GENERAL THORACIC SURGERY

RESULTS OF CANCER AND LEUKEMIA GROUP B PROTOCOL 8935

A multiinstitutional phase II trimodality trial for stage IIIA (N2) non-small-cell lung cancer

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From October 1989 to February 1992, 74 patients with mediastinoscopically staged IIIA (N2) non-small-cell lung cancer from 30 CALGB-affiliated hospitals received two cycles of preresectional cisplatin and vinblastine chemotherapy. Patients with responsive or stable disease underwent standardized surgical resection and radical lymphadenectomy. Patients who underwent resection received sequential adjuvant therapy with two cycles of cisplatin and vinblastine, followed by thoracic irradiation (54 Gy after complete resection and 59.4 Gy after incomplete resection or no resection at 1.8 Gy per fraction). There were no radiographic complete responses to the neoadjuvant chemotherapy, although 65 (88%) patients had either a response or no disease progression. During induction chemotherapy, disease progressed in seven patients (9%). Sixty-three patients (86%) had exploratory thoracotomy, and 46 of those (75%) had resectable lesions. A complete surgical resection was accomplished in 23 patients, and 23 patients had an incomplete resection with either a diseased margin or diseased highest node resected. Operative mortality was 3.2% (2/63). In 10 patients (22% of the 46 having resection) the disease was pathologically downstaged. There was no correlation between radiographic response to the induction chemotherapy and downstaging at surgical resection. The full protocol was completed by 33 patients (45% of original cohort). Overall survival at 3 years was 23%. Patients undergoing resection had significantly improved survival at 3 years compared with patients not having resection: 46% for complete resection (median 20.9 months), 25% for incomplete resection (median 17.8 months), and 0% for no resection (median 8.5 months). Five deaths occurred during the treatment period. A total of 18 of the 46 (39%) patients who underwent resection are either alive and disease-free or have died without recurrence. (*J THORAC CARDIOVASC SURG* 1995;109:473-85)

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Surgical resection alone in stage IIIA (N2) non-small-cell lung cancer is associated with poor survival. Five-year survival ranges between 5% for clinically diagnosed N2 disease to 29% for occult N2 disease found on pathologic staging.¹⁻³ Less than 10% of patients found to have occult N2 disease by preresectional staging mediastinoscopy who are then treated with surgery and postoperative radiation therapy achieve 5-year survival.⁴ Similarly, radiation therapy alone consistently produces median survivals of less than 1 year and 5-year survivals between 5% and 10%.⁵⁻⁷

Preoperative^{4, 8, 9} and postoperative radiation

therapy¹⁰ has been used in an attempt to improve survival in these patients. Although preoperative radiation therapy improves resectability rates and both strategies improve local control, neither strategy improves survival. The pattern of treatment failure is altered with radiation therapy. Local failure is reduced but relapse in distant sites increases, suggesting micrometastatic disease at the time of resection.

Multimodality combinations such as preresectional chemotherapy followed by surgery and adjuvant chemoradiation therapy offer several theoretical advantages.¹¹ The preresectional delivery of the

chemotherapeutic agents is not adversely affected by alterations in regional blood flow that accompany surgical scar or radiation therapy. The chemotherapy, if effective, may lead to increased resectability rates, downstaging of the original extent of disease, and a decrease in the risk of tumor dissemination during surgical resection. The chemotherapy may serve as a radiosensitizing agent with enhancement of local control and may lead to increased control of systemic disease by treating micrometastases.

These potential advantages are counterbalanced by theoretical disadvantages. Preoperative chemotherapy is accompanied by a delay before resection with possible disease progression during that interval. The induction therapy can be expected to carry its own morbidity and possible mortality, and the combination of treatment modalities within a short time frame may augment the individual treatment toxicities. The prolonged treatment regimen may also adversely affect the period of remission that the patient can expect before disease progression and may lead to a drop in functional status. Finally, if the induction chemotherapy is not well tolerated, surgical resection may not be feasible, so that the single best mode of therapy is precluded.

Several trials of combined multimodality protocols in the treatment of patients with stage IIIA non-small-cell lung cancer have been reported.¹²⁻¹⁷ Despite this, the best treatment for patients with N2 disease remains unclear for several reasons. First, in a number of trials,^{12-14, 17} eligible patients have included those whose disease was staged IIIA by noninvasive imaging of the mediastinum, although there is evidence that a considerable number of patients will have false-positive and false-negative results from noninvasive staging.¹⁸ Second, some trials^{13, 14, 17, 19} have combined patients considered to have stage IIIA disease by virtue of chest wall or mediastinal pleural invasion (T3 N0 or T3 N1) with those who have diseased ipsilateral mediastinal nodes (N2). This former group of patients may have a slightly better prognosis than patients with ipsilateral mediastinal node disease, so that it is difficult to judge the efficacy of new treatments on each of the two separate subsets of IIIA non-small-cell lung cancer.^{2, 3, 20}

The purpose of this prospective phase II multi-institutional trial of the Cancer and Leukemia Group B (CALGB protocol 8935) was to assess the feasibility, efficacy, and toxicity of neoadjuvant chemotherapy and postoperative, sequential chemotherapy and thoracic radiotherapy in the treatment of

patients with pathologically confirmed stage IIIA (N2) non-small-cell lung cancer. Specifically, the trial sought to quantify the percentage of patients undergoing thoracotomy and resection, the pathologic response to the induction chemotherapy, the toxicity associated with combined treatments, the surgical morbidity and mortality, the long-term survival, and the patterns of recurrence for patients treated in this trimodality manner.

