Preoperative Chemotherapy (Cisplatin and Fluorouracil) and Radiation Therapy in Stage III Non-small Cell Lung Cancer*

A Phase 2 Study of the LCSG

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Study objective: To determine the feasibility, toxicity, and potential efficacy of neoadjuvant chemoradiotherapy before surgery in patients with non-small cell lung cancer limited to the chest. Design: Phase 2 pilot study. Setting: Multi-institutional, multimodality cooperative group. Patients: Eight-five patients with advanced stage III-A or minimal stage III-B non-small cell lung cancer in whom attempted resection would have been likely to leave residual disease. Intervention: Cisplatin, 75 mg/m², was given on days 1 and 29; fluorouracil, 1 g/m² for 24 h, was given as a continuous infusion on days 1 to 4 and 29 to 32; thoracic radiation, 30 Gy in 15 fractions, was administered on days 1 to 19. Thoracotomy with tumor resection was planned for day 57. Measurements and results: Two patients achieved a complete and 46 achieved a partial response after the neoadjuvant chemoradiotherapy for an overall response rate of 56%. Toxicity was moderate but acceptable. Fifty-four patients underwent thoracotomy and tumor resection was attempted in 44; 29 (34%) had complete and 15 (18%) had incomplete resections. There was no apparent increase in postoperative complications. In eight patients (9%), no viable tumor was detected pathologically in the resection specimen. Of the 18 patients whose tumors were completely resected and had disease recurrence, none had recurrence only in the chest, 15 (83%) had recurrence in distal sites, and 3 (17%) developed second primary tumors. Median survival of all patients was 13 months. Conclusions: This neoadjuvant regimen did not appear to provide major benefit in patients with advanced but potentially resectable non-small cell lung cancer. Further studies are needed to better define the relative roles of preoperative radiotherapy and chemotherapy. In 1985, the Lung Cancer Study Group (LCSG) initiated a neoadjuvant trial in patients with non-small lung cancer limited to the chest but in whom attempted resection would have been likely to leave residual disease (adenocarcinoma of stage III-A and minimal stage III-B disease). This second neoadjuvant study of the LCSG was intended to capitalize on several preclinical and clinical observations regarding synergism of cisplatin, fluorouracil (FU), and radiation, which have been summarized. The results of this LCSG phase 2 trial, previously reported in detail, are summarized in this report.

METHODS

Patients

Patients with histologically proven non-small cell lung cancer were required to have no metastatic disease outside the hemithorax and be medically suitable for pulmonary resection. The study was intended for patients with technically unresectable disease in whom attempted resection would leave gross residual disease. It was not intended for patients with adenopathy demonstrated only by mediastinoscopy. Supraclavicular nodes, malignant pleural effusion, superior vena cava obstruction, or involvement of the contralateral lung were contraindications to study participation. Histologic confirmation of mediastinal nodal involvement was required. Patients were required to have a performance status of 2 or less. All patients must have an expected survival of at least 18 months. Complete blood counts with differential, serum chemistries, urinalysis, electrocardiogram, chest x-ray, CT scan of thorax, and bone scan were to be performed at baseline. Further laboratory studies were performed at the discretion of the oncologist. Evaluation at the time of thoracotomy included repeat examination of the chest x-ray, bone scan, and CT scan of thorax. Patients were to be reevaluated on days 30 and 60 after thoracotomy. In the event of disease progression, a second thoracotomy was to be performed. A second biopsy was to be performed in resected lung tissue. If the histologic response to chemoradiotherapy was less than complete, the patient was to be reevaluated and the biopsy examined by an independent pathologist and by the treating pathologist.

FIGURE 1. Schema of Lung Cancer Study Group protocol 852, including patient staging, neoadjuvant chemotherapy, reevaluation for thoracotomy, and further therapy (reproduced with permission from reference 1).

