clearly shows that low doses are not sufficiently effective even when combined with CT.

A promising field for research is combination with radiosensitizers. Several groups are exploring the radiosensitizing effect of small doses of CIS-Pt. Schaake-Koning reported the results of an EORTC study in which 100 patients were randomized between RT alone, RT and 300 mg/m² CDDP once a week, RT and 6 mg/m² daily. The incidences of local recurrence were, respectively, 56%, 47%, and 32%. Early and late toxicity were acceptable. Soresi et al randomized 103 patients between RT alone (50 Gy) and RT with CDDP (15 mg/m² weekly), with local recurrence rates, respectively, 43% and 24%. These two promising results have led to further studies on larger numbers of patients. Trovo et al and Lapukino et al in nonrandomized pilot studies have observed encouraging results. Currently randomized trials are and merit to be carefully watched, but conclusions have not yet been reached.

**Innovative Radiotherapy**

A few studies can be grouped under this heading. Three groups have reported studies on Lonidamine, an antispermatogenic agent. Magno et al presented data that suggest a favorable effect of Lonidamine, whereas Gallo-Curcio et al did not find any difference in the mean survival time. Maroun et al confirmed that the combination of Lonidamine and RT is well tolerated.

Kato described a new modality of RT under increased tumor oxygen tension with angiotensin 2. A nonrandomized pilot study on a small number of patients suggests a more rapid regression of the tumors. This observation needs confirmation. The use of a radiosensitizer (misonidazole) was investigated by Abbrat et al; the preliminary results show promising response but neurotoxicity is high. This approach should be reinvestigated with less toxic radiosensitizers.

Photodynamic therapy with a hematoporphyrin derivative was investigated by Furuse et al and Kato et al for cancers within the reach of a flexible bronchofiberscope. The results suggest that this type of treatment might be able to control small (less than 2 cm in diameter) unresectable lesions. Further, Komato et al showed that such treatment can be indicated in cases of superficial invasion on bronchial mucosa, thus reducing the extent of resection. The validity of this approach should be tested with rigor in controlled studies.

Three retrospective studies reported the results of low-dose rate intracavitary brachytherapy alone or in combination with laser for endobronchial tumors. This treatment is well tolerated and may have a palliative value; however, as stated by Huber et al, this must be proved in a randomized study.

A large number of avenues for research have been explored. However, most of the promising data need confirmation. This underlines the urgent need for large, well-designed controlled clinical trials. Only such studies will be able to objectively evaluate the role of RT in the treatment of this cancer, which unfortunately remains so difficult to control. Trials with an insufficient number of patients only add to the current controversies; only well-stratified studies will be able to identify the small subsets of patients for whom RT can improve local control and long-term survival. The increase in survival of patients with unresectable NSCLC which has been reported by Cox and the RTOG during this meeting show that better radiotherapy techniques can result in a higher percentage of local control and cure. This is a very promising observation which gives some hope.

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**Adjuvant Therapy for Non-small Cell Lung Cancer**

W K. Ecana, M.D.*

Progress in our efforts to increase the lung cancer cure rate has been frustratingly slow despite considerable effort in many countries worldwide. Nonetheless, there have been several promising developments in the adjuvant therapy of lung cancer which provide leads for future advances against this disease.

The problem of lung cancer is formidable both because of the numbers of individuals affected and their poor overall survival despite current best therapy. It is estimated that annually there are about 1 million new cases of lung cancer worldwide. Surgery is still the only modality which offers any substantial possibility of cure for patients with non-small cell lung cancer. Unfortunately, only about half of all patients present with localized disease, and only about one third overall are candidates for an attempt at curative resection. It is well recognized that the results of surgical resection correlate with pathologic stage as defined by tumor size and nodal status. The TNM definitions and stage groupings have recently undergone refinement. The new international staging system has a number of important changes from the previous AJC staging system. Stage 1 now includes only T1 and T2 N0 disease. T1 N1 has been placed in stage 2. Stage 3 disease has now been divided into stages 3A, and 3B, and a new stage 4 has been created. The careful use of this staging system to define groups for study and to report results of therapeutic interventions will be critical for the evaluation of adjuvant therapies in the future.