Patients and methods

Patient eligibility. Only patients with histologically documented stage IIIA non-small-cell lung cancer with metastases to the ipsilateral mediastinal nodes (T1-3, N2) were eligible. Patients with T3, N0-1 lesions were ineligible.

All patients underwent a staging cervical mediastinoscopy with evaluation of bilateral node stations 2 and 4 and subcarinal station 7 as defined by the American Thoracic Society.²¹ For patients with primary lesions of the left upper lobe, an initial anterior mediastinotomy with biopsy of station 5 or 6 nodes was generally done. If station 5 or 6 was involved, the anterior mediastinotomy was always followed by cervical mediastinoscopy and contralateral lymph node biopsy before study entry. Patients with extracapsular and intracapsular lymph node involvement were eligible. The results of the staging procedures were documented and patients were evaluated by a thoracic surgeon, medical oncologist, and radiation oncologist before the initiation of the treatment protocol. The primary tumor size was determined and followed by a chest computed tomographic (CT) scan or radiograph to assess response to chemotherapy.

In addition to histologic evidence of disease, eligibility criteria also included the following: at least 18 years of age, informed consent, expected survival 2 years or more, Eastern Cooperative Oncology Group performance status of 0 to 1, predicted postoperative forced expiratory volume in 1 second (FEV₁) greater than 900 ml, and candidate for postoperative thoracic irradiation. Except for postobstructive pneumonia, all active infections had to be controlled. Presence of serious psychiatric or medical illness that was perceived to preclude informed consent or survival for 2 years or less was grounds for ineligibility. The required laboratory values were as follows: granulocytes more than 1800/ μ l; platelets more than 100,000/ μ l; hemoglobin value more than 10 gm/dl; total bilirubin level less than 1.5 mg/dl; blood urea nitrogen level less than 1.5 times normal; creatinine content less than 1.5 mg/dl or creatinine clearance 60 ml/min or more; room air oxygen tension more than 50 torr; and carbon dioxide tension less than 50 torr.

Treatment. The treatment plan is graphically summarized in the schema of Fig. 1. Planned treatment began with vinblastine 5 mg/m² intravenous (IV) bolus given weekly for 5 weeks (days 1, 8, 15, 22, and 29) and two doses of cisplatin 100 mg/m² IV given 4 weeks apart (days 1 and 29) before surgical resection.

After induction chemotherapy, the disease was clinically restaged in all patients. Patients with progressive

Fig. 1. Schema summarizing the treatment plan in CALGB protocol 8935. Induction chemotherapy was two cycles of vinblastine (V) 5 mg/m² per week and cisplatin (P) 100 mg/m² given on days 1 and 29. Surgical resection was generally on day 57. Adjuvant chemotherapy was two additional cycles of vinblastine 5 mg/m² per week and cisplatin 100 mg/m² given on days 92 and 120. Adjuvant radiotherapy (XRT) was then given from day 155 to approximately day 200.

disease during neoadjuvant chemotherapy were removed from the study and followed up for survival. *Progressive disease* was defined as an increase of more than 25% in the primary lesion over the size present at study entry or a definite increase in tumor size along with the appearance of new lesions. *Stable disease* was defined as a change in the size of the measured lesions between a 50% reduction and a 25% increase with no additional disease discovered. *Partial response* was defined as a reduction of greater than 50% in the sum of the products of the cross-sectional diameters of all measurable lesions and the absence of new lesions. *Complete response* was defined as the disappearance of all measurable intrathoracic disease. Patients with response or stable disease underwent thoracotomy and attempted standard curative resection approximately 4 weeks after the last dose of chemotherapy.

The surgical procedure was based on the extent of tumor at the time of initial presentation rather than at the time of thoracotomy and consisted of a lobectomy, sleeve resection, bilobectomy, or pneumonectomy. The choice of operative procedure was made by the attending surgeon and was based on curative intent while preserving as much functional lung volume as possible.

A complete ipsilateral superior mediastinal lymphadenectomy was performed in all cases (resection of ipsilateral nodal stations 2, 4, 7, and 10). For patients with primary lower lobe lesions, station 9 lymph nodes were also resected. Patients with primary left upper lobe lesions also had resection of stations 5 and 6 lymph nodes. All ipsilateral hilar nodes were removed en bloc with the primary surgical specimen. Additionally, any grossly abnormal nodes found at operation outside these stations were removed and examined. All resected nodal groups were individually labeled by the surgeon at the time of the operation.

Patients were considered to have undergone resection so long as the primary tumor was excised and mediastinal node dissection was completed. Disease-free margins were considered to indicate complete resection. Diseased margins, diseased highest node sampled, and minimal gross disease left behind were considered to indicate incomplete resection. Known areas of residual tumor were clipped for later use in determining radiotherapy portals. The surgeon was obligated to obtain biopsy tissue of residual disease in patients who could not undergo resection. If thoracotomy revealed unresectable disease, the patient remained in the protocol but received no further chemotherapy and proceeded directly to postoperative thoracic irradiation to 59.4 Gy.