*From the Virginia Mason Medical Center Seattle (Dr. Weiden); and The Johns Hopkins Oncology Center, Baltimore (Dr. Piantadosi). Presented at the "Lung Cancer Study Group: Final Analysis" conference, March 5-12, 1984, Wesley Chapel, Fla. Supported by Public Health Service grant CA-56045 from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services.
involvement was encouraged, but CT documentation (single node >2 cm or multiple nodes >1.5 cm) was permitted. According to the revised TNM staging system, which was introduced after the initiation of this protocol, these criteria defined patients with relatively advanced stage III-A or minimal stage III-B disease.

The protocol therapy is depicted in Figure 1. Details of patient inclusion and exclusion criteria, chemotherapy administration and radiation technique, and quality assurance have been detailed previously. All institutional, National Cancer Institute, and federal regulations regarding informed consent and peer review were fulfilled. Standard response and toxicity criteria and statistical methods were employed. Patients who underwent thoracotomy were grouped as follows: (1) those with complete resection, ie, resection of all tumor with histologically free margins; (2) those with incomplete resection, ie, resection possible but grossly evident tumor remaining or margins of resection positive for tumor or tumor in the highest resected lymph nodes; and (3) those with unresectable disease. The major objectives were as follows: (1) to determine the proportion of patients receiving preoperative chemoradiotherapy who responded at the time of thoracotomy; (2) to estimate the frequency of toxic reactions from this treatment (in particular the proportion of patients who could undergo thoracotomy and tumor resection following initial therapy); and (3) to determine disease-free survival, patterns of disease recurrence, and overall survival.

**RESULTS**

**Patient Demographics**

This report is based on 85 eligible patients, 69 male and 16 female. Median age was 58 years (range, 28 to 78 years). Preoperative histologic types were squamous cell carcinoma, 27 patients; adenocarcinoma, 32 patients; large cell carcinoma, 13 patients; other non-small lung cancer, 13 patients.

Initial nodal status was known in 79 patients (93%): 45 (55%) had biopsy-proven N2 disease, 20 (24%) had CT-documented N2 disease, and 3 (4%) had N2 disease proven at thoracotomy (without tumor resection) before study entry. Eleven patients (13%) did not have N2 disease but were determined to have nonresectable disease and thus be study eligible. Sixty-eight patients (80%) had stage III-A disease, 11 (13%) had stage III-B disease, and 6 (7%) had insufficient data to determine their disease stage.

**Chemotherapy Results**

Of the 85 patients who began chemoradiotherapy, 6 did not complete induction therapy for various reasons. Overall protocol compliance, however, was good. In general, chemoradiotherapy was well tolerated. Esophagitis, hematologic, and other gastrointestinal side effects were the most common.

The response to the initial chemoradiotherapy program determined prior to surgery is shown in Table 1. The overall complete (2 patients) plus partial (46 patients) response rate was 56% (95% confidence interval = 46 to 65%). Of the 27 patients with tumors of squamous histologic features, 19 (70%) achieved a complete or partial response; of the 50 patients with tumors of nonsquamous histologic features, 28 (56%) achieved a partial response (p = 0.22).

**Surgical Results**

The extent of surgical resection by response to induction chemotherapy is detailed in Table 1. Fifty-four patients completing induction chemoradiotherapy underwent surgery. The 44 patients who underwent tumor resection represent 52% of the initial 85 eligible patients and 56% of the 79 patients who completed induction chemotherapy. Thirty-five of 48 patients (73%) who achieved a complete or partial response after initial chemoradiotherapy were able to undergo tumor resection: 24 had complete resection and 11 had incomplete resection. Seven partial responders underwent thoracotomy but could not undergo resection. In contrast to the 73% likelihood of tumor resection in a patient achieving a response, only 9 (29%) of 31 patients who completed but did not respond to the initial therapy underwent tumor resection.

