, inconvenience, and marginal therapeutic gains. Carboplatin (Paraplatin) has gained increasing usage in place of cisplatin in non–small-cell lung cancer because of its convenient administration, low toxicity profile, and equivalent or superior efficacy compared to cisplatin.[7]

Paclitaxel (Taxol) as a single agent was shown to have efficacy equivalent or superior to that of cisplatin and carboplatin.[8] When given as a short infusion, paclitaxel can be given on an outpatient basis with relatively mild toxicity. The activity and toxicity profiles of carboplatin and paclitaxel in non–small-cell lung cancer made them logical agents for combination therapy. Preliminary trials showed that both agents could be combined safely in full doses.[9-14] This led to phase II and III trials of the combination in advanced non–small-cell lung cancer, to combination with chest radiotherapy in stage III disease, and to neoadjuvant therapy in stage I and II non–small-cell lung cancer.

Carboplatin in Advanced Non–Small-Cell Lung Cancer

Carboplatin was introduced into clinical trials in advanced non–small-cell lung cancer because it could be administered easily as a short, outpatient infusion; because it lacked the toxicity and nephrotoxicity of cisplatin; and because it produced far less nausea and vomiting compared to cisplatin.[7] Since its introduction, several randomized trials have compared carboplatin, alone or in combination, to cisplatin-based combinations. The results of such trials are summarized in Table 1. The Eastern Cooperative Oncology Group compared single-agent carboplatin to several cisplatin-based combinations.[15] Patients not responding to carboplatin could receive a cisplatin combination after two cycles. As shown in Table 1, the 9% response rate to carboplatin was lower than the 13% to 20% response rates for cisplatin combinations. However, the toxicity rate was significantly lower and the survival was significantly longer in patients receiving carboplatin. The European Organization for Research and Treatment of Cancer compared a combination of etoposide and carboplatin to a combination of etoposide and carboplatin.[16] The dose of carboplatin in this trial (325 mg/m²) was low and was not based on renal function. Nonetheless, the efficacy of the two regimens was similar, whereas the toxicity was considerably less in the carboplatin arm.

More recently, a comparative randomized trial using a higher dose of carboplatin (500 mg/m²) was completed.[17] In this trial, mitomycin-C and vindesine were combined with either cisplatin (120 mg/m²) or carboplatin (500 mg/m²). The efficacy of the carboplatin arm was superior to that of the cisplatin arm both in response rate and survival. Myelosuppression in the two arms was similar although the rate of nausea, vomiting, ototoxicity, and nephrotoxicity remained lower in the...
carboplatin arm. These trials provide a strong rationale for the use of carboplatin in combination therapy trials in advanced non–small-cell lung cancer.

**Single-Agent Paclitaxel**

Paclitaxel was introduced into lung cancer therapy in the early 1990s and rapidly became established as one of the most effective agents for the disease. The earliest trials used a 24-hour infusion of high-dose paclitaxel (200 to 250 mg/m²).[18,19] This dose was given on an inpatient basis and required both granulocyte-colony stimulating factor (G-CSF) and combination premedication with diphenhydramine, cimetidine, and prednisone. The response rates to these 24-hour infusions are summarized in Table 2,[18-20] along with a summary of the results of single-agent paclitaxel given as a 3-hour infusion and as a 1-hour infusion at 3-week intervals.[21-25] This table also shows the results of a single trial in which the paclitaxel was given weekly.[26] The response rates appear to be quite similar with each schedule. In each of these trials, the survival results were also similar with 1-year survival rates of approximately 40% in each trial. The results of the weekly schedule gave the highest response rate and the longest survival. It also gave the greatest dose intensity. However, this was a single-institution trial and additional studies with this regimen are necessary. There were no phase II studies with a 96-hour infusion in untreated patients, but a single study in previously treated patients showed no responses.[27]