Patients who underwent resection began postoperative chemotherapy 4 to 6 weeks after thoracotomy. Adjuvant chemotherapy consisted of vinblastine 5 mg/m² IV bolus biweekly for a total of four doses beginning on day 92 of treatment (days 92, 106, 120, and 134) and two doses of cisplatin 100 mg/m² IV 4 weeks apart (days 92 and 120).

After adjuvant chemotherapy, patients underwent repeat pulmonary function tests before the start of adjuvant radiation therapy. Patients with an FEV₁ of 900 ml or more after chemotherapy and surgery began radiotherapy within 35 days of the last chemotherapy treatment (90 days from thoracotomy). Patients with an FEV₁ less than 900 ml did not receive adjuvant radiotherapy but were followed up for survival.

Patients having complete resection received a conventionally fractionated total thoracic dose of 54.0 Gy of adjuvant radiation therapy by means of a shrinking field technique. The initial volume treated the bronchial stump, ipsilateral hilum, bilateral supraclavicular fossae, upper mediastinum, subcarinal space, and any initially involved nodal stations within the lower mediastinum to 36.0 to

Table I. Patient demographics and clinical staging in CALGB protocol 8935 (*n* = 74 patients with stage IIIA (N2) non-small-cell lung carcinoma)

	No.	Percent
Sex		
Male	50	68
Female	24	33
Race		
White	69	93
Black	5	7
Age (yr)		
Median	52	
Range	45-75	
40-49	15	20
50-59	26	35
60-69	27	37
70+	6	8
Weight loss		
<5%	63	85
>5%	7	10
Unknown	4	6
Symptoms		
<3 mo	42	57
3-6 mo	18	24
>3 mo	7	10
Unknown	7	10
Histology		
Adenocarcinoma	26	35
Squamous cell	32	43
Large-cell	7	10
Undifferentiated	9	12
Primary		
T1	7	10
T2	50	67
T3	17	23

39.6 Gy at 1.8 Gy per fraction once a day. The "boost volume" treated the bronchial stump, ipsilateral hilum, and initially involved mediastinal nodal stations to a total cumulative dose of 54.0 Gy also at 1.8 Gy per fraction.

Patients with incompletely resected or unresectable disease received a total thoracic dose of 59.4 Gy at 1.8 Gy per fraction once a day. The initial volume for these patients was the same as for those patients with completely resected disease but also included any residual or gross disease at the primary site. This initial volume was also treated to 36.0 to 39.0 Gy. The boost volume was also the same as for those patients with completely resected disease but now included any initial sites of gross or residual tumor and involved mediastinal nodal stations. However, this boost volume was treated to a total cumulative dose of 59.4 Gy.

Patients who were ineligible for continuation in the study because of progressive disease or other conditions were eligible for palliative radiotherapy at the discretion of the radiotherapist. No prophylactic cranial irradiation was used. All radiotherapy treatments were centrally reviewed by the Quality Assurance Review Center.

Follow-up. Patients are being evaluated in an outpatient clinic every 2 months for 2 years, then every 4 months for 2 years, and yearly thereafter. Clinic visits included a history, physical examination, and posteroanterior and lateral chest x-ray films. Head CT, chest CT, and bone scans were required when clinical signs of recurrence developed. Histologic confirmation of recurrence was strongly encouraged.

Statistics. The Kaplan-Meier product-limit estimator²² was used to estimate the survival curve and failure-free survival curves. The log-rank test was used to compare the survival experience of subgroups.

Results

Patients characteristics. From October 1989 to February 1992, 80 patients from 30 CALGB-affiliated hospitals were enrolled in the study. Six patients were ultimately declared ineligible, leaving 74 patients for analysis. The six ineligible patients included four patients found to have stage IIIB disease (two had T4 primary tumors, one had a malignant pleural effusion, and one had contralateral mediastinal node disease), one patient found to have distant metastases at the time of registration, and one patient who withdrew consent and was not treated.

The demographic variables and tumor classification of the 74 evaluable patients are summarized in Table I. Fifty patients were male (68%) and 24 female (33%). Sixty-nine patients were white (83%) and five were black (7%). Ages ranged from 45 to 75 years with a median of 52 years. All patients studied were Eastern Cooperative Oncology Group performance status 0-1. Weight loss in the previous 6 months before study entry was less than 5% in 63 (85%) and greater than 5% in seven (10%) patients. Symptoms had been present for less than 3 months in 42 patients (57%), greater than 3 months in 25 (34%), and present for an unknown period in seven (10%). Histologic cell type of the final pathology specimen showed 26 patients had adenocarcinoma (35%), 32 had squamous (43%), seven had large-cell (10%), and nine had undifferentiated (12%) non-small-cell lung cancer. The primary tumor at initial presentation was classified clinically as T1 in seven (10%), T2 in 50 (67%), and T3 in 17 (23%). All patients had N2 nodal disease.

All 74 patients had surgical staging of the mediastinal lymph nodes with cervical mediastinoscopy or anterior mediastinotomy. All patients had histologically proved N2 disease of the ipsilateral mediastinum.