A review of the results of surgery according to tumor stage and histopathology helps to identify groups of patients in need of adjuvant therapy. Four-year postoperative survival data from the American Lung Cancer Study Group experience are helpful in this regard. The LCSD has the largest series of modern surgically staged cases available and

*From the Ontario Cancer Treatment and Research Foundation, Ottawa Regional Cancer Centre, Ottawa, Canada. Reprint requests: Dr. Ecana, 190 Melrose Avenue, Ottawa, Ontario, Canada K1Y 4K7

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provides an excellent reference for the current best surgical results. Although the 83% survival rate for patients with T1 N0 squamous cell cancer is excellent, the survival rate for T1 N0 adenocarcinoma is only 69%. The survival figures for T2 N0 and T1 N1 patients are substantially lower. Patients with adenocarcinoma generally fare less well than patients with squamous cell carcinoma, particularly when there is nodal involvement. An interesting observation from the LCGS data is the remarkably good survival reported for patients with N2 disease (46% 4-year survival for squamous cell cancer; 35% for adenocarcinoma). About half the patients entering LCGS studies have been staged by mediastinoscopy. Therefore, roughly half of the N2 patients included in these trials are those with N2 disease found at surgery. As Pearson et al. reported, patients with mediastinal lymph node involvement detected by mediastinoscopy have a worse 5-year survival (18%) than those whose mediastinoscopy is negative but have N2 disease found at thoracotomy (34%). Nevertheless, the survival of operable N2 disease is low, and there is certainly a need to find effective adjuvant therapies to improve survival for this group of patients.

A knowledge of the patterns of relapse following surgery also helps to define the most appropriate groups for study. In part, the relapse pattern is determined by histopathology. An autopsy study of patients dying within 30 days of apparently curative resection showed that one-third of squamous cell cancer cases had locally persistent disease but only 17% had distant metastases. 2 On the other hand, patients with adenocarcinoma had a 40% incidence of disease both locally and at distant sites. An analysis of sites of relapse in the LCGS Intra-pleural BCG Trial in stage I lung cancer identified the brain as a common site of first recurrence, especially in patients with nonsquamous histology. 3 Patients with a high risk of local recurrence by virtue of pathologic type and stage are candidates for studies that include local modalities such as postoperative radiotherapy and those at high risk of brain metastases might benefit from therapy directed to the CNS.

In retrospect, early efforts to study postoperative adjuvant therapies were flawed by the use of marginally active or ineffective therapeutic modalities, suboptimal staging, and poor clinical trial design. All of the initial adjuvant chemotherapy trials including the pioneering studies of the Veterans Administration Lung Cancer Group were negative, no doubt because the agents chosen for study were only weakly active against lung cancer. These early studies also commonly failed to stratify for cell type or tumor stage, and intraoperative lymph node mapping was not done.

ADJUVANT IMMUNOTHERAPY

The early interest in adjuvant chemotherapy trials gave way to a focus on adjuvant immunotherapy studies in the 1970s. A wide variety of "immune stimulants" or immune modulating agents has been explored in clinical trials including BCG administered by a variety of routes, BCG cell-wall skeleton, levamisole, tumor-associated antigens, Corynebacterium parvum, and others. The results from these studies have often been contradictory, in part because they, like the early chemotherapy trials, often lacked a randomized trial design with a proper control group, or failed to stratify by prognostic factors, and lacked intraoperative staging.

BCG has been administered by a variety of routes and in different preparations. Enthusiasm for intrapleural BCG administration was sparked by the report of McKneally et al. 4 on significantly improved survival in patients with resected stage 1 disease. After 4 years of follow-up, there continues to be a significant reduction in recurrences in the BCG treated group (p = 0.003) and better survival (p = 0.02). However, the results from the large American Lung Cancer Study Group trial were entirely negative. 5 Stage 1 completely resected lung cancer cases were stratified by age, histology, and extent of resection and then randomized to intrapleural BCG + INH or to control. All were carefully staged intraoperatively. Four hundred seventy-three patients were randomized, 401 were eligible and received the assigned treatment. The median time from randomization is now approximately 9 years, and there is no significant difference in overall survival. In a similarly designed trial, the Ludwig Lung Cancer Study Group also found no benefit with intrapleural BCG; in fact, there was a significant decrease in disease-free interval on the BCG arm of the study. 6 Studies evaluating levamisole, C. parvum, and other immune modulators have given either negative or contradictory results. No immune modulating substance has as yet convincingly demonstrated a consistently positive impact on post-surgical survival.

