Treatment of Advanced Non–Small-Cell Lung Cancer: A Review of Current Randomized Clinical Trials and an Examination of Emerging Therapies

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Background: Lung cancer continues to be the leading cause of cancer-related deaths for Americans. As most patients present with nonsurgically curable disease, major efforts have been made in the treatment of advanced non–small-cell lung cancer (NSCLC) with chemotherapy. Several new agents and new combinations of chemotherapy are available.

Methods: The author reviews randomized clinical trials investigating chemotherapy for advanced NSCLC in chemotherapy-naive patients, in patients who present with relapsed or progressive disease, and in elderly patients. Therapies that incorporate new biological agents to target specific aberrations in lung cancer are discussed.

Results: Several clinical trials demonstrate improvement in overall survival as well as quality of life with chemotherapy treatment of advanced NSCLC. Better options are available for patients who have relapsed after first-line chemotherapy, and treatment of elderly patients with chemotherapy has demonstrated benefit in survival and quality of life. New agents that target molecular pathways are being tested in patients with early-stage disease.

Conclusions: Despite progress with newer agents for the treatment of advanced NSCLC, only 14% of patients with the disease are alive at 5 years after initial diagnosis. New therapies are needed.

Introduction

Lung cancer continues to be the leading cause of cancer-related deaths for Americans. Despite nearly twice the estimated cases of prostate cancer in men, estimated deaths from lung cancer are nearly 3-fold higher. Similarly for women, estimated cases of breast cancer are nearly 2.5-fold higher than lung cancer, but...
the estimated death rate for lung cancer is nearly 2-fold higher. While age-adjusted cancer rates for lung cancer have fallen in the past decade for men, the same is not true for women. Overall, the 5-year relative survival rate for lung cancer is 14% for the years 1989-1995, which is significantly, albeit minimally, increased from 13% for the years 1974-1976 and 1980-1982.

Approximately 75% to 80% of cases are of the non–small-cell histology, and the majority of patients present with either locally advanced disease (stage III) or metastatic disease (stage IV). Importantly, patients who undergo curative surgical resection for apparent localized disease have survival rates ranging between 50% and 80%, implying the need for better systemic treatment to cure occult micrometastatic disease. Therefore, the majority of patients either present with advanced disease requiring chemotherapy or require chemotherapy at the time of relapse after surgical resection. While efforts to reduce smoking are crucial to the eventual control of the disease, newer treatments for patients who currently have the disease are critical.

For some time, the treatment of non–small-cell lung cancer (NSCLC) with cytotoxic chemotherapy remained controversial, given the unclear impact on patient survival. A review of chemotherapy for lung cancer in 1992 identified the active agents as cisplatin, mitomycin, ifosfamide, etoposide, and the vinca alkaloids vinblastine and vindesine. Response rates to single agents were approximately 20% and, while combination chemotherapy suggested improvements in response rates, the impact of chemotherapy on patient survival was unclear. This review concluded that the impact of chemotherapy on survival for patients with NSCLC was not demonstrated and “it is difficult to recommend incorporating chemotherapy into the standard care of patients with disseminated NSCLC.”

Support of treating patients with advanced NSCLC came from an international collaborative meta-analysis using updated data on patients from 52 randomized clinical trials. Eleven trials examined best supportive care vs best supportive care plus chemotherapy. Two trials used long-term alkylating agents, one trial used etoposide as a single agent, and the remaining eight trials used cisplatin-based chemotherapy. All except one trial enrolled patients with locally advanced disease (stage III) as well as metastatic disease (stage IV). Use of long-term alkylating therapy was associated with an increased rate of death, although given the limited number of trials, confidence intervals were wide and statistical significance was not reached. Patients treated with cisplatin-containing regimens demonstrated a 27% reduction in the risk of death. This was equivalent to an absolute improvement in survival of 10% at 1 year with a modest improvement in median survival of 1.5 months. Further analysis did not demonstrate that any grouping based on sex, age, histology, performance status, or stage benefited any more or any less than others. The demonstration that patients who received cisplatin-based chemotherapy in addition to surgery or radiotherapy also had improved outcomes gave more support to the idea that cisplatin plays an important role in the treatment of NSCLC. It was not clear which cisplatin combination regimen was superior, but the majority of combinations consisted of cisplatin plus either a vinca alkaloid or etoposide.

This study concluded that cisplatin-based chemotherapy programs may provide a 10% absolute benefit in 1-year survival. Although the results were modest, they were nonetheless important from a public health perspective, given the large numbers of patients with NSCLC who potentially would receive benefit. While cisplatin demonstrated an improvement in patient survival, its use was still greeted with a degree of unease due to its toxicity profile and difficulty in administration. The analog carboplatin was then developed, and two trials compared carboplatin to cisplatin. The first performed by the Eastern Cooperative Oncology Group (ECOG) compared three cisplatin-based regimens to single-agent carboplatin. The results demonstrated that carboplatin-treated patients had better overall survival and less toxicity compared with cisplatin-containing regimens. The second trial performed by the European Organization for Research and Treatment of Cancer (EORTC) compared cisplatin and etoposide vs carboplatin and etoposide and concluded that no significant differences in survival were apparent but that patients treated with carboplatin had significantly less leukopenia, nausea and vomiting, and diarrhea.