Response to induction chemotherapy. None of the patients had radiographic complete responses to

Fig. 2. Progression of patients through protocol treatment. Of the 74 patients offered preresectional chemotherapy, 63 patients progressed to exploratory thoracotomy. At operation, 17 patients had unresectable lesions and were followed-up for survival, with 11 of these patients receiving adjuvant radiotherapy (RT). Of the 23 patients with an incomplete resection, 20 received adjuvant chemotherapy and 15 of these completed the entire adjuvant protocol. Of the 23 patients with a complete resection, 20 received adjuvant chemotherapy and 16 of these completed the entire adjuvant protocol.

induction chemotherapy. Sixty-five (88%) had a partial response or stable disease, six (8%) had progression of disease, and three (4%) had an unevaluable radiographic response.

Fig. 2 summarizes the flow of the patient cohort through the treatment protocol. Sixty-three (86%) of the 74 patients proceeded to exploratory thoracotomy whereas 11 patients did not continue the protocol beyond the induction chemotherapy. Six of the 11 patients had clinical progression of their tumor at restaging: one of six patients received a single cycle of chemotherapy and was then found to have an increase in the size of the primary and satellite pulmonary lesions, three of six patients received two cycles of anterior chemotherapy and had a greater than 25% increase in the size of the primary lesion, and two of six patients had two cycles of chemotherapy and were then found to have distant metastases (one liver and one bone). One of the 11 patients received two cycles of anterior chemotherapy with a partial radiographic response in the tumor but then refused to have the operation. Another of the 11 patients was lost to follow-up for a 2-month period after having a partial response to the two cycles of chemotherapy. When she returned, the primary tumor had progressed to stage IIIB and she was treated off protocol with radiation therapy.

The participation of two of the 11 patients was terminated because of treatment toxicities. The first patient was a 78-year-old man who had moderately severe bone marrow suppression, esophagitis, colonic ulcers, and peripheral edema after a single cycle of chemotherapy with deterioration in his medical condition necessitating a prolonged stay in the intensive care unit. The second patient was a 77-year-old man with reversible severe nephrotoxicity after a single cycle of chemotherapy.

Grade 3 (severe) and grade 4 (life-threatening) toxicities of the induction chemotherapy are summarized in Table II. No grade 5 (lethal) toxicities occurred. The most common toxicity was myelosuppression, with severe granulocytopenia developing in 67% of the 74 patients. One patient died during the induction chemotherapy from a pulmonary embolus. This was not considered a treatment-related death.

Surgical results. Forty-six patients (75% of the 63 undergoing exploration) had resectable disease. Twenty-three patients (36.5%) had a complete surgical resection, 23 patients (36.5%) had an incomplete resection (seven had a diseased margin, 11 had a diseased highest node resected, and four had both a diseased margin and highest node), and 17 patients (27%) had unresectable lesions. Twenty-five patients were treated with a curative lobectomy, 17

Table II. Major toxicities of induction chemotherapy (*n* = 74)

	Grade 3		Grade 4	
	No.	%	No.	%
White blood cells	22	28	9	11
Granulocytes	14	18	38	49
Lymphocytes	13	22	1	1
Infection	5	6	0	
Nausea	4	5	0	
Diarrhea	2	3	1	1
Azotemia	4	5	0	
Renal failure	0		1	1
Stomatitis	0		1	1
Dyspnea	0		1	1
Edema	1	1	1	1
Total	65		53	

with pneumonectomy, two with a sleeve lobectomy, and two with a lobectomy and chest wall resection.

In 10 patients (22% of the 46 patients having resection) the tumor was pathologically downstaged at resection: four patients (9%) had only N1 diseased nodes (stage II) and six (13%) patients had no tumor identified in N1 or N2 nodes (stage I). Ten patients (22%) had a diseased level 2 node and 10 patients (22%) had a diseased level 7 node in the pathologic specimen. No pathologic complete responses were obtained.

There was no correlation between radiographic response to the neoadjuvant chemotherapy and downstaging at surgical resection. All patients whose tumor class was downstaged to stage II disease had been listed as having stable disease. Of the six patients whose tumor class was downstaged to stage I, three had stable disease, two a partial response to the chemotherapy, and one had an unevaluable response. Of seven patients found to have only microscopic foci of viable tumor within the primary lesion, four had been classified with a stable response (all with a T2 original lesion) and three a partial response to the chemotherapy (one originally with a T3 lesion and two with T2 primary tumors).

The operative mortality was 3.2% (two patients). One patient had postoperative respiratory failure and died on postoperative day 151, and the other patient died on postoperative day 51 of postoperative pneumonia. Both deaths are considered treatment related.

Postoperative morbidity is summarized in Table III. Five patients (9% of those reported) had postoperative pneumonia, four (6% of reported) had

Table III. Operative morbidity (*n* = 63)

	No.	Percent
Supraventricular tachycardia	4	7
Pneumonia	5	9
Tracheostomy	2	3
Respiratory failure	2	3
Bronchopleural fistula and empyema	3	5
Wound infection	1	2
Atelectasis necessitating bronchoscopy	1	2

supraventricular tachycardias, and two (3% of reported) had respiratory failure necessitating reintubation and mechanical ventilation. A bronchopleural fistula and empyema developed in three patients (5% of reported).

Sequential adjuvant therapy. Thirty-three patients of the 46 undergoing resection (69%) completed the full adjuvant protocol.

Of the 46 patients undergoing resection, six received no additional protocol therapy. One of the six patients with an incomplete resection was identified as having occult brain metastases after a seizure in the immediate postoperative period. One patient with an incomplete resection and one patient with a complete resection died after the operation, as reported earlier. Another patient with a complete resection and an additional patient with an incomplete resection refused further therapy but are included in the survival analysis according to the type of resection. Eleven of the 17 patients with unresectable lesions received postoperative radiation therapy off protocol, and an additional six received no further therapy.

