Chemotherapeutic intervention in advanced and metastatic non-small-cell lung cancer (NSCLC) has changed over the past 2 decades. The improvements offered by cisplatin (Platinol)-based regimens, though significant in

While it has long been accepted that chemotherapeutic intervention provided some benefit for patients with non-small-cell lung cancer (NSCLC) in terms of quality of life and symptomatology as well as modest improvements in survival,[1-3] the overall outlook for patients with this disease remained bleak. Despite development and evaluation of a number of agents found to produce at least a 15% response among patients with non-small-cell lung cancer (Table 1[4-13]), in the 1970s and 1980s the 1-year survival rate did not exceed 10% to 12%. Subsequently, cisplatin (Platinol)-containing combination regimens, such as Platinol/etoposide (VePesid) (PE), Platinol/vinblastine (Velban) (PV), or mitomycin-C (Mutamycin)/vinblastine/Platinol (MVP) resulted in increased activity in some phase II studies, but 1-year survival increased to only 15%. [14-20]

Although development of new agents remained a primary goal of research, cisplatin-based regimens were considered standard for over 2 decades. Carboplatin (Paraplatin), the less-toxic analogue of cisplatin, had previously shown marginal activity in non-small-cell lung cancer,[21,22] but gave a surprisingly strong single-agent showing when compared with three cisplatin-based combination regimens, producing a superior 1-year survival rate of 28% with considerably less toxicity than was seen with the cisplatin-based combination regimens.[21]

It has been shown[23] that conventional dosing of carboplatin according to body surface area leads to unpredictable myelosuppression. When carboplatin dose is determined by Calvert’s formula[24] using a targeted area under the concentration-time curve (AUC) and calculated glomerular filtration rate, myelosuppression is manageable and the therapeutic index appears to be improved.

Still greater improvements in survival rates were seen with the introduction of the taxanes in the 1990s. Although paclitaxel (Taxol), the first prototype of the taxanes, was found to be active in non-small-cell lung cancer, with response rates of 21% to 24%, the most significant result of paclitaxel therapy was the markedly increased 1-year survival rates, which reached 40%[25-29] (Table 2). Thus, in the early 1990s, paclitaxel became the most active agent evaluated by the Eastern Cooperative Oncology Group (ECOG).[26]

Initial Trials of Paclitaxel Plus Platinum for NSCLC

Encouraging data from early studies of paclitaxel prompted the initiation of a variety of studies designed to evaluate the agent in combination with other drugs active against non-small-cell lung cancer. Of all studies conducted, those incorporating one of the platinum agents—cisplatin or carboplatin—elicited the greatest interest.

Cisplatin/Paclitaxel

Cisplatin-based trials revealed a sequence-dependent drug interaction, with an increase in myelotoxicity seen when paclitaxel was given after cis-platin.[30,31] Putting aside the toxicity profile, which includes cumulative, dose-limiting peripheral neuropathy, three phase II studies showed response rates ranging between 35% and 47% with this combination.[32-34]

This impressive response inspired a three-arm comparative trial to evaluate the dose-response effect of either low- or high-dose paclitaxel plus cisplatin vs a standard combination of etoposide (VePesid) plus cisplatin.[35] As shown in Table 3, the response rates seen with both low- and high-dose paclitaxel-based combinations (26.5% and 32.1%, respectively) were significantly better than those seen with the standard treatment (12.0%), as were 1-year survival rates (36.9%, 39.1%, and 31.6% for the three groups, respectively). These results led to the replacement of paclitaxel/cisplatin for
etoposide/cisplatin as the new reference therapy for future ECOG studies involving patients with non-small-cell lung cancer.

**Carboplatin/Paclitaxel**

Given the activity seen with carboplatin and paclitaxel as single agents, and encouraging data from studies of cisplatin in combination with paclitaxel, combining paclitaxel with carboplatin was a logical next step. The carboplatin/paclitaxel combination proved to be exceptionally active in non-small-cell lung cancer and generated a great deal of interest. Initial studies of the combination used 24-hour infusions of paclitaxel and established that myelosuppression was the dose-limiting toxic reaction.[23,36,37] Other studies used a shorter infusion schedule of 1 or 3 hours and reported a significant decrease in myelosuppression, with neuropathy being dose-limiting.[38-42,45] The various infusion schedules, however, did not appear to have any important influence on the level of activity of paclitaxel/carboplatin in patients with non-small-cell lung cancer (Table 4).