First-Line Chemotherapy for Advanced NSCLC

The 1990s heralded the arrival of novel agents with significant activity against NSCLC and new enthusiasm for treatment of advanced NSCLC with chemotherapy. These novel agents included the taxanes (paclitaxel and docetaxel), a new vinca alkaloid (vinorelbine), a novel deoxycytidine analog (gemcitabine), and the topoisomerase I inhibitors (irinotecan and topotecan). In addition, carboplatin was developed as an analog of cisplatin that remained active yet was less toxic and more easily administered to patients. The increased activity and larger selection of compounds also re-ignited interest not only in the treatment of previously treated patients with relapsed or refractory disease, but also in attempting to identify compounds and combinations that were active yet minimally toxic for the treatment of elderly patients with NSCLC.
This article focuses on randomized phase III studies that compare the newer regimens to either older regimens (eg, cisplatin or cisplatin/etoposide) or other new regimens in an attempt to identify the best regimen for the treatment of chemotherapy-naive patients with advanced NSCLC, previously treated patients with progressive disease, and the subpopulation of elderly patients with NSCLC.

Gemcitabine/Platinum-Based Regimens

Three studies summarized in Table 1 compared gemcitabine/cisplatin-based regimens to other standard chemotherapy regimens. The Hoosier Oncology Group randomized chemotherapy-naive patients with stage III or IV NSCLC either to single-agent cisplatin at 100 mg/m² every 28 days or to cisplatin at 100 mg/m² every 28 days plus gemcitabine at 1,000 mg/m² on days 1, 8, and 15 of a 28-day cycle. Of the 522 patients randomized, approximately two thirds had stage IV disease, and adenocarcinomas predominated. The response rate for the combination arm was 30.4% compared with 11.1% for single-agent cisplatin. The estimated 1-year survival rate was 39% for the gemcitabine plus cisplatin regimen compared with 28% for the cisplatin-treated patients. Time to progression was also favored in the combination arm. Not surprisingly, hematologic toxicity was more pronounced in the combination arm with more grade 3/4 neutropenia, thrombocytopenia, anemia, and neutropenic fevers. No significant differences were noted in regard to nonhematologic toxicities. Finally, quality-of-life assessments did not differ between the two groups despite the higher hematologic toxicity profile in the cisplatin/gemcitabine-treated patients.

Another study compared gemcitabine at 1,250 mg/m² given on days 1 and 8 of a 21-day cycle with 100 mg/m² of etoposide administered on days 1, 2, and 3 of a 21-day cycle. Both arms received 100 mg/m² of cisplatin every 21 days. Approximately half of the 135 patients randomized had stage IV disease, and squamous cell histology predominated. The response rate for the gemcitabine/cisplatin-treated patients was 40.6% compared with 21.9% for etoposide/cisplatin-treated patients. A nonstatistically significant 1-year survival difference was noted for gemcitabine/cisplatin (32%) and etoposide/cisplatin (26%), a result not surprising given the sample size and choice of survival as a secondary end point. Grade 3-4 neutropenia and neutropenic fever were more common in the etoposide-treated patients, while grade 3-4 thrombocytopenia was more common in the gemcitabine-treated patients. Quality-of-life assessments demonstrated no clear advantage between the two regimens.

Finally, an Italian study compared gemcitabine/cisplatin to the more favored European regimen of mitomycin/ifosfamide/cisplatin (MIC) for stage IIIIB or IV NSCLC. The gemcitabine/cisplatin arm consisted of 1,000 mg/m² of gemcitabine administered on days 1, 8, and 15 of a 28-day cycle and 100 mg/m² of cisplatin on day 1. A total of 337 patients were randomized, with the majority (80%) having stage IV disease and adenocarcinomas as the predominant histology. The response rate for the gemcitabine/cisplatin arm was 38% compared with 26% for the MIC arm. No differences were noted in the median survival, and the 1-year survival rates were 33% and 34% for gemcitabine/cisplatin and MIC, respectively. Grade 3-4 thrombocytopenia was more pronounced in the gemcitabine/cisplatin arm, but no major differences in quality of life were noted.

Vinorelbine/Platinum-Based Regimens

The effectiveness of single-agent vinorelbine was demonstrated in a study by Crawford et al in which 216 patients with stage IV NSCLC were randomized to either vinorelbine at 30 mg/m² every week or 5-fluorouracil (5-FU) and leucovorin given every 4 weeks. The median survival time for patients who received vinorelbine was 30 weeks with 25% of patients alive at 1 year compared with a median survival time of 22 weeks and 16% of patients alive at 1 year for those treated with 5-FU/leucovorin. Objective response rates were 12% for the vinorelbine arm and 3% for the 5-FU/leucovorin arm. The major toxicity of vinorelbine was granulocytopenia.