Grade 3 (severe) and grade 4 (life-threatening) toxicities associated with postoperative chemotherapy are summarized in Table IV. No grade 5 (lethal) toxicities to the adjuvant chemotherapy developed. Myelosuppression was the most common toxicity, with 43% of patients having severe granulocytopenia.

Six patients discontinued protocol therapy during the period of postoperative chemotherapy: two had progressive disease, two patients withdrew consent for further therapy, and two patients died (one of a pulmonary embolus and the other of sepsis).

Of the 44 patients eligible for thoracic radiation therapy, 42 (95%) completed irradiation as planned; this group included 16 of 17 patients with completely resected disease, 16 of 16 patients with incompletely resected disease, and 10 of 11 with

unresectable tumor. One of the two patients failing to complete irradiation had an unresectable tumor that progressed after the patient had received only 16.2 Gy to the thorax; the other patient had undergone resection and was treated to 50.4 Gy until radiation therapy was discontinued because of grade 3 toxicity (esophagitis, anorexia, and pneumonitis). Grade 3 (severe) and grade 4 (life-threatening) toxicities that developed during adjuvant radiotherapy are summarized in Table IV. The hematologic toxicities that occurred during the period of radiation therapy are believed to be late toxic effects of the postoperative chemotherapy. No grade 5 (lethal) toxicities to adjuvant radiotherapy developed. Overall, radiation-related grade 3 or greater toxicity measured 2.4%, indicating consolidative radiation therapy was fairly well tolerated after "sandwich chemotherapy" and surgery.

Survival and recurrence. Overall, five deaths occurred during treatment (6.7% of the full cohort): one because of pulmonary embolus during the induction chemotherapy, two because of operative complications, and two during adjuvant chemotherapy. Four of the five deaths (5.4% of the full cohort) were considered treatment related.

Median follow-up of patients currently alive is 23.6 months. Overall 1-year, 2-year, and 3-year survivals are 63%, 34%, and 23%, respectively. Fig. 3 stratifies survival after thoracotomy according to type of resection with corresponding numbers of patients at risk per year survival. Median survival for patients with a complete resection was 20.9 months, compared with 17.8 months for those with incomplete resections and 8.5 months for those without resection ($p = 0.03$). The curves for the patients having complete resection and incomplete resection are better than those of patients with unresectable tumors throughout their course. Three-year survival was 46% (95% confidence interval of 19% to 73%) for patients having complete resection, 25% (95% confidence interval 10% to 47%) for those having incomplete resection, and 0% for those with unresectable lesions. Three-year failure-free survival was 36% after complete resection and 21% after incomplete resection. Fig. 4 shows disease-free survival of those patients who underwent resection and completed the full protocol treatment, stratified by type of resection. Seven of the 16 (44%) patients with complete resection and full treatment remain disease-free, compared with four of the 17 (24%) patients with an incomplete resection and full treatment ($p =$ not significant).

Table IV. Major toxicities of sequential adjuvant therapy

	Grade 3		Grade 4	
	No.	%	No.	%
Induction chemotherapy ($n = 40$)				
White blood cells	6	15	1	3
Granulocytes	3	8	14	35
Lymphocytes	6	15	1	3
Nausea	5	13	0	
Azotemia	3	8	0	
Cardiac function	1	3	0	
Dyspnea	1	3	0	
Hearing	1	3	0	
Total	26		16	
Radiation therapy ($n = 33$)				
White blood cells	1	3	0	
Granulocytes	0		1	3
Lymphocytes	5	15	8	24
Stomatitis	1	3	0	
Pneumonitis	1	3		
Fever	1	3		
Total	9		9	

Recurrence has been detected in 12 of the 23 patients who had complete resection: local disease only in one, distant disease only in nine, and both local and distant disease in two. One patient has died while remaining disease-free, one patient has died with an unknown recurrence status, and nine (39%) patients remain alive and disease-free. Of the 23 patients who had incomplete resection, 15 have had a recurrence: none with local disease only, seven patients with distant disease only, and eight patients with both local and distant disease. Three patients have died while remaining disease-free and five (22%) patients remain alive and disease-free. Eighteen of the 46 (39%) patients who had resection are either alive and disease-free or have died without recurrence. Of the 27 recurrences, 11 (41%) have included brain metastases.

Discussion

CALGB protocol 8935 was designed in 1989 as a multiinstitutional phase II trial of high-intensity trimodality therapy for patients with surgically staged IIIA (N2) non-small-cell lung cancer. It combined two cycles of neoadjuvant cisplatin and vinblastine with standardized surgical resection and radical lymphadenectomy, then sequential adjuvant therapy of two additional cycles of cisplatin and vinblastine followed by 54 to 60 Gy radiation therapy. Because surgical staging of the mediastinal nodes was required before protocol entry, a homo-

Fig. 3. Overall Kaplan-Meier survival estimates in months after thoracotomy stratified by type of resection. Survival is presented for patients with a complete resection (CR), incomplete or partial resections (PR), and unresectable lesions (UN). Numbers in parentheses indicate patients at risk at that time.

geneous group of patients with stage IIIA (N2) non-small-cell lung cancer who had a poor prognosis was selected for analysis.

