New Combinations in the Treatment of Lung Cancer*

A Time for Optimism

Paul A. Bunn, Jr., MD; and Karen Kelly, MD

Strides have been made in the treatment of lung cancer in the last decade that warrant a more optimistic outlook toward the disease. The recent development of several new agents with single-agent activity, including paclitaxel, docetaxel, vinorelbine, gemcitabine, and irinotecan, is important, and those agents offer even greater potential when they are used in combination chemotherapy regimens or in combined-modality programs. The experience to date with therapy results with these agents in the treatment of lung cancer is reviewed and is compared to results documented with the current standard treatments for lung cancer, namely, cisplatin and cisplatin-based combination regimens. Published and ongoing trials are outlined, and directions for future research and the future goals of lung cancer therapy are outlined. The availability of newer chemotherapeutic agents that are active in lung cancer has led to response rates as high as 40% in the treatment of non-small cell lung cancer. These drugs have been shown to be active in combination drug regimens as well as when combined with radiotherapy. Future research will focus on using these agents in two- and three-drug regimens as radiation sensitizers and in combination programs with new drugs and biological agents with apparent activity against this disease.

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Key words: cisplatin; combination therapy; docetaxel; gemcitabine; irinotecan; lung cancer; paclitaxel; response rates; survival; vinorelbine

Abbreviations: NSCLC = non-small cell lung cancer; UFT = tegafur and uracil

More than half of all lung cancer patients present with stage IIIB disease (22%) or stage IV disease (32%). Traditionally, these patients had median survival times of <1 year, and very few survived for 5 years. The vast majority of these patients died as a result of systemic metastases that could not be cured by available chemotherapeutic agents. The previously available treatments, such as alkylating agents and antimetabolites, which were highly effective against some cancers, produced response rates of <15% in non-small cell lung cancer (NSCLC) patients and did not improve survival rates. Consequently, there was great pessimism regarding the role of chemotherapy in advanced NSCLC.

More recently, cisplatin (Platinol; Bristol-Myers Squibb Co.; Princeton, NJ)-based chemotherapy has been shown to improve survival rates in patients of all stage groups of NSCLC, to improve quality of life, and to alleviate symptoms in the majority of patients. These results were achieved at costs < $20,000 per life-year gained. However, because survival gains are minimal and toxicity is greater in patients with performance status of 3 or 4, chemotherapy is clearly indicated only for patients with good functional status. Chemotherapy should rarely be considered for select patients with performance status 3 or 4.

During the 1990s, five new drugs were shown to produce response and survival rates equivalent or superior to that achieved with cisplatin. These agents include paclitaxel (Taxol; Bristol-Myers Squibb Co.), docetaxel (Taxotere; Rhone-Poulenc Rorer; Collegeville, PA), vinorelbine (Navelbine; Glaxo Wellcome Oncology; Research Triangle Park, NY), gemcitabine (Gemzar; Eli Lilly & Co.; Indianapolis, IN), and irinotecan (Camptosar; Pharmacia & Upjohn Co.; Kalamazoo, MI). Each of these drugs has since been studied in combination regimens with cisplatin or carboplatin, yielding responses in 40 to 50% of patients. In randomized trials, some of these combinations (vinorelbine/cisplatin, gemcitabine/cisplatin, and paclitaxel/cisplatin) were superior to cisplatin alone or cisplatin plus etoposide. This article will consider the activity of these new agents and new combinations relative to prior results with cisplatin alone.

Cisplatin-Based Chemotherapy

The first chemotherapeutic agent proven to improve survival among patients with advanced NSCLC was cisplatin. As a single agent, cisplatin produced responses in ≤20% of patients. Cisplatin in combination with older agents, such as alkylating agents or antimetabolites, produced higher response rates than cisplatin alone, but most randomized trials showed no survival advantage for combination therapy. However, a number of randomized trials from the 1980s did prove that cisplatin-based chemotherapy improved survival in all stages of lung cancer compared with best supportive care (stage IIIB/IV disease), radiotherapy alone (inoperable stage III disease), or surgery alone (stage I-IIA disease; Table 1). In patients with stage IV NSCLC, survival improved by an average of 2 months at the median and by 10% at 1 year (from 10 to 15% to 20 to 25%). In patients with stage III disease, the median survival time was about 4 months longer and the 5-year survival rate improved by 5 to 15%. Cisplatin-based therapies reduced the hazard rate of death in stages I and II NSCLC by 13%, yielding a 5% greater 5-year survival rate. The studies involving early-stage disease included the fewest number of patients, which perhaps is responsible for the borderline significance (p = 0.08).