In general, histologic specimens obtained from the resected tumors showed extensive cytopathic effect of the preoperative chemoradiotherapy. In eight patients, no visible appearing tumor was identified. These 8 patients represent 9% of the initial 85 eligible patients, 17% of the 48 patients who achieved a response to chemoradiotherapy, and 23% of the 35 responding patients who underwent tumor resection.

Surgical dissection was generally more difficult in these patients than in patients not pretreated with chemoradiotherapy, but this increased difficulty did not preclude resection or present an unacceptable obstacle. Pulmonary problems accounted for most of the postoperative complications; arrhythmias were also frequent. Four of 54 patients (7%) died of postoperative complications. Overall, postoperative complications did not appear to have been increased by the preoperative therapy employed.

**Disease Recurrence and Survival Data**

Disease recurrence was documented in 64 patients.

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### Table 1—Extent of Surgery by Response to Induction Chemoradiotherapy for 85 Eligible Patients

<table>
<thead>
<tr>
<th>Therapy</th>
<th>No Surgery</th>
<th>Complete Resection of Tumor</th>
<th>Incomplete Resection of Tumor</th>
<th>Total No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Partial response</td>
<td>6</td>
<td>7</td>
<td>22</td>
<td>11</td>
</tr>
<tr>
<td>No response</td>
<td>16</td>
<td>3</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Disease progression</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Did not complete therapy</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>31</td>
<td>10</td>
<td>29</td>
<td>15</td>
</tr>
</tbody>
</table>

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tails of the first sites of disease recurrence by surgery status are shown in Table 2. Of the 18 patients who underwent complete tumor resection and had recurrences, none had recurrence only in the chest, 3 (17%) had recurrence initially locally in the chest and in distal sites, 12 (67%) had recurrence only in distant site, and 3 (17%) developed second primary tumors. In contrast, of the 46 patients who underwent incomplete resections or who did not have resections and have had recurrences, 21 (46%) had recurrences initially locally, 20 (43%) had recurrences initially in distal sites only, 4 (5%) had simultaneous local and distal site recurrences, and 1 developed a second primary tumor. Among the 29 patients who were able to undergo complete tumor resections, 18 have had recurrences and in 5 of these patients, the brain was the initial site of recurrence. Thus, 5 (28%) of 18 first recurrences among patients with complete resections were in the brain, in contrast to only 3 (7%) of 46 first recurrences in the brain among patients who had no or incomplete resection. Thus, although resection status did not affect overall likelihood of recurrence, it did influence the site of first recurrence.

Median survival for all 85 patients was approximately 13 months (Fig 2). Thirteen patients died without tumor recurrence: 3 during chemoradiotherapy or before surgery, 4 because of postoperative complications, and 6 because of miscellaneous cardiac or pulmonary problems. Survival within the most favorable subset of patients, ie, those eight patients found to have no viable tumor at surgery, was as follows: one, alive and without disease at 38 months after initiation of therapy; one, alive at 30 months after treatment of a second primary tumor; one died with postoperative complications; and five died of recurrent tumor. Thus, even during the course of this study, it was not possible to identify a particularly favorable group of patients, ie, not those who responded to the initial chemoradiotherapy, those who were able to undergo surgery, those who were able to have complete resection, or even those who had no histologically viable tumor at the time of surgery.

**DISCUSSION**

These results demonstrate that patients with technically unresectable non-small cell lung cancer could undergo this chemoradiotherapy program with a response rate of 56%. Overall, 34% of patients underwent complete resections. Although surgical resection following neoadjuvant chemoradiotherapy was somewhat more technically demanding, it was feasible and postoperative complications did not appear to be increased. However, only 9% of the patients had no viable tumor in their resection specimens and survival, even in this most favorable subset of patients, was not especially promising. The overall survival experience does not suggest a major impact of the neoadjuvant chemoradiotherapy.

