Adjuvant and Neoadjuvant Chemotherapy for Non-Small Cell Lung Cancer*

A Time for Reassessment?

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

Surgical resection has limited success in curing non-small cell lung cancer (NSCLC), particularly among patients with locally advanced disease (stage IIIA). Combined modality regimens, utilizing surgery, radiotherapy, and chemotherapy, have improved response rates, although they have not been shown to significantly impact survival among patients with completely resected stage I and II NSCLC. Future improvements in NSCLC therapy, which has been shown to be active in this disease and from alternative schedules, such as neoadjuvant or concurrent combined modality treatments. Neoadjuvant cisplatin-based chemotherapy has already been shown to increase cure rates in stage IIIA NSCLC, from 10 to 15% to 25 to 30%. Newer active agents, such as paclitaxel, vinorelbine, and gemcitabine, may be able to advance the cure rate even further. Radiotherapy, which has been shown to decrease the rate of local recurrence, may play a role as well. (CHEST 2000; 117:119S–122S)

Key words: adjuvant therapy; cisplatin; lymph nodes; neoadjuvant therapy; non-small cell lung cancer; radiotherapy; recurrence

Abbreviations: BLOT = Bimodality Lung Oncology Team; NSCLC = non-small cell lung cancer

Lung cancer is the third most common cancer in the United States after prostate and breast cancers, but it is the leading cause of cancer death in both men and women. The low cure rate (14%) accounts for the discrepancy between the incidence and mortality ranking. The low cure rate can be attributed to lack of effective screening and early detection measures, the propensity for early spread of the cancer, and the inability of chemotherapy to cure advanced systemic disease. Less than 25% of non-small cell lung cancer (NSCLC) patients present with stage I or II disease, which has a reasonable chance for cure with surgical resection. Moreover, only about half of these resected patients remain free of disease for ≥ 5 years. The vast majority of recurrences are in distant sites, suggesting that systemic approaches will be required to improve the cure rate. Another problem in resected patients is the development of second primary cancers, which needs to be addressed with chemoprevention efforts. Fortunately, new therapeutic agents that prolong survival with reduced toxicities in advanced-stage patients are now available for study in early stage NSCLC patients in either neoadjuvant or adjuvant settings, and new chemoprevention agents are being evaluated. Combined modality approaches, novel classes of agents, and new chemotherapeutic approaches provide a real opportunity to improve the cure rate for patients with NSCLC.

STAGING AND PROGNOSTIC FEATURES OF NSCLC

The 1997 revised International Staging System should be used to determine prognostic and therapeutic options for NSCLC patients. The categories of the lung cancer staging system, the approximate frequency of each stage at diagnosis, and 5-year survival rates following older therapies are summarized in Table 1. Clearly, the involvement of regional lymph nodes worsens prognosis more than the extent of the primary tumor. The cure rate following surgical therapy is considerably lower when any lymph nodes are involved, and surgical cure is unlikely when there is clinically detected mediastinal lymph node (N2) involvement.

After stage, the next important prognostic features are performance status, weight loss, and gender (female patients fare better than male), in that order. Age does not appear to be a major independent risk factor. While there are many articles suggesting that individual biological or genetic markers are prognostically significant, no large series with multivariate analysis proves such markers have independent prognostic relevance. Thus, recent American Society of Clinical Oncology guidelines do not include routine determination of such markers.

Because of the value of lymph node status as a prognostic marker, complete staging has great importance. Neither chest CT nor MRI scans are reliable determinants of pathologic mediastinal lymph node status. Table 2 shows the frequency of pathologic involvement of mediastinal lymph nodes based on the size of the nodes by CT scan. As shown, markedly enlarged lymph nodes do not appear to be a major independent risk factor.

Table 1—1997 Revised International Staging Classification of Lung Cancer*

<table>
<thead>
<tr>
<th>Stage</th>
<th>TNM</th>
<th>Frequency, %</th>
<th>5-Yr Survival, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>T1N0M0</td>
<td>~ 10</td>
<td>67</td>
</tr>
<tr>
<td>IB</td>
<td>T2N0M0</td>
<td>~ 5</td>
<td>57</td>
</tr>
<tr>
<td>IIA</td>
<td>T1N1M0</td>
<td>~ 30</td>
<td>34</td>
</tr>
<tr>
<td>IIB</td>
<td>T2N1M0</td>
<td>~ 13</td>
<td>24</td>
</tr>
<tr>
<td>IIIA</td>
<td>T1–2N2M0</td>
<td>~ 22</td>
<td>13</td>
</tr>
<tr>
<td>IIIB</td>
<td>T1–3N3M0</td>
<td>~ 10</td>
<td>8</td>
</tr>
<tr>
<td>IV</td>
<td>T1–4N0–3M1</td>
<td>~ 32</td>
<td>1</td>
</tr>
</tbody>
</table>

*From Mountain.2

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contain tumor in 33% of cases, and completely normal nodes contain tumor 13% of the time. Patients with normal-sized nodes and T2, T3, and central lesions are found to have pathologic involvement in > 13% of cases. Thus, the majority of NSCLC patients should have mediastinal lymph node biopsies by bronchoscopy, mediastinoscopy, and/or mediastinotomy as part of staging prior to therapy assignment. Select patients, such as those with peripheral coin lesions (T1N0M0), may proceed to immediate surgery.