Conducting this protocol proved to be feasible in a multiinstitutional setting. Enrollment for this phase II trial was completed in 28 months. Despite the participation of 30 separate teams of surgeons, medical oncologists, radiation oncologists, surgical pathologists, and data managers, protocol treatment and its provisions were carried out as planned in the 74 eligible patients. Disease progression during induction chemotherapy was uncommon, occurring in seven of 74 patients (9%). The treatment plan was well tolerated with a total of four (5%) treatment-related deaths (two after operation and two after chemotherapy). The resectability rate was high. Eighty-six percent of all patients underwent exploration and 75% of those patients underwent resection. The operative mortality (3.2%) and morbidity (30%) were comparable to previous thoracotomy-associated rates without the use of chemotherapy or radiation therapy.²³ Downstaging on the basis of the final pathologic specimen was possible in 22% of the patients subjected to resection. The addition of adjuvant chemotherapy and sequential radiation therapy may account for the lack of difference in the survival curves between the patients having complete and incomplete resection for the first 2 years of follow-up, the lack of difference in the failure-free survival for the first 18 months after thoracotomy,

and the lack of difference in recurrence rates. The divergence in these survival curves after 2 years, however, suggests that complete surgical resection still plays a substantial role in long-term survival in this stage of disease. The greatest contribution of this treatment plan to the management of patients with N2 disease may be the increased resectability rates, with a concomitant increase in the ability to completely resect the tumor, because the 3-year survival of 46% was achieved in patients who had complete resection. Additionally, the majority of recurrences occurred in distant sites rather than local or locoregional areas.

Several other reports of induction chemotherapy or combined chemoradiation therapy have observed a high response rate, high resectability rate, and improved survival in patients with a complete resection. The resectability rate of 62% of all eligible patients in this study compares favorably with the single-institution induction chemotherapy trial from Toronto (56%)¹⁶ and the multiinstitutional combined induction chemoradiation trial from the Lung Cancer Study Group (52%)¹⁴ and the CALGB (58%).²⁴ The long-term survival in the patients having complete resection agrees with the Memorial Sloan-Kettering Cancer Center (MSKCC) single-institution experience after complete resection following induction chemotherapy (41% 3-year survival).¹²

It is important to note that although the survival data of these trials is similar, the Toronto¹⁶ and

Fig. 4. Disease-free survival estimates in months since completion of radiotherapy (RT) stratified by type of resection. Disease-free survival of patients with a complete resection (CR) and those with incomplete resection (PR) are shown. Numbers in parentheses indicate patients at risk at that time.

MSKCC¹² trials involved a variable overall treatment plan with only two to three cycles of induction chemotherapy and no further chemotherapy in patients having complete resection. This protocol called for adjuvant chemotherapy to all but the patients with unresectable lesions, and yet the treatment toxicities in our trial were less than those reported with the mitomycin/vinblastine/cisplatin combinations used in the Toronto and MSKCC trials. Specifically, less neurotoxicity, ototoxicity, and pulmonary toxicity and fewer treatment-related deaths occurred in this trial. The incidence of treatment-related death was 15.4% in the Toronto trial and 15% in the CALGB concomitant chemoradiation trial, compared with a 5.1% incidence in the MSKCC trial and a 5.4% incidence in this trial.

The improved toxicity rates in our trial may be due to the lack of mitomycin in the treatment regimen. Additionally, there were no cases of post-obstructive pneumonitis at study entry. Unlike the previous CALGB trial, this trial used sequential chemotherapy and radiation therapy instead of concomitant therapy, which may produce less cumulative toxicity.

Roth¹⁹ recently reported a single-institution phase III trial of patients with stage IIIA disease. The two arms included preoperative chemotherapy followed by resection and adjuvant chemotherapy versus surgery alone. Sixty patients (including 16 patients with T3 N0-1) were accrued before the trial was stopped because of compelling differences in

survival. Survival at 3 years was 56% in the chemotherapy-surgery arm and 15% in the surgery-alone group. Although these results further support multimodality treatment of stage IIIA disease, they also point out two caveats for future studies. Only patients with surgically documented N2 disease should be entered into these protocols, because survivals after resection of T3 N0-1 lesions have been shown to be different from those with N2 disease.^{2, 25} The utility of a surgery-alone arm in a trial of therapy for stage IIIA non-small-cell lung cancer may be sub-optimal.

The Southwest Oncology Group has recently published their most recent phase II trial assessing multimodality therapy in stage IIIA and IIIB non-small-cell lung cancer.²⁶ As was the case in this trial, all patients had surgical staging of their disease before enrollment. Included in the 126 patients studied were 51 patients classified with stage IIIB disease by either T4 tumor status or N3 nodal disease. Their 2-year survivals for IIIB disease with T4 ($n = 24$ patients) or N3 ($n = 27$ patients) were 50% and 24%, respectively.

These most recent phase II trial results add to the growing body of evidence that multimodality treatment regimens in advanced stage non-small-cell lung cancer can be performed in a multiinstitutional framework with acceptable treatment-related morbidity and mortality.

