Eastern Cooperative Oncology Group Experience With Chemotherapy in Advanced Non-small Cell Lung Cancer*

Philip Bonomi, MD

Eastern Cooperative Oncology Group (ECOG) investigators have tested a variety of single-agent and combination regimens in patients with non-small cell lung cancer (NSCLC) during the last 2 decades. The following observations have been made. (1) The mitomycin/vinblastine/cisplatin regimen produced a trend for higher response rates in two studies and a significantly higher response rate in a third study. Survival, however, tended to be shorter in patients receiving this regimen. (2) Carboplatin produced a 9% overall response rate and a median survival of 31.7 weeks, which was slightly but significantly longer than the median survivals obtained with three combination chemotherapy regimens. (3) Paclitaxel produced an overall response rate of 21% and a 1-year survival rate of 40% in previously untreated NSCLC patients. This observation led to a phase III trial in which paclitaxel (135 mg/m² and 250 mg/m²) was combined with cisplatin and compared with etoposide/cisplatin. Response rates for each of the paclitaxel/cisplatin regimens (26% for 135 mg/m² paclitaxel and 31% for 250 mg/m²) were significantly higher than the response rate for etoposide/cisplatin (12%), but response between the two paclitaxel/cisplatin arms was not significantly different. At this point, there is a trend toward longer survival in each of the paclitaxel/cisplatin arms, but the final survival analyses have not been completed. In the next phase III trial, ECOG will evaluate paclitaxel (135 mg/m²) plus cisplatin in comparison to three other regimens—docetaxel/cisplatin, gemcitabine/cisplatin, and carboplatin/paclitaxel.

(CHEST 1998; 113:135-168)

During the past 16 years, the Eastern Cooperative Oncology Group (ECOG) has conducted a series of phase III and randomized phase II trials in advanced non-small cell lung cancer (NSCLC). This period can be divided into four phases, each of which is characterized by a particular study design and philosophical approach. Initially, large phase III trials testing promising combination regimens were conducted. Then ECOG began a transitional phase during which single agents were compared with combination regimens and, simultaneously, databases were analyzed. Next, randomized phase II trials of new agents were started, and the results of these studies led to the most recent phase III trial comparing the survival results for two dose levels of paclitaxel combined with cisplatin and those obtained with etoposide/cisplatin. Each of these phases will be discussed briefly in this review.

Early Phase III Trials

In the late 1970s and early 1980s, a variety of cisplatin-and noncisplatin-containing combination regimens were reported to produce response rates ≥30% in patients with advanced NSCLC. The ECOG systematically evaluated each of these regimens in relatively large phase III trials. The results of two of these studies, summarized in Tables 1 and 2, showed none of the regimens was associated with significantly superior survival. However, the MVP (mitomycin/vinblastine/cisplatin) regimen produced the best response rate in the first trial and a slightly but significantly higher response rate among patients with either adenocarcinoma or squamous cell carcinoma in the second trial. These observations resulted in MVP being selected as the reference regimen for future ECOG trials.

The major objective of the phase III trials was to identify a regimen that significantly improved the survival of patients with advanced NSCLC. Unfortunately, this objective was not met. Similarly disappointing was the fact that response rates in the ECOG trials were considerably lower than those observed in smaller single-institution phase II trials.

A Time of Transition—Single Agents vs Combination Chemotherapy Regimens

Based on results from the phase III trials, ECOG investigators decided to test new agents in patients with previously untreated advanced NSCLC. Considerable controversy existed regarding the effect of chemotherapy on the survival of patients with advanced NSCLC while this study design was being developed. Randomized trials comparing chemotherapy with best supportive care had not been completed, and ECOG investigators were concerned that initial treatment with an ineffective single agent might have a detrimental effect on survival. Thus, the first ECOG trial design called for previously untreated patients to receive primary treatment with one of three combination regimens or one of two single agents followed by the MVP regimen. The combination regimens consisted of MVP (the reference regimen) vs vinblastine/cisplatin, vs MVP alternating with CAMP (cyclophosphamide/doxorubicin/methotrexate/procarbazine). Carboplatin and ifosfamide were selected as the single agents in this trial. As had been observed in earlier trials, the MVP regimen produced the best response rate, but in this trial, the difference was statistically significant for all cell types (20%; p = 0.03). In addition, both of the single agents produced significantly lower response rates ( ie, 9% for carboplatin [p = 0.001] and 6% for ifosfamide [p = 0.001]). Surprisingly, patients receiving carboplatin experienced a slightly but significantly longer median survival (31.7 weeks; p = 0.008), whereas patients given MVP had a shorter median survival (22.7 weeks; p = 0.08). Median survival for ifosfamide-treated patients was 26.1 weeks, which was slightly longer than that.
achieved with MVP and virtually identical to the median survival observed with vinblastine/cisplatin and with MVP alternating with CAMP. Response rates and median survival durations for this study are summarized in Table 3.