Sites of Failure

Disease recurs in a large fraction of NSCLC patients, despite complete surgical resection (Table 3). Less than 25% of first recurrences are in regional sites alone, regardless of the histology of the primary tumor. These data imply that effective systemic treatment must be part of any adjuvant or neoadjuvant therapy to have a major impact on survival.

ADJUVANT RADIOTherapy

Chest radiotherapy has been used as both preoperative and postoperative adjuvant therapy without improving survival or overall cure rates in multiple randomized trials and meta-analysis of these trials. Preoperative radiotherapy with doses > 45 Gy increases the operative morbidity and mortality and should not be used alone or with chemotherapy.

Postoperative chest radiotherapy produces a striking decrease in the rate of regional recurrence (from 20 to < 5%). Because local recurrences may cause symptoms and morbidity, some investigators believe routine use of radiotherapy is justified, especially for patients with N2 disease, in which the local failure rate is higher. Others prefer careful observation and periodic chest radiographs, with radiotherapy reserved for cases of regional failure, especially because a meta-analysis of all randomized trials showed a worse survival in patients receiving postoperative radiotherapy.

ADJUVANT CHEMOTHERAPY

The first chemotherapeutic agents widely studied in the postoperative setting were alkylating agents, which have been studied alone or in combination regimens. Unfortunately, these agents have considerable toxicity, and in some randomized trials and meta-analysis were associated with shortened survival. Thus, these approaches cannot be justified.

In contrast, cisplatin-based chemotherapy was shown in meta-analysis of all randomized trials to lengthen survival duration. Survival significantly improved in some of the individual randomized trials, whereas in others it did not, but this is not surprising given the small sample size in many of the trials and the limited magnitude of the effect. Compliance with cisplatin-based therapy was quite poor in many of the trials. In the meta-analysis, the hazard rate of death was reduced by 13%, translating into a 5% absolute improvement in 5-year survival rate; the number of patients studied was small, and the survival differences were of borderline statistical significance (p = 0.08).

Postoperative adjuvant cisplatin-based therapy has not been widely adopted on the basis of these results. In a patient survey, Yellam and Cell13 found that 95% of patients would elect to receive adjuvant chemotherapy that offered a 5% improvement in survival. After the results of the meta-analysis were published, < 1% of physicians surveyed in the United Kingdom indicated they would offer the postoperative adjuvant cisplatin-based chemotherapy to their patients, despite the fact that 95% might elect to receive it.

A number of additional larger adjuvant trials with postoperative cisplatin-based therapy given alone or combined with chest radiotherapy are in progress or were recently completed. There are no published results of trials using chemotherapy regimens based on the newer agents, such as paclitaxel, docetaxel, vinorelbine, or gemcitabine, in patients with stage I-IIIA NSCLC. However, in advanced disease, combinations with these agents are more effective than older cisplatin-based regimens. Thus, results of adjuvant and neoadjuvant trials with these new combinations are eagerly awaited. A US and Canadian intergroup randomized trial designed to compare surgery alone to surgery followed by chemotherapy with vinorelbine and cisplatin is underway, and an intergroup neoadjuvant study comparing preoperative carboplatin and paclitaxel followed by surgery to surgery alone will begin soon.

Adjuvant Therapy With Combined Chemotherapy and Radiotherapy

Randomized trials designed to compare chemotherapy plus radiotherapy to radiotherapy alone in patients with unresectable stage III NSCLC showed that combined modality therapy with cisplatin-based regimens significantly prolonged survival. When chemotherapy and radiotherapy were given concurrently, there was a significant decrease in local recurrence rates. Unfortunately,
randomized trials and meta-analysis of these trials have not found combined chemoradiotherapy to prolong survival in completely resected stage I and II NSCLC patients,9 perhaps reflecting the use of suboptimal cisplatin-based regimens. Results of studies with more current cisplatin-based combined modality regimens should be available within a few years. Studies in early stage NSCLC using the newer agents combined with radiation given before or after surgery should be conducted in the future.

