Surgical Adjuvant Therapy for Stage II and Stage III Adenocarcinoma and Large Cell Undifferentiated Carcinoma*

E. Carmack Holmes, MD

The Lung Cancer Study Group (LCSG) randomized 141 patients with resected stage II and III adenocarcinoma and large cell undifferentiated carcinoma to receive postoperative combined chemotherapy with cyclophosphamide, doxorubicin, and cisplatin (CAP) chemotherapy or bacillus Calmette-Guerin (BCG) and levamisole immunotherapy. Careful intraoperative staging was performed on all patients. Before randomization, patients were stratified by stage, weight loss, cardiac arrhythmia, and institution. Prognostic variables such as stage, age, weight loss, and nodal involvement were equally distributed between the two groups. Disease-free survival was significantly prolonged in the group receiving chemotherapy. There was no evidence of a deleterious effect of the immunotherapy. This study indicates that postoperative CAP chemotherapy is effective in prolonging disease-free survival in these patients.

Five-year survival rates after surgery for stage III adenocarcinoma and large cell undifferentiated carcinoma range between 8 and 15%, with median disease-free survival of 6 to 7 months.1-4 In 50 to 75% of the patients, the first site of recurrence is systemic. Previous studies evaluating adjuvant chemotherapy with a variety of agents including cyclophosphamide, methotrexate, nitrogen mustard, CCNU, and hydroxyurea did not improve survival.5,6 Recent studies have indicated that certain platinum-based regimens are more effective in non-small cell lung cancer than the chemotherapy used in these previous adjuvant studies.7,9 In 1977, the Lung Cancer Study Group began a prospective randomized trial in patients with completely resected stage II and stage III adenocarcinoma and large cell undifferentiated carcinoma of the lung. Following surgery and careful intraoperative staging, the patients were randomized to receive postoperative adjuvant chemotherapy (cyclophosphamide, doxorubicin, cisplatin [CAP]) or postoperative immunotherapy (intrapleural bacillus Calmette-Guerin [BCG] and levamisole). One hundred forty-one patients were randomized into this study, with a mean time since randomization of 7.5 years and a mean observation period of 2.4 years.

**MATERIALS AND METHODS**

**Eligibility**

Patients were required to undergo a complete resection of the tumor, and specimens from the subcarinal, paratracheal, hilar, and bronchopulmonary lymph nodes areas were required for pathologic staging. The old American Joint Committee recom-

*From the Department of Surgery/Oncology, University of California at Los Angeles.

Reprint requests: Dr. Holmes, 10833 LeConte Ave, Los Angeles, CA 90024
after randomization and before treatment, and a final patient had metastases proven within 1 week of randomization. Our analysis, therefore, focused on the remaining patients. Of these 130 patients, 23 patients did not receive the assigned treatment. Eight patients refused chemotherapy, and two patients refused BCG treatment after randomization. In addition, 13 eligible patients failed to receive the assigned treatment for other reasons. To avoid selection bias in the analysis that can arise by comparing only patients who received the assigned treatment, we performed our analysis on all of the 130 eligible patients including the 23 patients who did not receive the assigned treatment. The mean observation period for these 130 patients through February 1988, was 2.4 years, and the mean time since randomization was 7.3 years.

RESULTS

Treatment Balance

No statistically significant treatment imbalances were noted for the stratification factors or for other baseline covariates, including nodal status, performance status, race, gender, or history of heart disease. However, 16% of the immunotherapy patients had T3 tumors compared with 10% of the chemotherapy patients (trend test, p=0.024), whereas 60% of the chemotherapy patients were > age 60 compared with only 41% of the immunotherapy group (p=0.053). These two imbalances tend to cancel out. In addition, statistical adjustment for these factors did not change the results appreciably.

Toxicity

Previously reported side effects associated with CAP chemotherapy were observed, including primarily gastrointestinal (67%) and hematologic toxicity (48%) as well as alopecia. Toxicity was classified as mild, moderate, or severe based on the Eastern Cooperative Oncology Group toxicity criteria. In the chemotherapy group, there were five patients with severe hematologic toxicity, ten with moderate, and nine with mild. All but seven chemotherapy patients had gastrointestinal toxicity, but it should be noted that serotonin-antagonist antiemetics were not available during this trial. There were no fatalities attributed to the chemotherapy. Toxicity in the immunotherapy treatment group was mild and consistent with previous findings.

Treatment Compliance

Eight of 68 eligible patients assigned to BCG treatment failed to receive any treatment, and 15 of 62 eligible patients assigned to CAP therapy failed to receive any treatment. On those occasions on which CAP was administered, it was usually administered at full dosage. However, the average cumulative dose received was 58% of the full protocol dosage if those patients receiving no chemotherapy are included. In addition, some of this shortfall is attributable to patients with early recurrence and to scheduled dose reductions for toxicity.