Based on single-agent activity against NSCLC and the feasibility of combining vinorelbine with cisplatin, a large European multicenter randomized trial was undertaken and reported in 1994. Patients less than 75 years of age with stage III or IV NSCLC and with good performance status were randomized to one of three treatment regimens: (1) single-agent vinorelbine at 30 mg/m² weekly, (2) vinorelbine at 30 mg/m² weekly plus cisplatin at 120 mg/m² on days 1 and 29 and then every 6 weeks, or (3) vindesine at 3 mg/m² weekly for 6 weeks and then every 2 weeks plus cisplatin at 120 mg/m² day 1 and 29 and then every 6 weeks. The majority of patients had squamous cell histology, and...
stage IV predominated. Objective response rates were 30% for vinorelbine/cisplatin, 19% for vindesine/cisplatin, and 14% for vinorelbine. Median survival was 40 weeks for vinorelbine/cisplatin, 32 weeks for vindesine/cisplatin, and 31 weeks for vinorelbine. The tolerability of the vinorelbine regimens was acceptable but, compared with single-agent vinorelbine, vinorelbine/cisplatin treated patients had more neutropenia and nausea/vomiting. This study identified vinorelbine/cisplatin as a reference regimen in advanced NSCLC, and it suggested single-agent vinorelbine as an active treatment based on tolerability and overall survival.

The Southwest Oncology Group (SWOG) randomized good performance status patients with stage IIIB or IV NSCLC to one of two regimens: 100 mg/m² of cisplatin every 4 weeks or 100 mg/m² of cisplatin every 4 weeks and 25 mg/m² of vinorelbine weekly. Of the 415 patients randomized, more than 90% had stage IV disease, and the predominant histology was adenocarcinoma. Overall response rates were 12% for patients treated with cisplatin and 26% for those treated with cisplatin/vinorelbine. Overall survival favored the cisplatin/vinorelbine arm with 36% of patients alive at 1 year compared with 20% for cisplatin alone. Short-lived granulocytopenia with low episodes of septic episodes occurred more frequently in the vinorelbine/cisplatin arm, but nausea/vomiting, neuropathy, and renal toxicity were similar. This regimen was chosen by SWOG to be a reference regimen for future randomized studies and was recommended as a standard therapy for patients with stage IV NSCLC.

Table 2 summarizes the efficacy of vinorelbine either alone or in combination in the treatment of advanced NSCLC.

### Table 2: Randomized Trials of Vinorelbine

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Response Rate</th>
<th>1-Yr Survival</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluorouracil/leucovorin</td>
<td>3%</td>
<td>16%</td>
<td>9</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>12%</td>
<td>25%</td>
<td>10</td>
</tr>
<tr>
<td>Vinorelbine/cisplatin</td>
<td>14%</td>
<td>n/a</td>
<td>10</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>12%</td>
<td>20%</td>
<td>11</td>
</tr>
<tr>
<td>Cisplatin/vinorelbine</td>
<td>26%</td>
<td>36%</td>
<td></td>
</tr>
</tbody>
</table>

Paclitaxel/Platinum-Based Regimens

The use of paclitaxel either alone or in combination has been reported in multiple studies (Table 3). The impact of single-agent paclitaxel on survival and quality of life was recently reported by Ranson and colleagues. Patients with stage III or IV NSCLC were randomized to either best supportive care or 200 mg/m² of paclitaxel over a 3-hour period and repeated every 21 days until relapse or unacceptable toxicity occurred. Patients were evenly split between stage IIIB and IV. The majority had good performance status (0 or 1 on ECOG scale), and the predominant histology was squamous cell carcinoma. Survival was statistically superior for paclitaxel-treated patients, with a median survival of 6.8 months compared to 4.8 months for patients in the best-supportive-care arm. Quality-of-life scores were equivalent with the exception of improved functional activity, which was superior for paclitaxel-treated patients.

Table 3: Randomized Trials of Paclitaxel

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Response Rate</th>
<th>1-Yr Survival</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best supportive care</td>
<td>-</td>
<td>Not reported</td>
<td>12</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>16%</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>Cisplatin/etoposide</td>
<td>12.4%</td>
<td>31.8%</td>
<td>13</td>
</tr>
<tr>
<td>Cisplatin/paclitaxel 135 mg/m² over 24 hrs</td>
<td>25.3%</td>
<td>37.4%</td>
<td>13</td>
</tr>
<tr>
<td>Cisplatin/paclitaxel 250 mg/m² over 24 hrs</td>
<td>27.7%</td>
<td>40.3%</td>
<td>14</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>17%</td>
<td>36%</td>
<td>14</td>
</tr>
<tr>
<td>Cisplatin/paclitaxel</td>
<td>26%</td>
<td>30%</td>
<td>15</td>
</tr>
<tr>
<td>Cisplatin/etoposide</td>
<td>14%</td>
<td>35%</td>
<td>15</td>
</tr>
<tr>
<td>Carboplatin/paclitaxel</td>
<td>21.6%</td>
<td>35%</td>
<td></td>
</tr>
</tbody>
</table>
ent from the cisplatin/etoposide arm, which was believed to be related to the higher-than-expected survival for patients in the control arm. Quality-of-life measurements revealed no difference among the treatment groups but was complicated by decreasing compliance rates with the questionnaires over time.

