Adjuvant Chemotherapy for Non-small Cell Lung Cancer*

David H. Johnson, MD

In the late 1970s and early 1980s, the Lung Cancer Study Group conducted a series of adjuvant chemotherapy trials in patients with resected non-small cell lung cancer. Although some of these trials yielded modest survival benefit, the length of improved survival essentially equaled the time spent receiving chemotherapy. Consequently, few physicians routinely employ postoperative chemotherapy in spite of its theoretical appeal. Possible explanations for the failure of adjuvant chemotherapy to provide meaningful prolongation of survival in non-small cell lung cancer include lack of effective chemotherapy, incorrect chemotherapy regimen, inadequate dose intensity, and possibly inadequate trial design. Future postoperative adjuvant trials should focus on treating patients with resected early stage lesions (T1N1, T2N1, T2N0). What role, if any, newer antineoplastic agents will play in the postoperative setting remains to be determined. Neoadjuvant induction chemotherapy may well prove to be a superior treatment strategy and deserves further investigation.

The 1970s were full of promise for the then relatively new therapeutic approach of adjuvant chemotherapy. Preclinical studies employing adjuvant chemotherapy in animal tumors had consistently demonstrated prolongation of survival, and in some instances, cures were obtained. Several mechanisms were thought to play a role in the enhanced effectiveness of postoperative chemotherapy. Smaller lesions are known to have higher rates of proliferation, less drug-resistant cell lines and better blood perfusion allowing improved penetration of drug into the tumor, all of which contribute to greater susceptibility to chemotherapy. Furthermore, although somewhat controversial, the growth fraction of residual micrometastases had been shown to increase following removal of the primary lesion rendering occult micrometastases even more vulnerable to systemic therapy. Unfortunately, the early promise of postoperative adjuvant chemotherapy has not yet been realized in all solid tumors. Only in a few instances has this approach had a significant impact on survival.

**Adjuvant Chemotherapy in Non-small Cell Lung Cancer**

In both autopsy and clinical series, extrathoracic recurrence has been shown to be a substantial problem even in patients with early stage non-small cell lung cancer (NSCLC). For example, Matthews and colleagues performed postmortem examinations in a group of patients with NSCLC dying within 30 days of a "curative resection." More than 40% of patients with an adenocarcinoma were found to harbor residual disease which in most cases was found outside the chest. In contrast, among patients with squamous cell carcinoma, residual tumor was found within the chest in nearly half of all cases. The systemic nature of NSCLC also is illustrated by the patterns of relapse observed in patients undergoing curative resections. For example, reporting for the Lung Cancer Study Group (LCSG), Feld and colleagues recorded 43 recurrences in 162 patients with T1N0 lesions, 65% of which were in extrathoracic sites including the brain. Fifty-nine of the 81 recurrences seen in 196 patients with T2N0 lesions also occurred outside the chest. Even in more advanced stages of resectable NSCLC, systemic relapses predominate. Thus, it is patently obvious that some form of systemic therapy is needed if any improvement in NSCLC survival is to be realized.

**Review of Adjuvant Trials**

Over the past 20 years, several trials of adjuvant chemotherapy have been conducted in NSCLC. Perhaps the best known of these trials are those undertaken by the LCSG and reviewed in more detail elsewhere. As the LCSG studies were conceived and initiated more than 10 years ago, it is relatively easy to offer criticisms in hindsight. However, these studies provided invaluable data which can be helpful in designing future adjuvant trials. This brief review will focus only on the results of the published chemotherapy trials - studies 772, 791, and 801.

In study 772, cyclophosphamide, doxorubicin, and cisplatin (CAP) chemotherapy was prospectively compared to immunotherapy in 141 patients with completely resected stage II (T2N1) and III (any T3 or any N2) adenocarcinoma and large cell carcinoma. Patients with squamous cell carcinoma were relegated to a separate study of postoperative irradiation. Complete resection was defined as negative surgical margins and no evidence of tumor in the highest sampled mediastinal lymph node. All patients had a mediastinal lymph node dissection as part of their surgical procedure. Patients were randomized to receive 6 cycles of CAP every 4 weeks beginning within 30 days of surgery or an intrapleural injection of bacillus Calmette-Guerin (BCG) along with daily isoniazid for 12 weeks. In addition, the immunotherapy group received levamisole orally for 3 consecutive days every other week for 18 months. At a mean follow-up of 7.5 years, the recurrence rate in CAP-treated patients was significantly less than the immunotherapy arm (51 vs 38; p=0.005). The average cumulative dose of CAP received was 58% of the full protocol dosages. Median time to recurrence and overall survival (22.5 months vs 15.5 months) were approximately 7 months longer in the chemotherapy group. Only 17% of recurrences were exclusively local. The remaining recurrences were either exclusively in the brain or in other systemic sites prompting the investigators to conclude that postoperative radiotherapy would not have been beneficial.