### Neoadjuvant Chemotherapy

There are no randomized trials of neoadjuvant “modern” chemotherapy in stages I and II NSCLC, although there have been several in stage IIIA NSCLC. The latter studies were based on phase II results indicating increased survival compared with surgery alone. Many groups, however, found survival of patients with N2 nodal involvement to be very poor, with 5-year survival rates < 15%.6 A group of investigators at Memorial Sloan-Kettering Cancer Center went on to show that high response rates could be achieved in patients with advanced NSCLC using mitomycin, vinblastine, and cisplatin preoperatively to treat stage IIIA, N2 NSCLC patients, and survival markedly improved compared with historical control subjects.16 Other groups also have reported good results with mitomycin, vinblastine, and cisplatin, although the regimen produced excessive toxicity in some series.10 At least three randomized trials have been conducted to evaluate neoadjuvant cisplatin-based chemotherapy based on these results (Table 4).17–20 In all of the studies, survival improved among the patients receiving cisplatin-based chemotherapy before and after surgery. Although all three of the studies had small numbers of patients, the survival results were statistically different in two of the studies.17–19 Many investigators have interpreted these studies to mean that surgery alone is inadequate in stage IIIA, N2 NSCLC. Randomized trials are in progress to determine whether triple modality regimens are superior to two modalities, and whether chemotherapy plus surgery or chemotherapy plus radiotherapy are preferred when two modalities are used.

The results of these trials also were used as an impetus for neoadjuvant chemotherapy studies in stage I and II NSCLC, some using the newer chemotherapy agents. For example, the multicenter Bimodality Lung Oncology Team (BLOT) in the United States is evaluating the two-drug combination of paclitaxel plus carboplatin given for two or three cycles before surgery and for two or three cycles after surgery (Fig 1).21 As of January 1999, 106 patients had been enrolled in this trial. The objective response rate after two cycles was 59%, and > 90% of patients have had a complete resection. Final results should be available within a few years. This study will be followed by a phase III intergroup randomized study comparing this approach to surgery alone.

### Table 4—Randomized Trials of Neoadjuvant Cisplatin-Based Therapy

<table>
<thead>
<tr>
<th></th>
<th>Rosell et al17</th>
<th>Roth et al18,19</th>
<th>Pass et al20</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MIC and CEP</strong></td>
<td>Surgery</td>
<td>Surgery</td>
<td>Surgery</td>
</tr>
<tr>
<td><strong>Patients, No.</strong></td>
<td>32</td>
<td>33</td>
<td>33</td>
</tr>
<tr>
<td><strong>Complete resection, %</strong></td>
<td>80</td>
<td>61</td>
<td>NR</td>
</tr>
<tr>
<td><strong>Median survival, mo</strong></td>
<td>26†</td>
<td>64†</td>
<td>NR</td>
</tr>
<tr>
<td><strong>4-yr survival, %</strong></td>
<td>29†</td>
<td>40†</td>
<td>46</td>
</tr>
<tr>
<td><strong>5-yr survival, %</strong></td>
<td>NR</td>
<td>NR</td>
<td>21</td>
</tr>
</tbody>
</table>

*MIC = mitomycin C, ifosfamide, cisplatin; CEP = cyclophosphamide, etoposide, cisplatin; EP = etoposide, cisplatin; NR = not reported. †p < 0.05.

**Figure 1.** Ongoing phase II study of the BLOT is shown (left).21 Because of the encouraging results of this phase II study, an intergroup randomized study, shown schematically (right), will begin soon. The chemotherapy will consist of three cycles of paclitaxel plus carboplatin in the experimental arm of this trial.
Conclusion

Surgery alone fails to cure the majority of resected NSCLC patients because of systemic metastases that were undetected at the time of surgery. Postoperative chest radiotherapy virtually eliminates local-regional recurrences, but fails to increase and may even decrease survival. Alkylation agent-based chemotherapy fails to improve survival when used in an adjuvant setting. In contrast, cisplatin-based postoperative chemotherapy improves the cure rate by 5% in resectable NSCLC.

Neoadjuvant chemotherapeutic approaches have theoretical reasons for being superior to postoperative adjuvant approaches. In stage IIIA NSCLC, cisplatin-based chemotherapy improves the cure rate from 10 to 15% to as much as 40%. A preliminary study of paclitaxel and carboplatin used as neoadjuvant therapy shows even more promising results in stage IB and II NSCLC.

The new chemotherapy drugs, such as paclitaxel, vinorelbine, and gemcitabine, improve survival in advanced NSCLC, compared to older agents. These new therapies hold great promise to improve the cure rate of early stage NSCLC patients in the future.

References