A second trial randomized stage IIIIB or IV NSCLC patients to receive either single-agent cisplatin at 100 mg/m² given every 21 days or the combination of paclitaxel at 175 mg/m² over 3 hours plus cisplatin at 80 mg/m² given every 21 days. A total of 414 patients were randomized, the majority having stage IV disease, adenocarcinomas, and good performance status. Overall response rates favored the paclitaxel/cisplatin arm with a 26% response rate compared with 17% for single-agent cisplatin. However, overall survival was equivalent with 1-year survival of 36% in the cisplatin arm and 30% in the paclitaxel/cisplatin arm. Approximately 20% of patients in both arms went on to receive second-line chemotherapy, yet a taxane-containing regimen was rare, suggesting that the equivalence in survival was not due to an effect of second-line chemotherapy.

Finally, the popular combination of carboplatin and paclitaxel was compared to cisplatin/etoposide and reported in abstract form in 1998. A total of 369 patients, the majority of whom had stage IV disease, were treated every 3 weeks after being randomized to one of two regimens: (1) carboplatin at a dose based on an area under the concentration-time curve (AUC) of 6 mg/mL × min and paclitaxel at 225 mg/m² over 3 hours or (2) 75 mg/m² of cisplatin and 100 mg/m² of etoposide on days 1-3. Patients were treated until disease progression, unacceptable toxicity, or patient refusal. Overall response rates slightly but not significantly favored the carboplatin/paclitaxel regimen (21.6%) compared with the cisplatin/etoposide regimen (14%). The 1-year survival rate for the entire group was 35%. Toxicities were similar, with the exception of more myalgia/arthritis and peripheral neuropathy in the group treated with paclitaxel/carboplatin and more vomiting in the group treated with cisplatin/etoposide.

Comparisons of Newer Regimens

The data above suggested an improvement in survival for patients treated with a platinum-containing compound plus a newer agent, either gemcitabine, vinorelbine, or paclitaxel. However, the superiority of a regimen in terms of improved survival, quality of life, and toxicity profile remained unclear. Therefore, two studies were undertaken to compare more recent doublets.

Cisplatin/Vinorelbine vs Carboplatin/Paclitaxel

The SWOG performed a study directly comparing paclitaxel plus carboplatin to vinorelbine plus cisplatin in patients with untreated and advanced NSCLC and good performance status. Chemotherapy consisted of either paclitaxel at 225 mg/m² over 3 hours plus carboplatin at a dose based on an AUC of 6 mg/mL × min on day 1 of a 21-day schedule or vinorelbine at 25 mg/m² weekly and cisplatin at 100 mg/m² on day 1 of a 28-day cycle. Response rates of 27% were equal in the two arms, and 1-year survival rates were 36% in the paclitaxel/carboplatin arm and 33% in the vinorelbine/cisplatin arm. Peripheral neuropathy was more frequent in the paclitaxel/carboplatin arm. Hematologic toxicity and nausea were greater in the vinorelbine/cisplatin arm, and more patients in this arm stopped therapy due to toxicity. Quality-of-life scores were equivalent in the two arms.

ECOG 1594 Trial

An important study was recently reported by ECOG in which patients with stage IIIIB or IV NSCLC were randomized and stratified based on performance status, weight loss, stage IIIIB or IV, and presence or absence of brain metastasis. Patients were randomized to receive one of four regimens: (1) paclitaxel at 135 mg/m² over 24 hours on day 1 plus cisplatin at 75 mg/m² on day 2 every 21 days, (2) gemcitabine at 1,000 mg/m² on days 1, 8, and 15 plus cisplatin at 100 mg/m² on day 1 of a 28-day cycle, (3) docetaxel at 75 mg/m² on day 1 plus cisplatin at 75 mg/m² on day 1 with treatment every 21 days, and (4) paclitaxel at 225 mg/m² over 3 hours on day 1 plus carboplatin at a dose based on an AUC of 6 mg/mL × min on day 1 with treatment every 21 days. The trial accrued 1,207 patients from October 1996 until May 1999. A total of 1,163 eligible patients were evaluated with a median follow-up of 7.7 months. Overall survival was not significantly different among the four regimens, although time to progression favored the cisplatin/gemcitabine arm. This arm also demonstrated higher overall grade 3-4 toxicity related to anemia, thrombocytopenia, and nephrotoxicity. The carboplatin/paclitaxel arm had less overall nausea/vomiting, less neutropenic fever, and lower requirements for intravenous antibiotics. Unanswered questions include quality-of-life assessments among the four arms, a pharmaco-economic or cost-benefit analysis, and the role of second-line chemotherapy.