The patient self-assessed quality of life associated with cisplatin-based therapy vs best supportive care in stage IV NSCLC or vs radiotherapy in stage III NSCLC was also evaluated in some randomized trials. Cisplatin-based therapy was shown to improve quality of life compared with best supportive care (and radiotherapy where indicated) in both stages III and IV NSCLC. Although only about 25% of patients with stage IV NSCLC and 50 to
Table 1—Meta-Analysis of Randomized Trials With Cisplatin-Based Therapy*

<table>
<thead>
<tr>
<th>Stage</th>
<th>Cisplatin</th>
<th>BSC</th>
<th>Cisplatin</th>
<th>BSC</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV</td>
<td>6</td>
<td>4</td>
<td>20–25†</td>
<td>10–15†</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>III</td>
<td>14‡</td>
<td>10‡</td>
<td>10–20‡</td>
<td>5‡</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>I, II</td>
<td>30‡</td>
<td>20</td>
<td>67§</td>
<td>62§</td>
<td>0.08</td>
</tr>
</tbody>
</table>

*From Non-small Cell Lung Cancer Collaborative Group. 5 BSC = best supportive care.
†1-year survival.
‡Includes chest radiotherapy.
§5-year survival.

Table 2—Phase II Results with Vinorelbine, Gemcitabine, and Irinotecan Alone or in Combination With Cisplatin*

<table>
<thead>
<tr>
<th>Therapy</th>
<th>No. of Patients</th>
<th>Response, %</th>
<th>Median Survival, wk</th>
<th>1-yr Survival Rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vinorelbine</td>
<td>621</td>
<td>20</td>
<td>33</td>
<td>24</td>
</tr>
<tr>
<td>Vinorelbine/cisplatin</td>
<td>328</td>
<td>41</td>
<td>38</td>
<td>35–40</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>572</td>
<td>21</td>
<td>41</td>
<td>39</td>
</tr>
<tr>
<td>Gemcitabine/cisplatin</td>
<td>245</td>
<td>47</td>
<td>57</td>
<td>61</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>138</td>
<td>27</td>
<td>35</td>
<td>NR</td>
</tr>
<tr>
<td>Irinotecan/cisplatin</td>
<td>185</td>
<td>44</td>
<td>34</td>
<td>NR</td>
</tr>
</tbody>
</table>

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Activity in Patients With Stages I to III NSCLC

The greatest benefit of the new agents that are active in NSCLC is likely to be found in early-stage disease. A meta-analysis of cisplatin-based therapies showed that they lowered the hazard rate of death in stages I and II NSCLC by 13%, and the new agents could have even greater benefit. In the United States and Canada, an ongoing intergroup study will determine the benefit of postoperative adjuvant vinorelbine plus cisplatin compared with no further therapy among patients with completely resected stage I or II NSCLC. In another article in this supplement, we review studies of these new combinations that are being used preoperatively and postoperatively as adjuvant therapy. If randomized trials show that preoperative or postoperative administration of one of the new combinations improves survival, it may be possible to identify an adjuvant or neoadjuvant regimen for routine use.

Radiosensitization is an important property of many cancer chemotherapeutic agents. A meta-analysis of randomized trials of treatment for stage III NSCLC indicated that the addition of cisplatin-based chemotherapy combinations to radiotherapy results in improved survival compared with radiotherapy alone. Sequential, alternating, and concurrent delivery of chemotherapy and radiotherapy each have produced superior survival rates compared with radiotherapy alone. In a European study, concurrent daily administration of cisplatin plus radiotherapy increased local control and survival. In another randomized trial from Europe, daily carboplatin and etoposide were administered concurrently with twice-daily radiotherapy and were followed by full-dose chemotherapy when the radiotherapy was complete. With 23% of patients alive at 4 years, this regimen was deemed successful. Similarly, the concurrent approach was found superior to a sequential approach for patients with NSCLC in a randomized Japanese trial. Thus, concurrent chemotherapy and radiotherapy are currently believed to provide the best local control and survival rates for patients with stage III NSCLC; the administration of full-dose chemotherapy before or after the concurrent bimodality regimen may reduce distant recurrence and improve survival rates even further.