**Combination Studies with Paclitaxel Plus Carboplatin**

**Long-Infusion (24-h) Paclitaxel**

Studies with long-infusion paclitaxel (24 hours) plus carboplatin are summarized in Table 3. The study of Langer et al[9] escalated doses in each patient, starting from 135 mg/m² and escalating to 215 mg/m². The study of Johnson et al[11] gave doses of 135 mg/m² or 175 mg/m² to different groups of patients. The study of Belani et al[10] escalated doses of both paclitaxel and carboplatin. The overall response rate in these studies was 46% with the highest response rate (61%) seen in the escalating dose study of Langer et al.[9] This study required inpatient administration of the drugs and routine G-CSF administration due to the high rates of grade 4 neutropenia. The average median survival was 46 weeks in these studies and the average 1-year survival rate was 43%.

**Short-Infusion 1- or 3-h Paclitaxel**

A summary of United States studies combining 1-hour or 3-hour infusions of paclitaxel with carboplatin is provided in Table 4.[12-14,28-34] The studies of Bunn,[12] Natale,[13] and Rowinsky[14] were phase I dose-escalation studies. In these studies, paclitaxel doses below 175 mg/m² were associated with lower response rates and shorter survival.[12-14] Each of these three studies recommended paclitaxel at a dose of 225 mg/m² and carboplatin (area under the concentration-time curve of 6 [AUC in mg/mL · min]) for phase II and III studies. Surprisingly, these studies found a much lower rate of thrombocytopenia than expected. This was not due to a pharmacokinetic interaction but rather appeared to be due to a platelet-sparing effect of paclitaxel. Grade 4 neutropenia occurred in only a minority of patients given these doses and febrile neutropenia was rare. G-CSF was not administered, and all therapy was given on an outpatient basis. Some of the paclitaxel plus carboplatin combination studies with short paclitaxel infusion times gave lower doses of paclitaxel (175 mg/m²). These studies had slightly lower response rates and shorter survival compared to those with higher paclitaxel doses (200 mg/m²). There is an ongoing randomized trial in Greece to determine if 225 mg/m² of paclitaxel infused over 3 hours is preferred over 175 mg/m² over 3 hours.[35] Preliminary results show superiority for the higher dose. One study gave higher doses of carboplatin (AUC of 9 or 11).[33] This study reported greater toxicity without an apparent advantage in response or survival rates. Finally, one study gave the two drugs every other week.[34] This study reported a low response rate with considerable toxicity so it cannot be recommended.

The overall response rate in Table 4 (35%) and the 1-year survival rates 42% to 50% (average 45%) compare favorably to studies with paclitaxel combined with cisplatin, and with studies employing longer paclitaxel infusions with carboplatin (Table 3).

Due to the low rates of toxicity, the convenience, and the effectiveness of this combination, it was widely adopted into community practice. Cooperative groups selected this combination to compare to their previous standard. The ongoing cooperative group trials in advanced non–small-cell lung cancer are summarized in Table 5. This combination was also incorporated into combined-modality studies in stage III non–small-cell lung cancer with radiotherapy and stages I and II non–small-cell lung cancer with surgery.
Three-Drug Combinations
The low toxicity profile of the paclitaxel plus carboplatin combination make it possible to develop three- and four-drug combinations. The results of studies with three-drug combinations containing paclitaxel and carboplatin are summarized in Table 6. The group from the University of Colorado Cancer Center reported that full doses of paclitaxel (175 mg/m² infused over 3 hours on day 1 every 3 weeks) and carboplatin (AUC of 5 infused over 30 minutes on day 1 every 3 weeks) could be combined safely with gemcitabine (Gemzar) (1,000 mg/m² infused over 30 minutes on days 1 and 8 every 3 weeks).[36] Higher doses of carboplatin were associated with excessive thrombocytopenia. The response rates (36%) and median survival (10 months) reported in this phase I and II study were better than the group’s prior phase I and II experience with paclitaxel and carboplatin.[12] Similar results were obtained by Hainsworth et al at the Sarah Cannon Cancer Center with paclitaxel (200 mg/m²) and carboplatin (AUC of 5) on day 1, with gemcitabine (1,000 mg/m²) on days 1 and 8.