These results indicate, however, that neoadjuvant chemoradiotherapy altered the usual patterns of disease recurrence observed in patients with locally advanced non-small cell lung cancer. Patients whose tumors were completely resected were less likely to have recurrences initially only locally (17% vs 46%) and were more likely to have recurrences in the brain (17% vs 5%) than were patients whose tumors could not be completely resected. These results emphasize that the relative effectiveness of the local therapy, even after preoperative chemoradiotherapy, depends on the completeness of the resection. The likelihood of local tumor recurrence in patients with incomplete tumor resection poses the possibility of benefit from higher doses of radiotherapy in an optimal neoadjuvant regimen, while the high likelihood of systemic relapse in patients with complete resection highlights the need for more effective chemotherapy than that used in this study.

We have previously reported the relatively low incidence (6.8%) of first recurrences involving the brain after complete surgical resection of stage I to III non-small cell lung cancer and concluded that prophylactic cranial radiation would at best benefit only a very small proportion of these patients. Although the number of patients in this study is small, our results suggest that the likelihood of disease recurrence of the brain of patients whose tumors were completely resected after neoadjuvant chemoradiotherapy is high enough that these patients might benefit from prophylactic cranial irradiation. Alternatively, this group may provide an appropriate subset of all patients.

**Table 2—First Site of Disease Recurrence (Local vs Distant) by Surgery Status**

<table>
<thead>
<tr>
<th>Recurrence</th>
<th>No Thoracotomy/Unresected Tumor</th>
<th>Incomplete Resection of Tumor</th>
<th>Complete Resection of Tumor</th>
<th>Total No. of Patients with Recurrences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local only*</td>
<td>17</td>
<td>4</td>
<td>0</td>
<td>21</td>
</tr>
<tr>
<td>Distant only</td>
<td>12</td>
<td>8</td>
<td>12</td>
<td>32</td>
</tr>
<tr>
<td>Secondary primary tumor only</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Local plus distant</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Total</td>
<td>32</td>
<td>14</td>
<td>18</td>
<td>64</td>
</tr>
</tbody>
</table>

*Local only defined as recurrence in pleural, ipsilateral pulmonary, or mediastinal sites, or combination thereof.

![Figure 2](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21705/ on 04/02/2017)
with non-small cell lung cancer in which to study the efficacy of prophylactic cranial irradiation.

Other investigators have also explored the utility of neoadjuvant therapy in patients with locally advanced non-small cell lung cancer. These results, most of which have been reported subsequent to the initiation and patient accrual to the trial described in this report, were discussed at this meeting by Dr. Penfield Faber and have been also reviewed elsewhere. All investigators of neoadjuvant therapy have experienced difficulty in defining the extent of disease at the initiation of therapy, *i.e.*, defining both the methodology by which tumor extent is determined and defining which subsets of patients with locally advanced non-small cell lung cancer are appropriate candidates for neoadjuvant therapy. In the study described herein, the criterion employed was "technically unresectable disease which would likely result in gross residual disease," an admittedly somewhat subjective criterion. Pathologic staging of mediastinal nodes, e.g., by mediastinoscopy, was not a requirement for study entry. Most investigators today, however, would insist on pathologic staging of the mediastinum prior to institution of neoadjuvant therapy. In addition, in the study reported herein, 13% of the patients had stage III-B disease. Today, most, but not all, investigators would consider patients with stage III-B tumors categorically to have unresectable disease and thus not be eligible for studies of neoadjuvant therapy.

Ultimately, the determination of whether patients with stage III-A disease benefit from neoadjuvant therapy followed by surgery will require data from randomized trials. The trial reported herein, a phase 2 pilot study of concurrent cisplatin and fluorouracil chemotherapy and radiation therapy before surgery, was one of several phase 2 trials that provided the clinical background and impetus for the initiation of more definitive phase 3 trials, the results of which are eagerly awaited.

ACKNOWLEDGMENT: This report represents the cumulative efforts of the many investigators and dedicated staff of LCSG, whose members have been listed in detail previously.

REFERENCES