Adjuvant Chemotherapy With Cyclophosphamide, Doxorubicin, and Cisplatin in Patients With Completely Resected Stage I Non-small Cell Lung Cancer*

An LCSG Trial

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Objective: Two recent studies in resectable non-small cell lung cancer by the Lung Cancer Study Group (LCSG) suggested an advantage to adjuvant therapy with cyclophosphamide, doxorubicin (Adriamycin), and cisplatin (CAP). Neither study had a no-treatment control arm. The purpose of this study was to compare the CAP regimen with no treatment in patients with resectable early-stage non-small cell lung cancer.

Methods: After complete resection, eligible patients with T1N1 or T2N0 non-small cell lung cancer were randomly assigned to receive or not to receive four courses of CAP at 3-week intervals beginning on day 30 after surgery for stratification for histology, preoperative white blood cell count, and Karnofsky performance status before surgery. The CAP regimen consisted of 400 mg/m² of cyclophosphamide, 40 mg/m² of doxorubicin, and 60 mg/m² of cisplatin. Of the 209 eligible patients entered in the study, 101 had recurrence and 127 had died at the time of analysis. The mean time since randomization is 6.4 years; mean follow-up is 3.8 years. There were no differences in time to recurrence or overall survival between the two groups even when analyses were adjusted for prognostic variables. Only 53% of the eligible patients received all four courses of CAP, and only 57% of such patients received all four cycles on time. Among the patients who had recurrences, 74% had their initial recurrence at a distant site.

Conclusion: No survival benefit for CAP vs no-treatment control was found in this study. Therefore, adjuvant therapy with CAP should not be recommended for patients with resected early-stage non-small cell lung cancer. Further trials to test adjuvant therapy are indicated, but investigators should use better antiemetics to improve patient compliance as well as more active cisplatin-based chemotherapy regimens.

Most patients with stage I lung cancer who have recurrences have them at systemic sites, including the brain, and less often in the thorax. Therefore, systemic treatments such as chemotherapy are necessary for successful adjuvant therapy even for early-stage non-small cell lung cancer. Two published studies by the Lung Cancer Study Group (LCSG) suggest an advantage to adjuvant therapy with the CAP (cyclophosphamide, doxorubicin, and cisplatin) regimen. In the earlier study, patients with resectable stage II and III adenocarcinoma and large cell carcinoma of the lung were randomly assigned to receive either CAP or intrapleural bacillus Calmette-Guerin (BCG) plus levamisole as an adjuvant to complete surgical resection (protocol 772). There was a significant increase in disease-free interval and overall survival in patients treated with CAP. In the more recent study, patients with resected locally advanced non-small cell lung cancer (LCSG protocol 791) who were randomized to CAP plus thoracic radiotherapy had a superior outcome to those receiving thoracic irradiation alone. In 1980, since neither of the previous studies had an untreated control, LCSG protocol 801 was initiated. It included only patients with T1N1 or T2N0 non-small cell lung cancer. This randomized phase 3 trial compared CAP chemotherapy every 3 weeks for four courses to close follow-up. The detailed results of this study have already been published. This article contains no new data but has a more recent up-to-date review of the literature.

METHODS

Patients with T1N1 or T2N0 non-small cell lung cancer aged 75 years or younger who had sufficiently rapid recovery from surgery and could start treatment by day 30 were included in the trial. Patients with T1N1 were included since they were part of stage I in the staging classification prior to the new classification of Mountain. These patients were not to have received previous cancer treatment or to have had a history of cancer other than nonmelanoma skin cancer or in situ cancer of the cervix. They had to give informed consent and had to be available for appropriate follow-up. Eligible patients were assigned randomly by telephone from the central operations office. Stratification factors included histologic features (squamous vs nonsquamous, preoperative white blood cell count >9,100/mm³ vs <9,100/mm³), and Karnofsky performance status before surgery (90% vs 100%). The patients assigned to chemotherapy received cyclophosphamide (400 mg/m²), doxorubicin (40 mg/m²), and cisplatin (60 mg/m²) all at a single visit on day 1; this was then repeated at 3-week intervals for a total of four courses. Dose reduction based on blood cell counts and renal function were mandated. Patients on both arms were followed up every 3 weeks for 3 months, then every 3 months for 2 years and every 6 months thereafter.

