Recent Advances With Chemotherapy for NSCLC: The ECOG Experience

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Management of disseminated non-small-cell lung cancer has changed over the past 10 years. Newer agents, such as vinorelbine (Navelbine) and paclitaxel (Taxol), have been shown to modestly improve survival in patients with lung cancer.

The management of non-small-cell lung cancer (NSCLC) has evolved considerably within the past decade. New drugs and drug combinations appear to provide a modest but real improvement in the survival of patients, including those with far advanced, unresectable disease. A review of earlier therapeutic results may help to establish a frame of reference from which to understand this progress.

Early Findings

Between 1975 and 1985, the Thoracic Committee of the Eastern Cooperative Oncology Group (ECOG) conducted a number of randomized, prospective trials designed to identify an ideal chemotherapy regimen to treat advanced non-small-cell lung cancer. Eligibility for these trials required that patients have a good performance status (PS) (ie, ECOG PS 0 through 2) and stage IV disease. The regimens selected for evaluation were cisplatin based, and all had shown promising results in single-institution trials.

To summarize the results of these trials, no specific regimen emerged as superior to the others in terms of median survival, although the combination of cisplatin (Platinol) and etoposide (VePesid) (PE) provided the most consistent 1-year survival rate and tended to be the least toxic. Accordingly, ECOG selected PE as a reference arm for all subsequent randomized trials. Regardless of the drug combination used in any of these Eastern Cooperative Oncology Group trials, overall response rates averaged 25%, median survival averaged 6 months, and 1-year survival was usually ≤ 20%.[1]

Lessons Learned

Several lessons were learned or affirmed from these trials. First, although performance status had no impact on response rates per se, patients with a poor performance status were at greater risk to develop life-threatening toxicity. Second, survival correlated directly with performance status, an observation that actually confirms previous knowledge but seems to be rediscovered every few years. In the ECOG experience, median survival tracks with performance status in the following way: ECOG PS 0 = 9 months survival; PS 1 = 6 months, and PS 2 = 3 months.

Drug-Discovery Trials

The disappointing nature of randomized trials testing multiple-agent regimens in metastatic non-small-cell lung cancer prompted ECOG investigators to initiate a series of single-agent phase II trials in chemotherapy-naive patients. This approach seemed to provide an ideal setting in which to determine the true activity of a new agent.[2]

Characterization of a new drug’s activity is not easy, however, because accurate determination of tumor response in lung cancer can be complicated by such factors as the frequent lack of bidimensionally measurable lesions or the presence of atelectasis, pneumonia, pleural effusions, and, occasionally, radiation-induced fibrosis or pneumonitis.[3] In addition, there are substantial interobserver and intraobserver differences,[4] and phase II studies in non-small-cell lung cancer are commonly conducted in heterogeneous patient populations that may include both treated and untreated patients who have different disease stages and sometimes markedly different PS levels. All these factors are known to affect objective response rates and undoubtedly account for the widely diverse response rates reported for many drugs.
Eligibility Restrictions
Starting in 1983, ECOG investigators decided to perform drug testing in chemotherapy-naive patients with good PS (ECOG PS ≤ 2) and measurable stage IV disease. Patients with brain metastases or stage III disease were excluded. Restricting eligibility for these drug-discovery trials to patients with stage IV non-small-cell lung cancer was done in an attempt to keep the study populations as homogeneous as possible. Although patients with stage III disease usually experience higher chemotherapy response rates than those with more advanced disease,[5] the marked heterogeneity of this population makes comparisons between studies extremely difficult, prompting exclusion of this group.

First Single-Agent Trial
The first ECOG drug-discovery trial to test single agents in previously untreated non-small-cell lung cancer patients was EST-1583, a five-arm, randomized trial in which two new agents—iproplatin and carboplatin (Paraplatin)—were compared with three cisplatin-containing combination regimens.[2] Interestingly, with an overall response of only 9%, single-agent carboplatin yielded the best median survival, which was found to be statistically superior to that of patients treated with the popular multiagent regimen comprising mitomycin (Mutamycin), vinblastine (Velban), and cisplatin (Platinol), (MVP). One-year survival was 18% for the entire group of 686 patients, similar to results achieved in previous ECOG trials using combination chemotherapy in patients with stage IV non-small-cell lung cancer.

Later Trials
Subsequent to EST-1583, ECOG investigators performed a series of phase II trials using comparable patient populations. However, the later trials excluded PS 2 patients primarily because of their higher incidence of life-threatening toxicities.[1]

Agents tested over a 10-year interval included homoharringtonine, gallium nitrate (Ganite), amonafide, teniposide (Vumon), acivicin, echinomycin, trimetrexate (NeuTrexin), merbarone, and paclitaxel (Taxol).[2,6-8] All drugs were chosen either for their novel mechanism of action or because they had demonstrated some activity in preclinical models.