Critics of this study have suggested that the superior survival results obtained with carboplatin are purely coincidental, and certainly this is possible. It should be noted, however, that this was a relatively large study, and not only was carboplatin associated with slightly longer survival, but survival in iplatin-treated patients was virtually equivalent to that observed with the combination chemotherapy regimens.

Iplatin and carboplatin were also tested in a randomized phase II trial conducted by the Cancer and Leukemia Group B (CALGB). These investigators reported results that were similar to the findings of the ECOG study. The response rates for carboplatin and iplatin were 16% and 7%, respectively, and median survivals were 6.5 and 5 months, respectively. Although response rates in the CALGB trial were slightly higher and median survival was slightly shorter than those in the ECOG trial, it is interesting to note that in both trials, carboplatin achieved a higher response rate than iplatin, and that the differences in median survival for carboplatin- vs iplatin-treated patients in the ECOG and CALGB studies were 5 and 6 weeks, respectively. In the ECOG trial, both carboplatin and iplatin were associated with significantly less life-threatening and lethal toxic reactions than the combination regimens (p<0.0001). Although there is no clear-cut explanation as to why carboplatin-treated patients had a significantly lower response rate and a significantly longer survival, these observations suggest that increased toxic reactions from chemotherapy may exert a detrimental effect on survival or that chemotherapy may exert a positive effect on survival without producing a high rate of tumor shrinkage.

### Table 1—Response Rates and Survival Data: Four Cisplatin Regimens*

<table>
<thead>
<tr>
<th>Regimen</th>
<th>No. of Patients</th>
<th>Response, %</th>
<th>Median Survival, wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>MVP</td>
<td>104</td>
<td>27</td>
<td>23.7</td>
</tr>
<tr>
<td>CAP</td>
<td>107</td>
<td>24</td>
<td>23.5</td>
</tr>
<tr>
<td>AFP</td>
<td>109</td>
<td>18</td>
<td>21.6</td>
</tr>
<tr>
<td>CBP</td>
<td>112</td>
<td>22</td>
<td>22.1</td>
</tr>
</tbody>
</table>

*CAP = cyclophosphamide/doxorubicin/cisplatin; AFP = doxorubicin/5-fluorouracil/cisplatin; CBP = cyclophosphamide/bleomycin/cisplatin. Adapted from Buckdeschel et al.5

### Table 2—Response Rates and Survival Data: Four Most Active Regimens*

<table>
<thead>
<tr>
<th>Regimen</th>
<th>No. of Patients</th>
<th>Response, %</th>
<th>Median Survival, wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>MVP</td>
<td>121</td>
<td>31</td>
<td>22.0</td>
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<tr>
<td>VP</td>
<td>126</td>
<td>25</td>
<td>26.0</td>
</tr>
<tr>
<td>EP</td>
<td>124</td>
<td>20</td>
<td>26.6</td>
</tr>
<tr>
<td>CAMP</td>
<td>115</td>
<td>17</td>
<td>25.1</td>
</tr>
</tbody>
</table>

*VP = vindesine/cisplatin; EP = etoposide/cisplatin. Adapted from Buckdeschel et al.5

### Table 3—Response Rates and Survival Data: Combination Chemotherapy vs Single Agents*

<table>
<thead>
<tr>
<th>Regimen</th>
<th>No. of Patients</th>
<th>Response, %</th>
<th>Median Survival, wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>MVP</td>
<td>176</td>
<td>20</td>
<td>22.7</td>
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<tr>
<td>VP</td>
<td>175</td>
<td>13</td>
<td>25.1</td>
</tr>
<tr>
<td>MVP/CAMP</td>
<td>172</td>
<td>13</td>
<td>25.0</td>
</tr>
<tr>
<td>Carboplatin/MVP</td>
<td>88</td>
<td>9</td>
<td>31.7</td>
</tr>
<tr>
<td>Iplatin/MVP</td>
<td>88</td>
<td>6</td>
<td>26.1</td>
</tr>
</tbody>
</table>

*Adapted from Bonomi et al.5 See text and Table 2 footnotes for explanation of abbreviations.

### Database Analyses

While the randomized trial comparing single agents and combination chemotherapy regimens was ongoing, data from 893 patients who had participated in the earlier phase III trials2,3 were being analyzed.7 The following observations were made: (1) the overall 1-year survival rate for patients receiving chemotherapy was 19%; (2) the etoposide/cisplatin regimen achieved the highest 1-year survival rate (25%), although none of the regimens significantly improved 1-year survival; and (3) although the MVP regimen was associated with higher response rates in each trial (Tables 1 and 2), MVP-treated patients had the lowest 1-year survival rate (12%; p=0.08). These results are similar to those observed in the transitional protocol in which MVP was compared with other combination regimens and with single agents.5 The discordance between response rate and survival both for the MVP regimen2,3 and for single-agent carboplatin6 emphasizes the need to test promising treatments in phase III trials and should alert clinicians to exercise caution when selecting treatments based on data from smaller phase II trials.