Pretreatment Evaluation

Patients were evaluated with a complete history and physical examination, and a chest radiograph, posteroanterior and lateral, as well as routine hematology, chemistry, and an ECG. Only if the alkaline phosphatase or SGOT was >50% above institutional limits were additional tests carried out to further evaluate liver and bone as possible metastatic sites. The chest radiograph and blood work were repeated every visit but scans, when done, were repeated less frequently.

At surgery, stage was determined according to the TNM classification. A lobectomy or pneumonectomy was performed with the highest mediastinal nodes identified and labeled by the surgeon and the pathologist; all mediastinal areas were sampled by surgery plus mediastinoscopy. If the highest node obtainable was positive for tumor, the patient was ineligible for study. Pathologic specimens were reviewed by the pathology reference center at the M. D. Anderson Hospital in Houston.
Statistical Methods

The trial size was determined by the number of patients necessary for 90 events to occur (power 0.9 to detect a twofold difference in median survival with a two-sided log rank test using a significance level of 0.05). The Pearson $X^2$ test was used for contingency table analysis; Yates' continuity correction was used in the case of two-by-two tables. Survival and recurrence were estimated by the Kaplan-Meier method and two-sided significance tests were based on log rank statistics as given by Mantel but without continuity correction. Survival analysis stratification variables were used to adjust the data as were other important covariates by using the Cox model or by using stratified log rank score statistics. All end points were defined in the usual way starting on the day of randomization.

RESULTS

Patients were entered in the study from November 1980 to May 1986 and data for the analysis were collected until January 15, 1990. No further update is planned. Among the 283 randomized patients, 14 had major protocol violations and were declared ineligible. Among the 269 eligible patients, 29 did not receive the assigned treatment. Therefore, there were 240 (85%) eligible treated patients. Among the eligible patients, 82% were male, 59% were at least 60 years old, 56% had nonsquamous histologic features, and 84% had tumors classified as T2N0, the remainder as T1N1. There were no statistically significant differences by treatment arm for the potential important prognostic variables that were not included in the stratification (weight loss $>$ 10%, neutrophil count $>$ 7,000/mm$^3$, lobectomy, segmental resection vs pneumonectomy/wedge resection, sex, the presence or absence of heart disease prior to randomization, and complications following surgery).

Relapse and Survival

The mean time from random assignment of the 269 eligible patients was 6.4 years, with a mean follow-up of 5.8 years. One hundred one recurrences occurred along with 31 second primary tumors (all sites, not just lung) and 127 deaths at the time of analysis. We looked for individual potential prognostic variables. Only prior heart disease and a preoperative neutrophil count $>$ 7,000/mm$^3$ were associated with significantly greater death rates. A number of other parameters were associated with higher recurrence rates.

The time to first recurrence, excluding second primary tumors, is shown in Figure 1. The time to death from any cause is shown in Figure 2. No treatment difference is observed even when adjustment occurred using the Cox model or if the 23 patients who refused the assigned treatments were excluded. When all 283 randomly assigned patients were included, no treatment differences were observed. Among patients with squamous histology, the rates of recurrence (excluding second primary tumors) and death (from any causes) differed in favor of the CAP arm ($p = 0.05$, two-sided). Among patients with nonsquamous histology, those on the control arm had somewhat better survival ($p = 0.06$, two-sided). No explanation for this finding was forthcoming.

Toxicity of Treatment

As expected, most of the toxic effects occurred in patients treated with chemotherapy. Three patients on the CAP arm had life-threatening toxic effects (hematologic in one patient, cardiac in one patient, and attempted suicide associated with depression in the third). One death was associated with infection due to treatment-related neutropenia.