Second-Line Chemotherapy for Advanced NSCLC

Given the larger role demonstrated for chemotherapy in both metastatic and locally advanced cases of
than one third of patients continued to receive docetaxel 100 mg/m² per day for 3 consecutive days given every 3 weeks, (2) docetaxel at 75 mg/m² given every 3 weeks, or (3) a control arm of either vinorelbine at 30 mg/m² given days 1, 8, and 15 of a 21-day cycle or ifosfamide at 2 g/m² per day for 3 consecutive days given every 3 weeks. A total of 23 centers enrolled 373 patients and were well balanced for performance status, histology, stage, and prior paclitaxel use. As expected, overall response rates were low, with 7.9% in the higher docetaxel arm, 12.2% in the lower docetaxel arm, and 2.0% in the vinorelbine or ifosfamide arm. Importantly, prior paclitaxel therapy did not predict the likelihood of a patient’s response to docetaxel. While median survivals were similar among the three arms, a significant benefit in the 1-year survival rate favored the lower docetaxel arm, with 32% of patients being alive compared with 21% in the higher arm and 19% in the vinorelbine/ifosfamide arm. The investigators noted that more than one third of patients continued to receive chemotherapy on removal from the study, and nearly 50% received a taxane. To control for this effect, an analysis was undertaken that censored survival at the time of chemotherapy post-study. This analysis demonstrated significantly greater 1-year survival for docetaxel (32% in the higher arm and 32% in the lower arm) compared with 10% for vinorelbine/ifosfamide. While neutropenia and febrile neutropenia were greater in the two docetaxel arms, there was no difference in treatment-related deaths, and nonhematologic toxicities were similar among the three arms. A possible explanation for the superiority of the lower docetaxel dosage over the higher dosage is the finding that patients in the lower dosage group with responding or stable disease had a longer duration of chemotherapy exposure than those in the higher dosage group, at least in part because of poorer tolerance to therapy. Because of the poor prognosis of these patients in general and the high likelihood of drug resistance, it is not surprising that no benefit in median survival was found. Nonetheless, a subset of patients did derive benefit from docetaxel therapy as evidenced by the larger percentage alive at 1 year. Finally, while a complete analysis is forthcoming, preliminary analysis of quality of life favored patients treated with docetaxel.

The results of this trial are further supported by a second randomized trial of docetaxel in patients with NSCLC who were previously treated with platinum-containing compounds. In this study, patients were excluded if they had received prior paclitaxel therapy, which represents the major difference between this study and the TAX 320 study. Patients were randomized to either docetaxel or best supportive care. Docetaxel was initially administered at 100 mg/m² given every 21 days but was later amended to 75 mg/m² given every 21 days due to an unacceptable toxic death rate at the 100 mg/m² dose. Chemotherapy was continued until disease progression or unacceptable toxicity. A total of 204 patients were randomized from 36 centers, and both arms were well balanced with respect to sex, performance status, stage, and best response to prior platinum-based chemotherapy. Despite the low overall response rates to the two doses of docetaxel (5.8%), patients treated with docetaxel survived longer. The median duration of survival was 7.0 months for patients receiving docetaxel compared with 4.6 months for patients receiving best supportive care. The 1-year survival rate was 29% for patients receiving docetaxel compared with 19% for patients receiving best supportive care. Given the high toxic death rate of docetaxel at 100 mg/m², survival was analyzed separately for patients in the second half of the study who received either 75 mg/m² of docetaxel or best supportive care. The 1-year survival of patients treated with docetaxel at 75 mg/m² was 37% compared with 12% for the group receiving best supportive care. Grade 3-4 hematologic

### Table 4. — Randomized Trials for Second-Line Therapy in Advanced NSCLC

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Response Rate</th>
<th>1-Yr Survival</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vinorelbine or ifosfamide</td>
<td>2.0%</td>
<td>19%</td>
<td>19</td>
</tr>
<tr>
<td>Docetaxel 75 mg/m²</td>
<td>12.2%</td>
<td>32%</td>
<td></td>
</tr>
<tr>
<td>Docetaxel 100 mg/m²</td>
<td>7.9%</td>
<td>21%</td>
<td></td>
</tr>
<tr>
<td>Best supportive care</td>
<td>-</td>
<td>12%</td>
<td>20</td>
</tr>
<tr>
<td>Docetaxel 75 mg/m²</td>
<td>5.8%</td>
<td>37%</td>
<td></td>
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</tbody>
</table>
toxicities were higher in the docetaxel-treated group but notably only 1 patient developed neutropenic fever in the 75 mg/m² arm. Nonhematologic toxicities were similar although sometimes worse for the best supportive care arm, notably in terms of more asthenia and neurotoxicity. Quality-of-life analysis demonstrated less worsening of performance status and less common use of tumor-related medications for docetaxel-treated patients. This study concluded that patients with good performance status who progressed after platinum-based chemotherapy received a survival and quality-of-life benefit when treated with docetaxel at 75 mg/m².

While other agents have been studied in previously treated patients with NSCLC, their impact on survival is unclear. Gemcitabine has demonstrated activity in the second-line setting. A recent study²⁰ reported on gemcitabine use in patients who had received prior platinum therapy with stage IIIIB or IV NSCLC. Patients received gemcitabine at 1,000 mg/m² on days 1, 8, and 15 of a 28-day cycle. The majority of patients on this study had an ECOG performance status of 0 or 1, nearly 40% of patients had stage IIIA-B disease, and squamous histology predominated. The response rate to therapy was 19.3% the 1-year survival rate was 45% and the median survival time was 72 weeks. Hematologic toxicity was mild, with only 7% of patients developing grade 3-4 leukopenia, and 7% of patients developed grade 3 thrombocytopenia. Similar results have been reported by another group of investigators in patients previously treated with carboplatin and paclitaxel.²³ It remains to be seen how gemcitabine compares to best supportive care or single-agent docetaxel in terms of overall survival and quality of life.