Examination of the toxicity data from the ECOG phase III trial comparing the four most active regimens showed that nonambulatory patients (ECOG performance status of 2) experienced a 10% rate of lethal toxicity. In comparison, patients whose ECOG performance status was 0 or 1 experienced a 3% rate of lethal toxicity. Based on these observations, ECOG has excluded patients with an ECOG performance status of 2 from subsequent trials.

### Drug Discovery

Having observed no apparent detrimental effect of single agents on survival in the carboplatin trial,8 ECOG initiated a series of phase II trials of new agents in previously untreated NSCLC patients. Acivicin, the first drug tested in the ECOG Drug Discovery Program, was compared with etoposide/cisplatin (the reference regimen) in a randomized phase II trial.8 The rationale for including the reference regimen was to assess the constancy of the ECOG patient population. In early studies,1,2 the overall response rates for MVP were 27% and 31%,

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while in a more recent trial, the response rate was 20%. The observations suggest a trend toward lower response rates in more recent studies. In fact, in the trial comparing acivicin with etoposide/cisplatin, the overall response rate for etoposide/cisplatin was 11%. The reasons for the apparent lower response rates are not readily recognized, but it is possible that responses are being defined more rigorously because of the increasing use of CT scans.

In the Drug Discovery Program, the ECOG observed no significant activity with six consecutive single agents (Alex Chang, MD; personal communication; April 1996), including acivicin. However, paclitaxel at a dose of 250 mg/m² given IV over 24 h produced a 21% overall response rate in 24 patients. Investigators at M.D. Anderson Cancer Center, using a 24-h infusion of paclitaxel at a dose of 200 mg/m², observed a 24% response rate in 25 patients. Perhaps more important, both studies reported a 40% 1-year survival rate. Although the confidence intervals for the 1-year survival rates observed in these small trials are wide, these results are nevertheless encouraging considering the 1-year survival rate observed with previously tested combination regimens was 19%.7

**Testing the Impact of New Agents on Survival**

Encouraged by the 40% 1-year survival rate observed with paclitaxel, ECOG investigators decided to test the survival effect of paclitaxel in a large phase III trial. Etoposide/cisplatin was compared with paclitaxel, 135 mg/m², combined with cisplatin, 75 mg/m²; and paclitaxel, 250 mg/m², combined with cisplatin, 75 mg/m², plus granulocyte colony-stimulating factor, 5 μg/kg given daily following chemotherapy. Paclitaxel was given as a 24-h IV infusion. Etoposide/cisplatin was chosen as the reference regimen because it had produced the highest 1-year survival rate (25%) in a prior ECOG trial. The lower dose of paclitaxel (135 mg/m²) was selected because it had shown significant activity and acceptable toxicity when combined with cisplatin, 75 mg/m², in women with ovarian carcinoma. The higher dose of paclitaxel (250 mg/m²) combined with cisplatin was selected based on the results of a phase I trial conducted at Johns Hopkins. In this study, the use of granulocyte colony-stimulating factor overcame the dose-limiting toxic reaction of granulocytopenia and fever. At doses higher than 250 mg/m², however, neurotoxicity became prohibitive.

Accrual to the ECOG phase III study was completed rapidly (600 patients in 16 months). The paclitaxel/cisplatin regimens produced significantly higher response rates (26% for 135 mg/m² and 31% for 250 mg/m² paclitaxel) than etoposide/cisplatin (12%). There was, however, no significant difference in response rates between the paclitaxel-containing regimens. Preliminary analyses have shown a trend toward longer survival in patients receiving each of the paclitaxel-containing regimens. Additional data are being collected, and final survival analyses will be completed shortly. Significant grade 4 granulocytopenia was observed with each regimen, but the incidence of febrile episodes during granulocytopenia was relatively low (<10%). In addition to the major objective of this trial (evaluation of survival, response, and toxicity), a serial quality of life data have been collected and are currently being analyzed.

**Future Directions**

During the last 5 years, at least five new agents with response rates >20% in advanced NSCLC have been identified. Two of these compounds, docetaxel and gemcitabine, will be combined with cisplatin and tested in the next phase III trial. In addition, the carboplatin/paclitaxel regimen, which has produced relatively high response rates and a median survival of approximately 1 year in two relatively large phase II trials, will be evaluated in this study. Paclitaxel (135 mg/m² given IV over 24 h) combined with cisplatin (75 mg/m²) will serve as the reference regimen in this study, and comparison of survival will be the primary end point.

**References**