Postoperative CAP chemotherapy also was evaluated in 172 patients with incomplete resection with stage II and III NSCLC (study 791). Incomplete resection was defined as the presence of tumor in the highest sampled paratracheal lymph node or a positive surgical margin. The study differed from 771 in that it included patients with squamous
cell carcinomas. Patients received postoperative irradiation (20 Gy in 10 fractions, 3 week rest, 20 Gy in 10 fractions - total dose 40 Gy) with or without CAP chemotherapy; CAP was administered every 4 weeks for 6 cycles with treatment starting on day 1 of radiotherapy. Median survival was 20 months in the CAP plus radiotherapy group and 13 months in the group receiving radiotherapy only (log rank p=0.133). Median time to tumor recurrence also favored the CAP-treated group (14 months vs 8 months; p=0.004). Recurrences were more common in the patients who had radiotherapy compared to those given CAP plus radiotherapy and were usually extrathoracic (66 vs 50; p=0.001). Only 20 patients experienced local relapse, nine of which were confined to the mediastinum. Chemotherapy with CAP did not appear to add significantly to local control. Treatment compliance was not good. In the chemotherapy arm, 7% refused any treatment while another 12% refused further treatment after cycle 1 of CAP. Just 51% of patients completed all six cycles of treatment. In the radiotherapy arm, more than 90% of patients received the intended dose of irradiation.

More recently, the LCSG evaluated the effects of postoperative chemotherapy in completely resected, stage I NSCLC (study 801).15 Patients were eligible if the pathologic stage was T1N1 or T2N0. In the most recent modification of the lung cancer staging system, T1N1 is classified as stage II.16 Treatment consisted of four cycles of CAP chemotherapy administered every 3 weeks starting within 30 days of surgery. The dose of cisplatin was higher than that employed in earlier LCSG trials (60 mg/m² vs 40 mg/m²). The study accrued 283 patients of whom 269 were eligible. Twenty-nine patients did not receive their assigned treatment. Of the 240 eligible and treated patients, 84% had T2N0 lesions. There were no significant differences in the known prognostic factors between the treatment arms. Neither time to recurrence nor overall survival was improved in the chemotherapy arm. There have been 101 recurrences most of which were extrathoracic. In addition, second primary tumors were identified in 31 patients. Treatment compliance was poor as fewer than 55% received all four planned cycles of CAP. The LCSG investigators concluded that continued investigation of adjuvant or neoadjuvant chemotherapy was warranted since the bulk of recurrences was systemic and that a better systemic therapy was needed. However, because some recurrences were local, thoracic irradiation was felt to be needed “where appropriate.”

Although it could be argued that LCSG trials 771 and 791 demonstrated a “biological effect” of chemotherapy, the results of these two trials have not altered routine clinical practice. The magnitude of survival benefit, some 6 to 7 months, more or less equals the duration of adjuvant therapy essentially offsetting the meager survival advantage. As pointed out by others, given the reticence of the oncology community to embrace the modest benefits of adjuvant chemotherapy for breast cancer, it is perhaps not surprising adjuvant therapy has not found its way into the routine management of NSCLC.17 The results of LCSG 801 are particularly disappointing. Presumably stage I patients represent the group with the smallest tumor burden and are theoretically the group most likely to benefit from adjuvant treatment.

Why have the LCSG studies failed to demonstrate survival benefit with adjuvant chemotherapy? Several reasons can be postulated. The most obvious reason is the lack of effective systemic therapy. In NSCLC, drug resistance is present ab initio. Randomized studies comparing chemotherapy to supportive care in advanced NSCLC, for the most part, have been disappointing.18 To be effective in the adjuvant setting, a chemotherapy regimen ideally should be capable of effecting a high response rate in patients with more advanced disease. More specifically, the chosen regimen should be able to produce complete responses, an extremely rare event with any chemotherapy regimen in NSCLC.19 One could argue that CAP is not the best chemotherapy regimen for adjuvant trials. In a Canadian National Cancer Institute trial, CAP and cisplatin plus vindesine were prospectively compared in advanced NSCLC. Both regimens yielded superior median survivals compared to no treatment.20 However, CAP proved inferior to cisplatin plus vindesine suggesting the latter may be a better regimen for adjuvant treatment. On the other hand, most prospective studies have not found major differences in the effectiveness of various cisplatin-based chemotherapy regimens.21,22 Thus, the argument that the wrong chemotherapy regimen was used in the LCSG is relatively weak. Will changing the composition of the adjuvant chemotherapy regimen “make a difference” in the outcome of future postoperative adjuvant chemotherapy trials? In a recently completed Japanese trial, 209 patients with completely resected stage III disease were randomized to cisplatin and vindesine or no further treatment.23 There was no statistically significant differences in disease-free or overall survival. Median survivals were 31 months in the chemotherapy group and 37 months in the control arm. Five-year survivals were 35% and 41%, respectively. These data would appear to negate the view that the LCSG studies would have been positive had the “right” chemotherapy regimen been used.