The results with vinorelbine have been less convincing in previously treated patients. Two trials reported no responses, and another small trial involving 10 patients demonstrated a 20% response rate.²⁴-²⁶ In addition, the TAX 320 study demonstrated a response rate of only 2% with single-agent vinorelbine and inferior survival when compared with docetaxel-containing regimens.²⁰

### Treatment of Elderly Patients With NSCLC

Given what some believe is a marginal benefit of chemotherapy in advanced NSCLC, it is not surprising that the treatment of elderly patients with NSCLC is even more controversial. Older patients typically have increased likelihood of comorbid conditions as well as reductions in physiologic reserves that make treatment with chemotherapy unsuitable, especially cisplatin-based regimens. Recent studies have suggested that elderly patients with NSCLC can undergo treatment and that age alone is not necessarily an independent negative prognostic factor. A review of 2,531 patients treated by the Southwest Oncology Group from 1974 to 1988 found that good performance status, female sex, and age over 70 years actually were independent predictors of better outcome.²⁷ Another study reported the retrospective record of treatment of advanced NSCLC and found no major differences in outcome between patients older or younger than 65 years of age.²⁸ Older patients tended to have slightly more grade 3 or hematologic toxicities compared with younger patients, but severe grade 4 toxicities were no different. In addition, older patients tended to have more stable disease and less progressive disease on chemotherapy compared with younger patients. Finally, studies have demonstrated that older patients cope with the impact of chemotherapy as well as, if not better than, younger patients, with fewer reports of emotional distress and life disruption.²⁹ These studies supported the idea that age alone should not be a factor in the decision to treat patients with chemotherapy, but they did not suggest which treatment regimen was preferred.

Two important phase III randomized studies of chemotherapy in the elderly patient have been recently reported (Table 5). The Elderly Lung Cancer Vinorelbine Italian Study Group (ELVIS) performed a multicenter randomized trial of single-agent vinorelbine vs best supportive care in patients older than 70 years of age.³⁰ Both survival and quality of life were end points of the study. All patients had stage IIIIB or IV biopsy-proven NSCLC and a good performance status, which was defined as spending no more than 50% of the waking day in bed. Treatment consisted of vinorelbine at 30 mg/m² given on days 1 and 8 of a 21-day cycle for a maximum of 6 cycles or best supportive care at the discretion of the physician. The median age was 74 years, three fourths had stage IV disease, and more than 80% of patients had a performance status equal to or greater than 1 on an ECOG scale. The overall response rate for vinorelbine was 19.7%, with 30.3% of patients having stable disease and 42.1% of patients having progressive disease. Patients randomized to vinorelbine treatment demonstrated improved survival over best supportive care, with 1-year survival rates of 14% in best supportive care, 15.0% in single-agent vinorelbine, and 22.0% in the combination regimen.

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Response Rate</th>
<th>1-Yr Survival</th>
<th>Reference</th>
</tr>
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<tbody>
<tr>
<td>Best supportive care</td>
<td>-</td>
<td>14%</td>
<td>19</td>
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<tr>
<td>Vinorelbine</td>
<td>19.7%</td>
<td>32%</td>
<td>20</td>
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<tr>
<td>Vinorelbine/gemcitabine</td>
<td>15.0%</td>
<td>13%</td>
<td>20</td>
</tr>
<tr>
<td>Vinorelbine/gemcitabine</td>
<td>22.0%</td>
<td>30%</td>
<td>20</td>
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Table 5. — Treatment of Elderly Patients With Non-Small-Cell Lung Cancer
care and 32% in the vinorelbine arm. Despite missing data and difficulty with compliance to quality-of-life questionnaires, patients treated with vinorelbine had a better quality of life. They benefited in terms of dyspnea, pain, and pain medication consumption, but they suffered from drug-induced constipation, nausea and vomiting, hair loss, and peripheral neuropathy. Hematologic toxicities were mild, with only 7% of patients having grade 3/4 leukopenia. The trial was the first to specifically examine the effect of chemotherapy treatment of advanced NSCLC in the elderly patient subset. The survival benefit was not at the expense of poorer quality of life, and toxicities were mild and easily managed.