Several trials have attempted to determine if specific active immunotherapy using a polypeptide tumor-associated antigen is of benefit as an adjuvant. Unfortunately, the results from these studies have not been clear cut. The first study reported by Stewart et al. 7 from Ottawa had 4 arms: a control arm, an arm that received adjuvant methotrexate, an arm immunized with tumor-associated antigens and Freund's complete adjuvant, and a fourth arm that received the same immunotherapy plus methotrexate. In reporting the results of this study, the arm receiving methotrexate was grouped with the control arm, and the 2 arms receiving immunotherapy were grouped together. The 5-year survival of the immunized group (78%) was significantly longer than that of the control groups (46%).

Two subsequent randomized phase 3 trials have given conflicting results. Takita et al. 8 reported significant improvement in disease-free and overall survival in node negative patients who received specific immunotherapy with TAA and Freund's adjuvant. On the other hand, no differences were seen in a similar 3-arm trial coordinated by the National Cancer Institute of Canada. 9 Unfortunately, there were a large number of major protocol violations in this study. A recently reported further analysis of this trial including only those patients from centers with an acceptable level of protocol violation claims a significant 5-year survival advantage for the specific active immunotherapy group compared with the control group. 10

ADJUVANT CHEMOTHERAPY

The past few years have seen renewed interest in chemotherapy—principally combination chemotherapy in both the postoperative and preoperative or neoadjuvant setting. There are now a number of combination chemotherapy regimens such as CAP, vindesine-cisplatin, mitomycin, and others which cause major tumor regression in a significant
number of patients with advanced disease. None of these regimens is as effective as the chemotherapy for lymphoma or testicular cancer, but nonetheless, responses are seen in 30-40% of patients with advanced disease. In addition, a recently reported randomized trial from the National Cancer Institute of Canada does show that chemotherapy modestly increases survival in advanced disease compared with best supportive care.14 As well, the NCI-C observed not only a higher response rate to vindesine and high-dose cisplatinum but also longer survival relative to CAP. However, in 1977 when the first adjuvant chemotherapy trials were planned by the Lung Cancer Study Group, CAP was the most active regimen available, and it has been used in LCSG trials since then.

LCSG Study 772 prospectively evaluated CAP compared with immunotherapy in completely resected stages 2 and 3 adenocarcinoma and large cell undifferentiated carcinoma.15 Patients were stratified by stage of disease, degree of weight loss, and the presence or absence of arrhythmias. Within 14 days of surgery, they were randomized either to CAP for 6 months or to immunotherapy consisting of intrapleural BCG followed by levamisole for 18 months. Prognostic variables including stage, extent of nodal involvement, performance status, and weight loss were equally distributed between the two treatment groups. With follow-up data to February 1988, the mean time from randomization for the 130 eligible patients is now 7.5 years. The recurrence rate is significantly lower on the chemotherapy arm, with the main benefit concentrated in the first year following randomization. The median disease-free interval is increased about 6 months, which is a statistically significant result. The median survival is also about 7 months longer on chemotherapy but, in this case, the 2-sided log rank test is not statistically significant. In this study, systemic recurrence was the most common site of relapse, and brain metastases were a common first site of recurrence.

The LCSG has also observed a benefit with CAP chemotherapy in patients who have incompletely resected non-small cell tumors.16 An incomplete resection is defined by the LCSG as the presence of residual tumor in the resection margin or presence of tumor in the highest paratracheal lymph node sampled. Although originally designed as a 3-arm study, the chemotherapy alone arm was dropped due to poor accrual. Patients were randomized either to thoracic radiation administered on a split-course schedule or to radiotherapy plus CAP chemotherapy given every 4 weeks for 6 cycles. Patients were stratified according to histology, extent of residual disease, and performance status. The study accrued 172 patients of whom 164 patients were eligible. Results of this study were reported in the Journal of Clinical Oncology in January 1988. A total of 120 recurrences have been seen with significantly fewer on the CAP-radiotherapy arm. The reduction in recurrence rate is significant in both squamous and non-squamous histologies. The number of deaths is also lower on the CAP-radiotherapy arm. Only the Wilcoxon-Gehan statistic gives a significant p value in the comparison of death rates. This pattern of differences between the two statistics is a reflection of the fact that the Wilcoxon-Gehan statistic places greater weight on the early portions of the survival curves. In fact, the difference in median survival is about 7-8 months, and the survival curves begin to converge at about 2.5 years.

Although these two LCSG studies have both demonstrated a biologic effect of chemotherapy, many will question whether the 6-7-month increase in disease-free and overall survival, which is about equal to the time spent on chemotherapy, is clinically important enough to justify its use, particularly given the morbidity of treatment. When one considers the slowness of the oncology community to adopt adjuvant chemotherapy in breast cancer, even when a survival advantage was demonstrated at 5 years and treatment toxicities were modest in comparison to CAP, one can appreciate the difficulty of convincing physicians and patients alike of the utility of this approach, which shows only a very small extension of median survival time.