The taxanes have been successfully combined with concurrent radiotherapy. Caution must be observed, however, when combining some of the other new chemotherapeutic agents with radiotherapy due to their potential for radiosensitizing healthy tissues as well as tumors. For instance, the concurrent administration of full-dose gemcitabine and chest radiotherapy resulted in a high rate of esophageal and pulmonary toxicity in early studies. Full-dose irinotecan or gemcitabine plus full-dose chest radiotherapy should remain experimental until definitive studies are published.

**Future Directions**

Combination therapy using paclitaxel, vinorelbine, gemcitabine, or irinotecan together with cisplatin or carboplatin has produced results superior to older therapies. However, none of the new two-drug combinations provides a clear benefit, with respect to efficacy or toxicity, over the other. A direct comparison of five of the new combinations is being conducted by the Southwest Oncology Group and the Eastern Cooperative Oncology Group to determine the most effective and least toxic combination. Still, for the future we must attempt to increase the 1-year survival rate beyond 40%.

One approach to this goal is to develop two- or three-drug combinations utilizing these new agents. With five new active compounds, in addition to cisplatin and carboplatin, the number of potential combinations is large. Because each of these agents causes myelosuppression, the risk of this dose-limiting toxicity with all of the agents will likely warrant dose reductions when they are given in combination. The combinations of paclitaxel and docetaxel or cisplatin and carboplatin are unlikely to be useful because the mechanisms of action are the same.

Phase I studies of new combination regimens are currently underway (Table 4). Preliminary results from some of those studies suggest that full doses of docetaxel, paclitaxel, or vinorelbine can be combined with full doses of gemcitabine. Various schedules being explored in phase II trials include the following: every other week; weekly × 2 every 3 weeks; and day 1 paclitaxel or docetaxel with day 1 and 8 gemcitabine every 3 weeks. It also appears that paclitaxel, docetaxel, or vinorelbine can be combined safely with gemcitabine and carboplatin, with all three

**Table 3—Results of Randomized Trials Comparing Combinations of New Agents to Older Cisplatin-Based Therapy**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Reference</th>
<th>No. of Patients</th>
<th>Response, %</th>
<th>Median Survival, wk</th>
<th>1-yr Survival Rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>10</td>
<td>218</td>
<td>10</td>
<td>26</td>
<td>20</td>
</tr>
<tr>
<td>Cisplatin/vinorelbine</td>
<td>10</td>
<td>214</td>
<td>25</td>
<td>35</td>
<td>36</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>11</td>
<td>208</td>
<td>14</td>
<td>31</td>
<td>25</td>
</tr>
<tr>
<td>Vinorelbine/cisplatin</td>
<td>11</td>
<td>206</td>
<td>30</td>
<td>40</td>
<td>35</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>14</td>
<td>154</td>
<td>9</td>
<td>33</td>
<td>28</td>
</tr>
<tr>
<td>Gemcitabine/cisplatin</td>
<td>14</td>
<td>155</td>
<td>31</td>
<td>39</td>
<td>40</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>15</td>
<td>26</td>
<td>19</td>
<td>37</td>
<td>40</td>
</tr>
<tr>
<td>Cisplatin/etoposide</td>
<td>15</td>
<td>24</td>
<td>21</td>
<td>48</td>
<td>35</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>16</td>
<td>66</td>
<td>18</td>
<td>29</td>
<td>NR</td>
</tr>
<tr>
<td>Cisplatin/etoposide</td>
<td>16</td>
<td>72</td>
<td>15</td>
<td>33</td>
<td>NR</td>
</tr>
</tbody>
</table>

*See Table 2 for abbreviation.*
drugs given at full doses. It will be important to determine whether such three-drug combinations offer superior results compared with the two-drug combinations.