The ELVIS trial also served as a starting point to build combination chemotherapy regimens for elderly patients. The South Italian Cooperative Oncology Group recently reported a planned interim analysis of their study comparing single-agent vinorelbine to the combination of gemcitabine and vinorelbine. This study randomized patients 70 years of age or older with stage IIIB or IV NSCLC to either vinorelbine at 30 mg/m² given on days 1 and 8 of a 21-day cycle or gemcitabine at 1,200 mg/m² and vinorelbine at 30 mg/m² given days 1 and 8 of a 21-day cycle. Overall survival was better in the two-drug arm, with a median survival time of 29 weeks and projected 1-year survival of 30% compared with median survival time of 18 weeks and 13% in the vinorelbine-only arm. Temporary symptom relief and the probability of being alive without deterioration of symptoms at 6 months were also improved in the combination arm. Despite more hematologic and nonhematologic side effects in the combination arm, no statistically significant differences in the occurrence of life-threatening toxicity were observed. Furthermore, this study demonstrated that a higher degree of comorbidity was related to treatment tolerance and survival. One surprising finding of the study was the poorer outcome in the single-arm vinorelbine patients compared with those in the ELVIS trial. The authors believed that the presence of CNS metastasis (excluded from ELVIS) and higher proportion of patients with comorbidities could lead to the different results.

These studies demonstrate that elderly patients with NSCLC treated with chemotherapy live longer with a better quality of life. They also demonstrate that careful attention should be paid to coexisting comorbidities in elderly patients.

Emerging Therapies for the Treatment of NSCLC

While the importance of chemotherapy is indicated in the randomized studies previously discussed, the results of the ECOG 1594 trial and other studies have suggested the idea of a “chemotherapy plateau” being reached in patients with advanced NSCLC. A large body of work has begun to define molecular mechanisms of oncogenesis and suggest new targets for cancer therapy. A major advancement in the field of oncology has been the recognition that alterations in proteins and genes involved in cellular signaling, the cell cycle, and control of programmed cell death are hallmarks of cancer. By better defining these lesions in lung cancer, therapies directly targeted to the molecular alteration may be able to reverse the malignant phenotype and lead to cancer cures. Also of critical importance is the realization that solid tumors must create their own blood supply in order to grow in size, and thus the targeting of tumor angiogenesis has exploded in recent years.

Targeting Signal Transduction Pathways

Studies from many laboratories have begun to reveal how signaling pathways regulate the growth and survival of tumor cells. Knowledge gained of the role of these pathways has identified targets for potential cancer therapeutics. The receptor tyrosine kinase family of molecules has gained the most attention in recent years. These receptors located on the surface of cells bind to soluble growth factors and activate multiple pathways important in cellular proliferation and survival. Growth factor receptors important in lung cancer formation include the platelet-derived growth factor receptor (PDGF-R) and the epidermal growth factor family of receptors (EGF-R). Overexpression of EGF-R is a frequent occurrence in NSCLC and is associated with a poor prognosis and resistance to cytotoxic agents. Clinical trials are underway using agents that target these receptors either with monoclonal antibodies (eg, C225) or with ZD1839 (Iressa), a low-molecular-weight inhibitor of EGF-R. In phase II studies of previously treated patients, partial responses and stable disease were observed in patients treated with single-agent ZD1839. Based on these findings, several studies are currently investigating the survival benefit of ZD1839 added to either carboplatin/paclitaxel or cisplatin/gemcitabine.

The Cancer and Leukemia Group B (CALGB) has initiated a phase II trial of trastuzumab (Herceptin) that targets the HER2 receptor, a member of the EGF family of receptors, which is overexpressed in approximately 25% of NSCLCs and portends a poor outcome. A number of studies are also in progress to test the combination of standard chemotherapy agents with receptor inhibitors based on the finding that inhibition of growth factor signaling may sensitize tumor cells to standard cytotoxic agents. ECOG is planning a phase III trial of carboplatin and paclitaxel plus or minus trastuzumab in patients with HER2 overexpression.
Agents that target the Ras oncogene, which is mutated in approximately 25% of NSCLCs, are also becoming available.\textsuperscript{33,34} Ribozymes (RNA molecules with catalytic activity) or antisense oligonucleotides to downregulate Ras signaling have been used in preclinical studies and are starting to be tested in patients with NSCLC.\textsuperscript{40} Compounds targeting prenyltransferases that posttranslationally modify the carboxyl-terminus of certain proteins are also being studied as treatments for lung cancer. The best-studied agents are the farnesyl transferases and geranylgeranyl transferases, inhibitors that can inhibit prenylation of important signaling molecules such as H-, N-, and K-ras, as well as RhoA, Rac1, and Cdc42.\textsuperscript{41} These agents have demonstrated antitumor activity in human xenograft mouse models as well as in transgenic mouse models of cancer that express oncogenic forms of H-ras or K-ras. Phase I studies have been performed with farnesyl transferase inhibitors (FTIs),\textsuperscript{42,43} and several trials are examining combinations of FTIs with standard chemotherapy agents such as gemcitabine and paclitaxel. These studies have demonstrated good bioavailability and overall tolerability for patients with solid tumor malignancies, a number of these agents are currently being tested in NSCLC in phase II studies both as single agents and in combination with standard chemotherapy used in this disease. Some preclinical data suggest that FTIs may sensitize lung cancer cells to taxanes, and a phase I study combining docetaxel and FTI is being performed at the M.D. Anderson Cancer Center.

Finally, antisense oligonucleotides that target signaling pathways important in human cancers are currently under development and testing. Antisense oligonucleotides targeting c-raf and protein kinase C have been tested in phase I studies,\textsuperscript{44,45} and future studies in lung cancer may be forthcoming.