The benefits of multimodality treatment are not without cost. This treatment regimen was a long and

difficult course for the patients that participated. Only 42% of the entry patients completed the full protocol. Eleven patients (15%) discontinued treatment during neoadjuvant chemotherapy, 12 patients (16%) discontinued after thoracotomy, six patients (8%) discontinued during postoperative chemotherapy, and two patients (3%) discontinued before the completion of the radiation therapy. The time taken for the entire treatment was approximately 200 days (6.5 months) with an overall median survival of 15 months and a chance at a best median survival of 21 months. However, a substantial subgroup of patients seem to have been granted a long-term disease-free survival period by the treatment protocol. At the time that this trial was designed, there was little demand for a reliable measure of the impact of treatment on the quality of life of the patient. These results highlight the difficulty in assessing the impact of new treatments for stage IIIA (N2) disease: the balance of the risk of toxicity, early death, and negative impact on quality of life to the chance for a long period of improved life. A reliable measure to quantify the impact of such treatments on the quality of life of the patient is sorely needed.

Combined trimodality therapy trials of surgically staged IIIA (N2) non-small-cell lung cancer can be conducted efficiently in a multiinstitutional setting. Several future directions remain. The survival benefit suggested by combined modality phase II trials needs to be substantiated by carefully designed and executed multiinstitutional phase III trials. If the survival benefit is substantiated, treatment combinations must then be evaluated for the appropriate timing of interventions. Further studies led by cooperative oncology groups may soon change the standard of care for this challenging subgroup of patients.

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The Cancer and Leukemia Group B Thoracic Surgery Group

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Discussion

Dr. Benedict D. T. Daly (Boston, Mass.) Because stage IIIA disease by definition is anatomically resectable, presumably the rationale for choosing induction chemotherapy as the first treatment modality is to adversely affect the metastases likely to be already present in a majority of the patients. Judging by the survival results and the prevalence of distant metastases on follow-up, it was at least efficacious in serving this purpose in 40% of the patients. Furthermore, it necessitated a 2-month delay in surgical treatment. During this interval, a subset of patients (8%) was identified who would not benefit from the operation. Thus approximately 50% of the patients benefited from induction chemotherapy. On the other hand, only 73% of the patients undergoing operation had resection, and only half of these had curative resections. The

induction chemotherapy, therefore, was not efficacious in treating the local disease in a majority of the patients. Although the disease was downstaged in 22% of the patients and 50% of the disease in level 2 and level 7 nodes was eradicated, 25% of the patients undergoing resection had tumor at the margin of resection and one third had tumor in the highest node resected. Postoperative adjuvant radiation was, however, delayed 2 months by two cycles of postoperative chemotherapy in those patients who had incomplete resection.

This is an excellent study. It has demonstrated the efficacy of chemotherapy in eradicating, or at least delaying, the emergence of distant metastases. But it has shown the need for earlier radiation given concomitantly with preoperative or postoperative chemotherapy, to provide better local control and ideally to improve long-term results.

I have three questions. What was found at operation that made the lesions in 17 patients unresectable, and do you think giving the radiation preoperatively in these patients could have improved the resectability rate? Was there a difference or trend in survival based on histologic characteristics or the number of nodal stations involved with tumor? Finally, when you reported that patients had diseased margins, were you referring to the bronchial mucosa, the stapled fissures, or the peribronchial lymphatics?

Dr. Sugarbaker. Thank you very much, Dr. Daly. The majority of the patients with unresectable disease were found to have extension of nodal disease into mediastinum that was not determined by preoperative CT scanning. It may be that with better imaging, particularly with the use of magnetic resonance imaging, we may get a better idea of where the nodes are actually involving the vena cava; that was the major structure that was involved in that group of patients. The proximal carina and trachea were also significant structures that were not determined to be involved before thoracotomy.

Dr. Willard A. Fry (Evanston, Ill.). What do you mean by T4 nodal involvement?

Dr. Sugarbaker. The definition is unresectable nodal disease that has invaded the mediastinum and is contiguous with the primary lesion.

Dr. Fry. Is this local tumor advancement, not nodal?

Dr. Sugarbaker. In these patients the nodal disease in the mediastinum was involving the cava or the trachea and, therefore, was deemed unresectable when the operative notes were reviewed.

The CALGB did not use preoperative radiotherapy to help downstage these lesions before surgical resection because of reports by Wanebo and others that have suggested that the perioperative mortality in patients receiving concomitant radiation/chemotherapy is substantial; therefore, a single modality induction treatment strategy was used. The efficacy of preoperative radiotherapy needs to be evaluated, and in selected patients it may be of benefit. Conducting such a trial in a multiinstitutional setting, where generic conclusions are to be drawn, conclusions that will affect a large number of patients treated with lung cancer, is problematic given the high mortality rates noted. I am not sure it is feasible even in single-institution reports.

The trend in survival in terms of nodal stations did not hold up in this group of patients. We could not *trend* either the number of mediastinal nodes involved or level 7 subcarinal nodes, which in some studies have been suggested to foretell a very poor prognosis. In terms of the number of nodes or nodal stations, there was no correlation with survival at this time.

There was no consistent group of diseased margins. Some were vascular margins, pulmonary artery margins; several were bronchial margins; and there was one stapled fissure margin and one margin at the apex.

Dr. Robert J. Ginsberg (New York, N.Y.). Dr. Sugarbaker, I congratulate you for trying to standardize preoperative staging in this difficult group of patients.

You indicated that in left upper lobe tumors surgeons would obtain biopsy tissue from level 5 and then ensure that the patient did not have contralateral nodes. How was that done?