Yet another posited reason for the negative outcome of the LCSG trials was the use of inadequate dosages of active agents and lack of proper chemotherapy dose-intensity. In recent years, these two concepts have become oncologic dogma and were even posed by the LCSG investigators as a possible explanation for the failure of chemotherapy to effect a survival benefit in stage I NSCLC. Preclinical studies have consistently shown that maintenance of the optimal dose of each effective agent is critical to the success of an adjuvant chemotherapy regimen. Inadequate doses of active agents can negate the benefits of adjuvant treatment.4-5 Retrospective analyses performed by Hryniuk24 and others25 have consistently demonstrated the importance of maintaining chemotherapy dose intensity in human adjuvant trials. In more advanced disease, both response rates and survival appear to directly correlate with increasing dose intensity in some solid tumors.24

Did the completed LCSG adjuvant trials employ adequate chemotherapy doses and dose intensity? Most experts agree that cisplatin is one of the more effective agents available to treat NSCLC. This agent was a key component of the regimen used in the LCSG trials. In laboratory
studies, there is a dose-response relationship between cisplatin and NSCLC suggesting that high doses of cisplatin are necessary to achieve optimal clinical outcome.\textsuperscript{26} It could be argued that the dose of cisplatin used in LCSG trials was modest or even inadequate by current standards and that this may have contributed to the poor outcome. Higher doses of cisplatin, eg, 80 to 120 mg/m\textsuperscript{2}, may be necessary to obtain improved results. Clinical data supporting the alleged dose relationship in NSCLC, however, are relatively weak. In fact, the existing data could arguably be used to support the opposite view in patients with advanced disease.\textsuperscript{27-29} Thus, attributing the failure of the LCSG trials to demonstrate a survival benefit to the dosage of cisplatin seems to be a poorly defensible position. It should be noted that the Japanese trial\textsuperscript{28} with negative results did employ a high cisplatin dose (80 mg/m\textsuperscript{2}).

One can argue that none of the LCSG trials achieved “optimal” dose intensity. For example, in study 771, of the 62 patients assigned to CAP chemotherapy, 15 failed to receive any treatment. In other words, nearly 25% of patients assigned to receive adjuvant chemotherapy never received it. Furthermore, the average cumulative dose received was just 58%. Likewise, in study 701 just over 50% of patients assigned to the CAP arm received all six planned cycles of chemotherapy. In study 801, 55% of eligible patients received the four planned cycles of CAP and 57% received all four cycles on time. Thus, in all three LCSG studies, dose intensity was severely compromised. None of these trials can be considered an adequate trial of postoperative adjuvant chemotherapy.

Yet another potential shortcoming of the LCSG trials is the inadequacy of trial design. Putting aside the contentious issues of dose and dose intensity, did any of the trials accrue sufficient patient numbers to provide an adequate assessment of adjuvant chemotherapy? Even in breast cancer, the benefits derived from adjuvant chemotherapy are modest - a 20 to 30% reduction in mortality in the first 5 years after diagnosis and a 5 to 10% difference in absolute mortality at the end of 5 years.\textsuperscript{30} While most oncologists would agree these differences are worthwhile, they are difficult to detect in trials consisting of fewer than 2,000 patients. The LCSG trials were usually designed to detect a twofold increase in the median survival of chemotherapy-treated patients which is probably an unrealistic end point given the relative ineffectiveness of existing chemotherapy regimens. Future trials will need to take into account the efficacy of existing drug combinations and plan for larger patient accrual.

COMMENTS

At a workshop sponsored by the International Association for Study of Lung Cancer (IASLC) held in Bruges in 1990, a consensus report was issued regarding the status of postoperative adjuvant chemotherapy in NSCLC.\textsuperscript{11} The committee concluded that there is little evidence to support the routine use of adjuvant chemotherapy. Further study was recommended and the suggestion was made that future trials be confined to patients with T1N1, T2N1, and T2N0 disease. These patients have a 5-year survival of 40 to 55%. In addition, it was felt that patients with negative mediastinoscopy but positive mediastinal nodes (N2) at thoracotomy should be included in postoperative chemotherapy trials. Preoperative staging should include mediastinoscopy and possibly parasternal exploration. Careful intraoperative staging is considered imperative.