One LCSG study that has not demonstrated a benefit for adjuvant chemotherapy is study 801 in which patients with T1N1 and T2N0 disease are randomized to CAP for 4 treatments or to no further therapy. Intuitively, one would guess that CAP chemotherapy should have at least the same effect as seen in Protocols 772 and 791 and quite possibly more because of a smaller tumor burden. Two hundred eighty-three patients have been randomized to this study, and the median time from randomization is 4.4 years. Kaplan-Meier survival curves for time to recurrence and time to death show no treatment differences.

Aynob et al13 from Montreal, Canada, have also generated interesting results from a prospective randomized trial of adjuvant chemotherapy in operable non-small cell lung cancer. This study is still in progress, but preliminary results were reported at the Tucson Adjuvant Meeting in 1987. All patients have careful intraoperative lymph node mapping. Patients with N0 disease are randomized to chemotherapy with vindesine and cisplatin or control. Those with N1 or N2 disease are randomized to radiotherapy alone or to radiotherapy plus vindesine-cisplatin. One hundred fifty-four patients had been entered in this study as of the report at the Tucson meeting. Fifty-two percent of the patients with lymph node involvement who were treated with radiotherapy alone had recurrence compared with 37% treated with combined modality therapy. Although there are fewer recurrences on the chemotherapy arm, this reduction is not statistically significant.

In the past several years, considerable effort has been directed to the evaluation of preoperative therapy consisting of either chemotherapy alone or chemotherapy in combination with radiation therapy in both marginally resectable patients, where the goal is to improve survival, and in categorically unresectable cases, where the goal is to allow surgical resection to be performed. Marginally resectable tumors are those with only moderately extensive local disease (T3) or unilateral intranodal mediastinal involvement (N2). All of the studies of preoperative chemotherapy reported thus far have been pilot studies, and no prospective randomized trials have been undertaken yet. It is difficult to make comparisons between studies as the eligibility criteria vary from study to study, and, in particular, the extent of pretreatment stage 3 disease varies. The thoracic surgeons and medical oncologists at the Memorial Sloan Kettering have pioneered the neoadjuvant approach in patients with clinical evidence of mediastinal node involvement. Preliminary results of their experience were reported by Martini et al.13 The Memorial group defines clinical N2
disease as enlarged mediastinal lymph nodes on plain chest x-ray film or widening of the carina at bronchoscopy. Forty-one patients with this extent of disease received 2 to 3 cycles of high-dose cisplatin with vindesine or vinblastine with or without mitomycin-C. Following chemotherapy, 73% had a major response. Of these 30 patients, 28 had a thoracotomy and 21 (75%) had complete surgical resection of their cancer. Eight of these patients had a pathologically determined complete response. The survival at 3 years from diagnosis was 34% for all patients entered on study and 40% for those who completed the combined chemotherapy and surgery treatment. For those who had a complete resection the 3-year survival was 54%. The Toronto group has achieved very similar results with the same combination of high-dose cisplatin, vindesine and mitomycin.

A number of studies have given chemotherapy prior to radiotherapy in a sequential fashion. The Dana Farber group used CAP followed by radiotherapy and observed a major response rate of 43% in 41 marginally resectable patients of whom 97% could be resected. Similarly, vindesine and cisplatin followed by radiotherapy led to a high rate of complete resection in a series reported by Sherman et al., and both studies had surprisingly long median survivals.

A number of groups have attempted to capitalize on the apparent radiosensitizing effects of 5FU given by infusion and cisplatin and have given the chemotherapy and radiation concurrently. The largest of these studies has been reported by Taylor et al for the group at Rush Medical College. 5FU and cisplatin were given simultaneously with radiotherapy to a total of 40 Gy. The patients they treated in this program were considered to be surgically unresectable either because of primary tumor extension to the mediastinum or because of mediastinal node involvement identified by CT scan, mediastinoscopy, or thoracotomy. Fifty-six percent of patients had a major tumor regression, and 29 of 39 patients taken to surgery were completely resected. Approximately 20% of resected specimens were histologically negative. Although we cannot make too much of the survivals reported in these studies, they do appear higher than anticipated for patients with T3 and N2 disease.