The studies of paclitaxel/carboplatin yielded two important observations. First, the combination was not associated with platelet toxicity, suggesting that paclitaxel may exert a myeloprotective effect that counters the thrombocytopenia generally associated with carboplatin.[46] Although the precise mechanism involved in this platelet-protective effect is not yet clear, there may be some alteration of megakaryocytopoiesis or thrombocytopoiesis, resulting in increased levels of endogenous thrombopoietin or other cytokines. Ongoing studies are measuring the effect on thrombopoietin with this combination. It is possible that the inhibition of proplatelet formation associated with carboplatin may be suppressed with prior exposure to paclitaxel when measured in terms of pharmacodynamic effect on platelets, and a greater exposure to carboplatin can be achieved when it is given in combination with paclitaxel than when it is given as a single agent.[46]

The second noteworthy outcome from the paclitaxel/carboplatin studies was that most responses occurred in patients treated at paclitaxel doses greater than 175 mg/m². This observation suggests the presence of a dose-response effect.[37,40]

To date, the best results have come from the Fox Chase Cancer Center study,[36] which reported an impressive 62% response rate and 54% 1-year survival rate from a regimen involving intrapatient escalation of the paclitaxel dose between 135 and 215 mg/m² and carboplatin dosed to achieve an AUC of 7.5 mg/mL · min. Based on the reported phase I and II study results, recommended doses for the combination of paclitaxel/carboplatin call for paclitaxel to be given as a 24-hour infusion at 175 mg/m² or, in shorter infusions of 1 or 3 hours, at 200 to 225 mg/m², with carboplatin doses generally targeted to attain an AUC of 6 or 7.

The first large, randomized study of paclitaxel/carboplatin for advanced or metastatic non-small-cell lung cancer compared this combination with the standard cisplatin/etoposide regimen (Table 5). The study accrued 369 patients over 15 months. The median survival is 8.25 months, and the 1-year survival is 35%. The number of events required to perform a survival analysis by arm has not occurred.

**Paclitaxel/Carboplatin in NSCLC: Future Directions**

The paclitaxel/carboplatin combination has elicited a great deal of interest among oncologists. The encouraging improvements in 1-year survival from 10% to approximately 50% seen with paclitaxel/carboplatin have prompted evaluations of this combination in large, randomized studies of patients with advanced and metastatic non-small-cell lung cancer (Table 6) in combined-modality programs for unresectable and potentially resectable disease, in earlier stages of disease, and in patients with minimal tumor burden. In hopes of achieving further improvements and developing an optimal means of managing non-small-cell lung cancer, however, development of new agents and treatment approaches remain important goals of research. The development of three-drug combination regimens, for example, is currently under way and includes studies in which agents active in non-small-cell lung cancer, eg, gemcitabine (Gemzar), vinorelbine (Navelbine), or irinotecan (Camptosar), are being combined into the paclitaxel/carboplatin combination. Paclitaxel/carboplatin is also being investigated in a number of combined-modality programs, including an induction regimen for patients with early stage disease and a trial of paclitaxel/carboplatin with either sequential or concurrent radiation. A large, multicenter randomized study (locally advanced multimodality protocol, or LAMP) will evaluate the efficacy of paclitaxel and carboplatin given either sequentially or concurrently with radiation therapy for patients with potentially unresectable disease (Figure 1). Other evaluation approaches include use of the paclitaxel/carboplatin combination as adjuvant therapy for resected non-small-cell lung cancer and in dose-dense weekly schedules for patients with metastatic disease.
Conclusions

The future of non-small-cell lung cancer management will incorporate strategies that combine these active chemotherapeutic regimens with selective approaches like gene therapy (adenovirus p53 gene), antiangiogenic agents, and monoclonal antibodies. With the use and efficacy of these regimens in earlier stages of non-small-cell lung cancer, most patients diagnosed with non-small-cell lung cancer will be offered chemotherapy as a part of the overall management.

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