Paclitaxel’s Activity Against NSCLC
The only agent to emerge from this series of trials showing activity against non-small-cell lung cancer was paclitaxel. Paclitaxel binds preferentially to the microtubules, promotes microtubule assembly, and stabilizes the equilibrium between microtubule and tubulin dimer. Thus, it interferes with the depolymerization of the tubulin molecules, a process required for mitosis and cell division.[9]

Single-Agent Findings
In the ECOG trial, paclitaxel was administered by 24-hour continuous infusion at a dose of 250 mg/m² given every 3 weeks, with the now-standard premedication program of oral dexamethasone (20 mg given 14 and 7 hours before paclitaxel and intravenous diphenhydramine (50 mg) and cimetidine (300 mg) both given 1 hour before paclitaxel. Treatment was continued until disease progressed or the treatment became intolerable.

In total, 24 patients (17 men, 7 women) with a median age of 61 years received paclitaxel; 15 had ECOG PS 1. Prior radiation had been administered to eight of the patients and seven patients had experienced a weight loss of ≥ 5% in the 3 months preceding diagnosis. Five partial responses were observed in this group, for an overall response rate of 21% (95% confidence interval [CI], 7% to 42%). To put these data in perspective, the 10-year ECOG drug-discovery experience documented in Table 1 shows that none of the single agents tested before the introduction of paclitaxel had produced a double-digit response rate. Carboplatin had been associated with the highest recorded overall response at just 9%. The durations of the five partial responses to paclitaxel were 3.7, 5.0, 6.4, > 6.5, and > 15.4 months.

Median survival was 24.1 weeks, similar to that observed with cisplatin-based combination chemotherapy. Unexpectedly, paclitaxel was associated with an apparent improvement in 1-year survival (approximately 40%) compared with historical ECOG data. We may have dismissed this finding except that investigators from the University of Texas, M. D. Anderson Cancer Center, Houston, Texas, reported virtually identical results.[10]

These results prompted ECOG investigators to further evaluate the role of paclitaxel in non-small-cell lung cancer. Thus, a series of phase II trials was carried out to evaluate the feasibility of combining paclitaxel with cisplatin, a combination that had previously demonstrated synergistic cytotoxicity in preclinical studies.[11,12]
Paclitaxel Combination Regimens

These results culminated in a phase III study (E5592) in which patients with advanced non-small-cell lung cancer were randomized to receive cisplatin plus etoposide or cisplatin plus low-dose (135 mg/m²) or high-dose (250 mg/m²) paclitaxel.[13] Paclitaxel was administered over 24 hours and, in the case of high-dose paclitaxel, was administered with granulocyte colony-stimulating factor. Among the 574 eligible patients accrued between August 1993 and December 1994, 108 had stage IIIIB lesions and 466 had stage IV disease. The three arms of the trial were evenly balanced for the usual prognostic factors. Both the objective response rates and the survival figures were superior in the paclitaxel-treated groups (Table 2). Based on these findings, cisplatin plus paclitaxel has become the new reference regimen for future ECOG trials in the treatment of advanced non-small-cell lung cancer.

Future Directions

In recent years, several drugs in addition to paclitaxel have emerged as active against non-small-cell lung cancer, including docetaxel (Taxotere), vinorelbine (Navelbine), gemcitabine (Gemzar), and irinotecan (Camptosar). Vinorelbine has undergone extensive evaluation and, like paclitaxel, appears to provide a survival advantage over older drugs when combined with cisplatin.[14,15] Data from nonrandomized trials suggest that other platinum combinations using one of the newer agents may provide similar if not superior survival benefits.[16-21] To test this hypothesis, ECOG investigators have undertaken a phase III trial to evaluate patients with advanced non-small-cell lung cancer treated with cisplatin plus paclitaxel vs cisplatin plus docetaxel, cisplatin plus gemcitabine, and carboplatin plus paclitaxel. The accrual goal is 1,200 patients. After just 6 months, through July 1997, more than 300 patients had been entered into this trial. Accrual should be completed by late 1998.

Conclusion

Chemotherapy is appropriate for selected non-small-cell lung cancer patients. Regardless of the outcome of this ongoing Eastern Cooperative Oncology Group trial, the available data indicate that the therapeutic nihilism of the past is no longer warranted. Although survival benefits remain modest, they are real and comparable with those achievable in other solid tumors (eg, breast cancer). Further, the newer agents may prove to have more favorable toxicity profiles, which in turn should benefit all patients.

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