At the University of Colorado Cancer Center, we completed a phase I/II study of the three-drug combination of paclitaxel, gemcitabine, and carboplatin (Table 5). Growth factor support was not used routinely, however, in the event of grade 4 neutropenia lasting for > 2 days or febrile neutropenia, granulocyte colony-stimulating factor was administered on subsequent courses. Only 2 of the first 35 patients received granulocyte colony-stimulating factor during any cycle. Grade 4 thrombocytopenia, which never occurred in our phase I and II studies of paclitaxel and carboplatin, occurred with the three-drug regimen in several patients on the first three dose levels after four to six cycles. The carboplatin area under the concentration-vs-time curve dose subsequently was lowered from a target of 6 to 5, and protocol dose reductions were required when nadir platelet counts were below 100,000/µL. Grade 4 thrombocytopenia has not been a problem since these changes were instituted.

The major toxicities in this study were myelosuppression and myalgia/arthralgia/neuropathy, which have been sufficiently severe in some patients to require analgesics, anti-inflammatory agents, steroids, or gabapentin. These toxicities have been reversible and did not warrant the removal of patients from the study. In fact, all patients received at least four cycles of therapy, with none exhibiting disease progression during these cycles. The preliminary response and survival data have been encouraging. The next step would be a randomized trial comparing the three-drug regimen to the combinations of paclitaxel and carboplatin or paclitaxel and gemcitabine.

Because myelosuppression limits the ability to give full doses of many of these combinations, another strategy is to alternate the administration of the agents or of the two-drug combinations. This strategy has been used in patients with breast cancer, although no results have yet been published. Results of phase II studies using this approach in lung cancer are eagerly awaited.

A number of other new agents are being evaluated in patients with lung cancer (Table 6). Although several years ago it appeared unlikely that any antimetabolite would be effective against NSCLC, gemcitabine has proven to be a highly active agent. Two other new antimetabolites are now being studied in NSCLC patients. Eli Lilly & Company is studying a new multitargeted antifolate that has shown preliminary responses in > 20% of patients. Bristol-Myers Squibb is studying the oral combination product tegafur and uracil (UFT). In a Japanese study, both UFT alone and UFT in combination with cisplatin were shown to prolong survival when given postoperatively.

Tirapazamine (Sanofi Pharmaceutica, New York, NY) is a hypoxic cell sensitizer to drugs (such as cisplatin) and to radiotherapy. Phase II studies have established the safety and efficacy of the two-drug combination of tirapazamine and cisplatin. Phase III studies comparing tirapazamine and cisplatin to cisplatin alone are in progress. Sanofi Pharmaceutica also makes oxaliplatin, a drug that is structurally similar to cisplatin and carboplatin, with a considerably different preclinical spectrum of activity. Many cisplatin-resistant NSCLC cell lines are sensitive to oxaliplatin; clinical trials involving NSCLC patients are in progress.

Amifostine is a drug-protective and radiation-protective agent that has been shown to reduce nephrotoxicity, ototoxicity, neurotoxicity, and myelosuppression in patients receiving multiple cycles of high-dose cisplatin and carboplatin. It also has been evaluated among NSCLC patients receiving cisplatin alone, radiation and chemotherapy, paclitaxel plus cisplatin, and paclitaxel plus carboplatin.

**Summary**

Chemotherapy prolongs survival, relieves symptoms, and improves quality of life (as assessed by the patients...
themselves) among patients with NSCLC. The cost per life-year gained that is associated with chemotherapy for NSCLC is similar to or lower than that of other accepted medical therapies. Therefore, we should abandon the prior pessimistic attitude toward the treatment of lung cancer patients and offer them optimal therapy. New chemotherapy combinations are more effective and less toxic than older cisplatin-based combinations and, in addition, can improve their quality of life. These combinations, therefore, should be considered for all lung cancer patients.

Future studies will attempt to improve patient outcomes by using the newer agents that are active against NSCLC, with or without cisplatin (or carboplatin), by testing these combinations in earlier stages of disease, and by evaluating these chemotherapy regimens when they are combined with radiotherapy. The results of these trials will determine whether any new combination offers a benefit over others and whether the combination of two or more of the new agents is superior to one of the new agents when it is combined with cisplatin or carboplatin. There are now sufficient phase II study results with concurrent paclitaxel, carboplatin, and radiation therapy to proceed to randomized comparisons against older cisplatin-based concurrent programs. There are phase I and II studies investigating the role of new agents in combined-modality regimens, which, hopefully, will warrant future phase II randomized studies. Perhaps the greatest potential for increasing the cure rate lies with the neoadjuvant and adjuvant use of these new combinations.

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