The group from the University of Chicago reported that both 24-hour and 1-hour infusions of paclitaxel combined with carboplatin and ifosfamide provided relatively low response rates (12% to 20%) and considerable toxicity.[38] Zaniboni and coworkers reported more encouraging results (64% response) with the same three-drug combination.[39] In a preliminary report with a small number of patients, Neill et al reported no responses with the three-drug combination of paclitaxel, carboplatin, and etoposide.[40] Additional combination study results are necessary before conclusions can be drawn.

Chest Radiotherapy in Stage III Non–Small-Cell Lung Cancer
Previous studies showed encouraging results in patients with stage III non–small-cell lung cancer who were treated with carboplatin in combination with chest radiotherapy. Thus, the combination of paclitaxel and carboplatin with chest radiotherapy was a logical extension of these studies. A summary of five studies evaluating this combined-modality approach is provided in Table 7.[41-45] In four studies, the combination of paclitaxel and carboplatin was given weekly with concurrent chest radiotherapy.[41-43,45] In two of these studies, the radiotherapy was given once daily and in two studies it was hyperfractioned and given twice daily.[42,46] The weekly paclitaxel doses were either 45 or 50 mg/m² as a short infusion and the carboplatin doses were 100 mg/m² or calculated on the basis of a projected AUC of 2. Each of these studies reported no unexpected toxicities, and esophagitis was the most frequent severe toxicity. The response rates were high (67% to 77%) and the early survival results were encouraging with 1-year survival rates of 54% to 63%.

Another approach was taken by Langer et al who gave two induction cycles of paclitaxel and carboplatin prior to concurrent therapy with paclitaxel, carboplatin, and chest radiotherapy.[44] In this study, the carboplatin and paclitaxel were given in 3-week intervals. The reported response rate after the induction and concurrent therapy was 59% and 62% of patients were alive at 1 year. Randomized trials comparing these approaches to older approaches are warranted.

Neoadjuvant Therapy in Operable Disease
Surgery alone fails to cure the majority of operable non–small-cell lung cancer patients. The majority of first recurrences following surgery are in distant sites. Meta-analysis of randomized trials employing alkylating agent–based therapy showed that survival was shortened by this approach.[3] In contrast, this meta-analysis showed that cisplatin-based postoperative therapy reduced the hazard rate of death by 13%, which led to a 5% improvement in the 5-year survival rate.[3] More recent studies used cisplatin-based chemotherapy in a neoadjuvant approach in patients with stage IIIA non–small-cell lung cancer. These randomized trials showed even more impressive improvement in survival.

Based on the results of these trials and the excellent results with paclitaxel plus cisplatin or carboplatin in advanced non–small-cell lung cancer, it was logical to use this combination in a neoadjuvant fashion in patients with operable non–small-cell lung cancer. The preliminary results of two such trials are summarized in Table 8.[46,47] As shown in the table, the response rates (71% to 75%) were higher than reported in more advanced stages. There were few toxicities reported and there were no increases in operable morbidity or mortality. The vast majority of patients were able to undergo a complete surgical resection of their disease. If these results hold up in later analyses of these trials, randomized trials versus conventional approaches will be indicated.

Conclusions
Paclitaxel plus carboplatin is currently the most widely used combination for advanced
non–small-cell lung cancer in the United States. The efficacy results with this combination are similar to the best results with any other combination. The convenience of drug administration and the relative lack of toxicity are the primary reasons for the widespread use of this regimen in the palliative setting. This combination has produced exciting results in combination with radiotherapy in stage III non–small-cell lung cancer, and in combination with surgery in stage I and II disease. Future randomized trials will be necessary to determine the role of this combination as standard therapy for these stages of non–small-cell lung cancer.

References:


Source URL:
http://www.diagnosticimaging.com/review-article/emerging-role-paclitaxel-plus-carboplatin-non-small-cell-lung-cancer

Links:
[1] http://www.diagnosticimaging.com/review-article