The consensus committee also recommended certain trial design features to include recognition of competing causes of death in the study populations. Overall survival was felt to be the principal relevant end point. It was generally agreed that cisplatin-based therapies given for six cycles represented the “best available” systemic treatment and that dose reductions should be avoided. Because of the propensity for recurrences to occur early within the first 18 postoperative months, early initiation of chemotherapy was encouraged. For protocols incorporating postoperative irradiation, the committee recommended a minimum radiation therapy dose of 50 Gy delivered over 5 weeks in a continuous course. The IASLC committee also favored a chemotherapy regimen with radiation sensitizing properties and recommended that irradiation not delay the initiation of chemotherapy. Rather, the two modalities should be given concomitantly if possible.

At least one ongoing trial—INT-0115—has incorporated many of the above recommendations. The latter trial, a US intergroup effort, randomizes patients with completely resected stage II and III disease to thoracic radiotherapy (50.4 Gy in 5 weeks) or concomitant cisplatin and etoposide with thoracic irradiation. Chemotherapy is administered beginning shortly after surgery and is continued for four courses. The dose of cisplatin is 60 mg/m\textsuperscript{2} delivered every 3 weeks. Although local recurrence is not a major site of relapse as shown in the LCSG trials, local control may be improved with postoperative irradiation. The concomitant administration of cisplatin, etoposide, and radiotherapy has been shown to be feasible both in randomized trials involving small cell lung cancer and in single institutional pilot trials in NSCLC.

Although INT-0115 has attempted to address some of the shortcomings of previous postoperative chemotherapy trials, it is hardly a perfect study. The phenomenon most likely to be responsible for the failure of adjuvant chemotherapy is the presence of drug-resistant cells at the very beginning of treatment or their emergence during the course of chemotherapy. Given the relative lack of activity of existing agents (including cisplatin and etoposide), one may feel further study of adjuvant treatment should await the discovery of more active agents. Fortunately, the past few years have seen the identification of several new drugs with promising activity against NSCLC including taxanes, camptothecin derivatives, vinorelbine, and gemcitabine.\textsuperscript{31} As we gain experience with these new agents, both singly and in combination regimens, it is highly likely a new “standard” regimen will emerge. Newer regimens may effect higher objective response rates and higher complete response rates which is desirable in an adjuvant regimen. However, while we would prefer to use a regimen with a high response rate against advanced disease, we should remember that this is not a sine qua non for effectiveness in the adjuvant setting. Levamisole and 5-fluorouracil are virtually inactive in advanced colon cancer and yet the combination is effective adjuvant therapy.\textsuperscript{32} Furthermore, the latter combination has modest toxicity.
a highly desirable trait for an adjuvant therapy.

Many experts have stated that patients with T1N0 disease should be excluded from future adjuvant trials arguing that such individuals have a 5-year survival of 85%.

11,15,17 Is this a reasonable a priori exclusion criterion? Not too many years ago, adjuvant chemotherapy was rarely used in the management of stage I breast cancer largely due to the excellent 5-year survival (>90%). More recently, adjuvant chemotherapy has become a routine component of the management of selected patients with node negative, stage I breast cancer. The difference in approach is due to a number of factors. First the customary treatment given to patients with breast cancer is perceived to be less toxic (and possibly more effective) than the usual treatment given in lung cancer trials. Second, we believe we have a better understanding of the biology of breast cancer and that we are better able to identify subsets of patients with stage I disease with poorer prognosis and therefore more likely to benefit from chemotherapy. Are we not capable of making similar distinctions in patients with lung cancer? Are all T1N0 patients the same? We know, for example, that the 5-year survival rate for T1N0 squamous cancer is substantially better than that of an adenocarcinoma (≈85% vs. ≈70%). In addition, several recently published studies have identified other putative prognostic features including ras mutations, blood group antigen expression, presence of angiogenesis, and others. These recent developments indicate much remains to be learned about the behavior of lung cancer. Future adjuvant therapy trials, whether they are postoperative or preoperative studies, must incorporate provisions that allow the prospective collection of information which will allow more rationale design of subsequent trials.

Finally, is it time to completely reassess our approach to adjuvant chemotherapy? There is considerable theoretical appeal for the use of chemotherapy as early as possible in the management of solid tumors even before the use of local treatment modalities. This approach, referred to as neoadjuvant or induction chemotherapy, has as its main assumption the notion that mutation to drug resistance is a process that can transpire over a relatively brief period of time. As a result, the curability of a tumor is lost with a relatively small (≈2 log) increase in tumor burden. If our understanding of tumor growth is correct and our conjectures regarding development of drug resistance are accurate, then investigation of neoadjuvant or induction chemotherapy is not only warranted but essential if survival benefit is to be realized. Paradoxically, institution of chemotherapy may one day become an emergency procedure that should not be unduly delayed in early stage NSCLC.

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