**Adjuvant Radiation Therapy**

In practice, radiation therapy has commonly been given postoperatively in the hope of reducing the frequency of local recurrence. Five prospectively randomized trials of postoperative radiation therapy have now been reported. In the studies of Paterson and Russell and Bangma, postoperative radiation did not improve survival. These studies have been criticized for their lack of stratification for tumor histology and stage. In addition, the irradiation fields were relatively small. The large EORTC trial reported by Israel et al showed no survival advantage for resected squamous cell cancer although locoregional relapses were decreased. Only patients with NSCLC who had a complete resection of tumor and no involvement of regional nodes by tumor were treated in a study from the Institute Jules Bordet reported by Van Houette et al. Again, there was no statistically significant survival difference between the 2 groups, although in this study the irradiated group had a somewhat lower survival rate, especially after pneumonectomy. Postoperative irradiation did slightly reduce the frequency of locoregional relapses within the radiation field.

The Lung Cancer Study Group evaluated postoperative radiotherapy in completely resected stages 2 and 3 squamous cell cancer. Patients were randomized to (50 Gy in 5 weeks) or to a control arm. Careful intraoperative node sampling was done and patients were stratified according to stage, weight loss, age, and institution. Radiotherapy did not improve survival, although local recurrences were fewer. These studies seem to indicate that postoperative irradiation for both node-negative and node-positive patients does not affect overall survival but does reduce the frequency of local recurrence.

Preoperative radiotherapy has not been shown to benefit patients with operable lung cancer. Retrospective studies have suggested a possible role in those patients with borderline operability such as those with invasion of the chest wall or the apex of the lung. Whether preoperative radiotherapy is truly of value in these situations is still uncertain.

**Prophylactic Cranial Irradiation**

CNS metastases are a common site of distant metastases in non-small cell lung cancer, particularly with adenocarcinoma and are often the first site of metastases. A clear role for adjuvant cranial irradiation has not been established, although 1 retrospective study and 2 prospective studies demonstrate a reduction in CNS metastases with prophylactic PCI. The retrospective review by Jacobs et al of 78 cases of adenocarcinoma with N1 or N2 disease showed that only 5% of those receiving PCI developed brain metastases compared with 24% in those who did not (p = 0.06). Reduction in CNS metastases was also observed by Umsavasdi et al in patients with locally advanced NSCLC. The incidence of CNS metastases was 4% in the treated group compared with 27% in the control group (p = 0.002). The Veterans Administration Lung Group prospectively randomized 281 inoperable patients with NSCLC to PCI or not. Brain metastases developed in 13% of the non-PCI patients but in only 6% of the PCI patients. The reduction in brain metastases was most notable for patients with adenocarcinoma. No survival benefit has been seen in any of these studies, although the investigators suggest that morbidity was decreased. However, many clinicians remain apprehensive of the long-term morbidity of prophylactic cranial irradiation in this population, and further study of the late effects of PCI on neuropsychiatric function is necessary.

Improvement of the survival of surgically resected lung cancer is likely only to occur when truly effective systemic therapies are developed. The latest chemotherapy regimens offer a small possibility of improved survival, and the neoadjuvant approach, based on initial reports, warrants further careful evaluation. Postoperative radiotherapy has been shown to reduce the frequency of locoregional recurrence and may be complementary to chemotherapy in achieving long-term disease control. The adjuvant therapy trials of the future are likely to employ the products of our rapidly increasing knowledge of molecular biology. The second generation of immunotherapy trials, rather than employing crude bacterial adjuvants, will likely use monoclonal antibodies directed against growth factors or their receptors or immunoconjugates consisting of monoclonal
antibodies linked to radioisotopes, toxins, drugs, or immunologic agents. As well, specific cytokines such as TNF and interleukin 1 and 2 may increase tumor susceptibility to elements of the host's defense. Agents to overcome multidrug resistance or reduce the risk of metastases will likely be found and will need to be evaluated in the adjuvant situation. Our studies also need to integrate methods that minimize toxicity. The recombiant hematopoietic colony-stimulating factors have the potential to significantly reduce or eliminate morbidity from myelosuppression while permitting escalation of chemotherapy doses. The newer antiemetic agents and combinations also have the potential to substantially lessen treatment-related toxicity. All such evaluations should be carried out in carefully conducted randomized trials, building on the knowledge gained from earlier experience. Attention to careful clinical trials design with particular emphasis on intraoperative staging and patient stratification will help to ensure that the results achieved are true, clinically relevant observations. In this way, adjuvant treatment results for lung cancer will be advanced and optimal use will be made of patient resources.

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