Treatment Compliance

Only 80% of the eligible patients received the initial dose of CAP. 86% of these receiving the treatment on time. Sixty-six percent of the eligible patients received at least two cycles of CAP (73% of these received at least the initial two cycles on time). Only 53% of the eligible patients received all four cycles of CAP (57% of these received all four cycles on time). Dose intensity analysis was not done.

Sites of First Recurrence

The sites of first recurrences are shown in Table 1. Nonlocal recurrences predominate with isolated brain recurrences (26% of the total) equal to local recurrences and constituting the most common single distant metastatic site. No statistically significant treatment differences were found among the three categories of relapse used (local recurrence, isolated brain recurrences, and other systemic recurrences).

DISCUSSION

Earlier studies performed by the LCSG (Protocols 772 and 791) suggested a positive effect with chemotherapy. As previously mentioned, one study compared intrapleural...
BCG and levamisole with the CAP regimen in stage II and III adenocarcinoma and showed approximately a 7-month survival benefit. However, in the absence of an untreated control, it was hard to interpret these data. The second study compared radiation with radiation plus CAP in stage II and III non-small cell lung cancer of all histologic features. Again there was a suggested prolongation of survival in the combined modality arm, but the p value was not significant and again there was no untreated control arm.

Lung Cancer Study Group Protocol 801 compared adjuvant CAP with an untreated control arm in early-stage disease (mainly stage I) but unfortunately did not find a survival benefit. A Finnish group randomized 110 patients with T1-3NO non-small cell lung cancer to adjuvant chemotherapy with CAP or no active treatment. After 10 years of follow-up, 61% of the patients were alive in the chemotherapy group and 48% were alive in the control group (p=0.050). The 5-year survival rate was 67% in the chemotherapy group and 56% in the control group (p=0.05). Niiranen and colleagues concluded that patients with non-small cell lung cancer of pathologic stage I who undergo radical surgery benefit from adjuvant chemotherapy. They pointed out that the greatest benefit was observed in the group of patients treated with CAP who received their planned six courses of chemotherapy.

In our study and the Finnish study, the main compliance problem was associated with chemotherapy-induced nausea. Vomiting was often intractable with the antiemetic agents in use at the time of the two studies. It was particularly difficult to motivate patients to continue treatment after they were informed that their surgery had been successful and no disease remained. The use of new marketed antiemetics such as ondansetron or granisetron in ongoing and future studies should ensure reasonable compliance, hopefully with better survival on a treated arm compared with an untreated control.

The other issue that must be considered is that in 1994, other chemotherapy regimens seem more promising than CAP. Still virtually all active regimens are cisplatin based. They may contain etoposide or vinca alkaloids and may have mitomycin added as well. High-dose anthracyclines such as epirubicin may also contribute to cisplatin-based combinations. Although none of these regimens is clearly superior, at least in the Canadian study by Rapp et al comparing best supportive care to vindesine plus cisplatin and CAP, the vindesine-cisplatin arm was superior to either of the other two arms, suggesting that a vinca-alkaloid-cisplatin combination might be preferable to the standard CAP regimen. This might be particularly advantageous in earlier-stage disease. In addition, new drugs such as vinorelbine (Navelbine), gemcitabine, opt-11, taxol, and taxotere combined with cisplatin may prove to be even better than available vinca-alkaloid-cisplatin combinations.

The fact that at least one study shows a survival benefit with a relatively ineffective regimen (CAP) argues strongly for further studies with new combinations and appropriate supportive care such as the new antiemetics presently available. One such study is expected to begin in Canada sometime in 1994. The Lung Site Group of the National Cancer Institute of Canada will compare vinorelbine plus cisplatin with close observation in stage I non-small cell lung cancer. Other studies using different regimens will undoubtedly begin in other parts of the world and should be encouraged. If we can improve compliance and hopefully improve antineoplastic activity with new combinations, the best hope for survival improvement in the lung cancer population (particularly early stage) is with the use of adjuvant treatment. Therefore, testing new adjuvant treatments should be among the main research priorities in the 1990s to try to improve survival in resectable non-small cell lung cancer.

REFERENCES
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