Recurrence and Death Rates

There were 94 recurrences, excluding one rectal adenocarcinoma second primary detected 29 months after randomization, and 87 deaths among eligible patients (Table 1). The median time to recurrence is about 7 months longer in the chemotherapy group (Fig 1), and the treatment difference is statistically significant (log rank analysis p=0.032 and Gehan analysis p=0.009). Analysis of all deaths shows that the median survival is also about 7 months longer with CAP therapy (log rank p=0.113 and Gehan p=0.047) (Fig 2). Adjustment with the Cox model for baseline risk factors including arrhythmia, stage, weight loss, performance status, age, sex, race, nodal status, T status, and extent of operation did not affect the log rank significance levels appreciably.

We also analyzed death with cancer, namely death in a

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<th>Table 1—Recurrence-free Survivals, Death Rates for All Causes of Death, and Cancer Death Rates in the Two Treatment Arms</th>
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<td>Recurrence Rate, per Person/yr</td>
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<td>*LEV=levamisole.</td>
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FIGURE 1. Recurrence-free survival for the two treatment groups excluding second primaries by treatment for 130 eligible patients in Study 772. Treatment A=levamisole and BCG; Treatment B=CAP chemotherapy.

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patient with evidence of cancer at death. Patients who died of cardiovascular disease or other noncancer causes, without previous documented recurrences, were regarded as live withdrawals in this analysis. Thirteen patients (15% of the deaths) died without evidence of cancer. The hazard rates for death with cancer are lower in the CAP-treated group (log rank p=0.013; Gehan p=0.005).

If those 15 patients who were randomized to receive CAP but did not receive it are excluded from the analysis, the difference in favor of the chemotherapy group is enhanced (log rank p=0.005 for recurrence and p=0.013 for survival). However, this comparison is not protected by the randomization and may be affected by unidentified selection factors that make the chemotherapy group more favorable. Nonetheless, a comparison of performance status, prior weight loss, and initial stage of disease did not suggest that those who received CAP had a better initial prognosis than those who did not receive assigned CAP.

Analyses of patterns of recurrence revealed that only 17% of the first recurrences were exclusively local, ie, mediastinal or ipsilateral pulmonary recurrences. In addition, 17% of the first recurrences were brain only. The remainder, 66%, were in other systemic sites, or the first site of recurrence occurred simultaneously in several sites.

**DISCUSSION**

These studies indicate that CAP chemotherapy following surgery in patients with stage II and III adenocarcinoma and large-cell undifferentiated carcinoma demonstrate a longer disease-free interval and survival than patients who are receiving BCG and levamisole. CAP chemotherapy seemed a logical choice for adjuvant use since previous studies with platinum-containing regimens indicated improved response rates in patients treated with these regimens. The immunotherapy arm was used because we were reluctant to use a no-treatment arm in these patients in view of their poor prognosis after surgery. In addition, at the time this study was designed, the data of McKneally et al suggested that BCG might be effective in these patients and studies with levamisole were also promising. Subsequent studies, however, have shown that neither levamisole nor BCG has a beneficial effect on survival in patients with resected lung cancer. One study actually suggested that levamisole was associated with a higher death rate because of postoperative complications.

However, in that study there was no evidence of increased risk of recurrent cancer, and the excessive death rate in the levamisole group was, indeed, due to non-cancer-related postoperative complications. Survival in the patients receiving immunotherapy in this study is essentially identical to the survival of patients with similar disease treated by surgery alone. For instance, Kirsh and Sloan report a 5-year survival rate in N2 adenocarcinoma of 13%, Mountain reports a survival rate of 12%, and Choi et al report a survival rate of 8%. The median survival of the immunotherapy patients in this study is almost identical to that previously reported in patients receiving surgical resection for stage II and III adenocarcinoma and large-cell undifferentiated cell carcinoma. Therefore, there is no suggestion in this study that the immunotherapy had a negative effect on survival.

Our primary analysis includes all eligible patients randomized to receive adjuvant therapy, regardless of whether they received the assigned treatment. As mentioned in the Results section, if one excludes the 15 patients who did not receive the assigned CAP, the survival in the chemotherapy group is even more impressive (log rank p=0.013). However, the clinician must be cautious in interpreting these comparisons because they are not protected by the randomization. Nonetheless, we have not found any significant difference in the distribution of prognostic variables between those patients who received CAP chemotherapy and those who did not receive the assigned chemotherapy. Thus, this ancillary analysis reinforces the positive findings obtained from the main analysis of all eligible patients.

These studies indicate that adjuvant systemic chemotherapy in the form of CAP is effective in prolonging the disease-free survival and the overall survival in patients with stage II and III adenocarcinoma and large-cell undifferentiated cell carcinoma. The data indicate that few recurrences occur after 18 months.

It is now agreed that CAP may not be the ideal combination of agents for adjuvant therapy in lung cancer. New randomized studies using more effective therapy are now maturing. While these studies have yet to be published, they show a marked improvement over the results reported herein.
REFERENCES


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