### Targeting Tumor Angiogenesis

The use of a monoclonal antibody that targets the receptor for vascular endothelial growth factor (VEGF) located on endothelial cells was studied in patients with advanced NSCLC.\textsuperscript{46} Patients were randomized to either carboplatin/paclitaxel or the same chemotherapy with two doses of rhuMAb VEGF. Unfortunately, sudden life-threatening hemoptysis occurred in 6 of 99 patients treated and was fatal in four cases. Response rates and time to progression appeared to favor the high dose of rhuMAb VEGF, although survival was not significantly different among the three arms. In fact, survival of all three groups was higher than historical controls, which may have been the result of crossover of patients treated with chemotherapy only to receive rhuMAb VEGF at the time of disease progression. Final analysis of the data and an evaluation of the safety of the combination with respect to hemoptysis have yet to be reported.

Thalidomide, also an angiogenesis inhibitor, was investigated in a pilot study in combination with carboplatin and paclitaxel. Patients with stage III or IV NSCLC received standard doses of carboplatin and paclitaxel with thalidomide at a starting dose of 200 mg/wk and escalated as tolerated to 1,000 mg/wk.\textsuperscript{47} Overall, thalidomide was well tolerated without any undue toxicity over chemotherapy alone, and a preliminary analysis demonstrated that all 6 evaluable patients had stable disease. No tumor regressions occurred. Finally, the antiangiogenic natural products angiostatin and endostatin are currently being studied in phase I studies.

### Adenoviral Therapy

The use of adenoviral vectors to re-introduce functional p53 tumor suppressor protein into lung cancers is a safe and biologically effective approach.\textsuperscript{48-50} A recent study\textsuperscript{51} sought to determine the safety and tolerability of Ad-p53 in sequence with cisplatin administration. Twenty-four patients with NSCLC and tumor p53 mutations assayed by sequencing were treated with cisplatin at 80 mg/m\textsuperscript{2} on day 1 and Ad-p53 in escalating dose levels on day 4 of a 28-day course. Ad-p53 was administered by fine-needle injection directly into the tumor. The most common adverse effect was transient fever associated with Ad-p53 injection occurring in nearly one third of patients but limited to grade 2. Treatment biopsies revealed increased tumor necrosis and apoptosis. Two patients obtained a partial response, 17 had stable disease, four had progressive disease, and one was not assessable. The use of adenovirus to deliver functional p53 via bronchioloalveolar lavage has also been reported in the subset of patients with bronchioloalveolar carcinoma.\textsuperscript{52} After two cycles of treatment, two patients demonstrated a pathologic response on repeat biopsy, four had improvement in diffusing capacity, and four of 11 treated patients had symptomatic improvement. Only one patient had grade 4 pulmonary toxicity, but other patients treated at the same viral dose did not demonstrate toxicity.

In a novel approach, adenoviruses have been genetically engineered to replicate and lyse tumor cells with a deregulated p53 pathway.\textsuperscript{53,54} These viruses are lethal to lung cancer tumor cells, but normal cells are spared. These oncolytic viruses have been found to be safe when administered in an intravenous fashion, and studies are being planned that incorporate this adenovirus with standard carboplatin and paclitaxel chemotherapy for advanced NSCLC.
Finally, preclinical studies have been performed that demonstrate antitumor effects of reintroduction of other tumor suppressor proteins, such as the cyclin-dependent kinase inhibitors p16 and p27, on model human lung cancer cell lines. The relevance to such an approach in human patients has yet to be demonstrated.

Harnessing the Immune System Against Lung Cancer

Interest in immune therapies for lung cancer has been sparked by the observations that the immune system is capable of destroying tumor cell lines and that tumor-associated antigens (TAAs) can be recognized by T cells and used for tumor vaccine approaches. A number of tumor-associated antigens have been identified in human lung cancers and are being used as targets for lung cancer vaccines. These include carcinoembryonic antigen (CEA), human epithelial mucin MUC-1, the cancer-testis antigen NY-ESO-1, and the ganglioside Fuc-GM1. Another approach takes advantage of the observation that granulocyte-macrophage colony-stimulating factor (GM-CSF)-transduced tumor cells induce the recruitment and activation of host antigen-presenting cells leading to increased tumor antigen presentation to T lymphocytes and systemic immunity. Early-stage clinical trials are underway to study the effect of vaccination with autologous, lethally irradiated NSCLC cells engineered to secrete human GM-CSF.

Conclusions

While advanced lung cancer continues to be a lethal disease, progress in the treatment with chemotherapy in the last decade has allowed more patients to live longer and with better quality of life. The subsets of patients with progressive disease after chemotherapy treatment and elderly patients with NSCLC benefit from select chemotherapy regimens. Advances in the study of the molecular biology of lung cancer have identified new molecular targets for therapy, and new agents that target these molecules and pathways are beginning to be introduced into the clinical arena. While efforts to promote smoking cessation and lung cancer screening remain paramount, continued efforts to treat advanced lung cancers with medical therapy should remain a high priority.

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