Dr. Sugarbaker. It was done by cervical and anterior mediastinoscopy.

Dr. Ginsberg. They obtained biopsy tissue from the right four, I would presume, not from levels 2L and 4L. Is that correct?

Dr. Sugarbaker. We encouraged that a biopsy of one contralateral node be done.

Dr. Ginsberg. In left upper lobe tumors, according to your paper, complete node dissection was done, including levels 5, 4, and 2. Is that correct?

Dr. Sugarbaker. That is correct. Node sampling was attempted in all of those areas.

Dr. Ginsberg. The manuscript said "dissection," not node sampling.

We have to define what *contralateral nodes* actually means. In the Lung Cancer Study Group map, the midline defines the contralateral nodes. I think that within cooperative groups everybody should define what contralateral nodes are. I presumed from reading your paper that anything in the superior mediastinum was a contralateral node, not just right paratracheal, but I may be wrong.

The other thing to remember is that the prognosis with solitary level 5 and 6 node involvement has been well defined in many studies now in Europe, Canada, and the United States.

We showed at the recent VATS course that without any kind of induction chemotherapy or chemoradiotherapy, the overall survival if only levels 5 and 6 are involved is better than what you reported for even the best group of patients with resected N2 disease and equal that seen for resected N1 disease. How many of your patients had only level 5 and 6 nodes?

Dr. Sugarbaker. I think there were only a couple of patients.

Dr. Ginsberg. We must decide whether this group of patients should be involved in induction trials, for unresectable N2 disease and, if they are, they should be stratified because they are such a good prognostic group.

Dr. Sugarbaker. Are you referring here to single-institutional trials or to multiinstitutional trials?

Dr. Ginsberg. I am just talking about the survival of patients with solitary level 5 and 6 nodes as reported by Vogt-Moykopf, Patterson, and our own institution, when they only have solitary level 5 and 6 nodes. If a trial is

contaminated by a large number of solitary level 5 and 6 nodes, there may be a more optimistic result because of it.

I certainly concur with you that multiinstitutional trials should be done. I think it has been well shown now with your study and previously with the Lung Cancer Study Group and Southwest Oncology Group that induction chemotherapy or chemoradiotherapy protocols can be done multiinstitutionally with reasonable mortality. I think the large cooperative groups now should concentrate on one phase III trial comparing the combined modality approach with what is now standard, or considered standard treatment by most places around the world, and that is chemoradiotherapy without any operation. I think that further phase III trials should be done only if new and exciting combinations of chemotherapy or chemoradiotherapy appear to be efficacious in nonsurgical phase II trials. We have gone through the whole gamut now of induction chemotherapy and chemoradiotherapy phase II "feasibility" trials, and it is time we answered the original question we wanted to answer: Is *surgery* really indicated for "unresectable" N2 disease?

Dr. Sugarbaker. I would simply react in one way to the comment regarding the standard of therapy. Since the report of the Barcelona study in the *New England Journal of Medicine* in January 1994, which demonstrated a survival advantage to induction chemotherapy followed by surgery versus surgery alone, there has been and may be in the community a license to proceed with this treatment strategy. I am not sure that this is the correct approach, but I think it is something that we all need to be aware of.

Dr. Valerie W. Rusch (New York, N.Y.). I have a couple of comments and one question. With respect to the use of concurrent induction chemoradiotherapy, both the Southwest Oncology Group (J THORAC CARDIOVASC SURG 1993; 105:97-106) and the Rush-Presbyterian Group (Ann Thorac Surg 1989;47:669-77) have shown the feasibility and effectiveness of this approach. However, other single-institution experiences, such as that reported from the Fox Chase Cancer Center (Ann Thorac Surg 1993;55:986-9) this past year, suggest that when chemotherapy is combined with *high-dose* radiotherapy (i.e., doses higher than 45 Gy) the risk of postoperative adult respiratory distress syndrome and of bronchial stump leak becomes prohibitive. Whether chemoradiotherapy is better induction treatment than chemotherapy alone remains an unanswered question.

One of the useful points of information from this study is that you report the response rates of an induction chemotherapy regimen that does not contain mitomycin. There has certainly been a lot of controversy about the risks and benefits of including mitomycin in the induction chemotherapy regimen. This study suggests that the resectability rate after vinblastine sulfate (Velban) and cisplatin is roughly equivalent to that after mitomycin, vinblastine, and cisplatin.

Finally, I have one question: Are you able to determine how many patients had bulky N2 disease versus those who had single node, intranodal disease only at mediastinoscopy?

Dr. Sugarbaker. We do have information regarding whether the patients had bulky disease seen by both plain film and CT scan or whether they had microscopic disease.

Although there appears to be a survival advantage in the patients with microscopic disease, that advantage does not hold up statistically. However, there is a trend toward that.

Your comments regarding multiinstitutional trials, as well as those of Dr. Ginsberg, are right on target. Any oncologist will tell you that if they take an oncology regimen into a multiinstitutional setting, morbidity will double and response rates will fall in half. From a surgical standpoint, Dr. Rusch and Dr. Ginsberg and others know from the Lung Cancer Study Group experience that results from single-institution trials of a given treatment regimen do not necessarily correlate to results obtained in a multiinstitution trial.

Dr. Donald L. Morton (*Santa Monica, Calif.*). I notice that the disease was downstaged in only about 22% of the patients whom you treated preoperatively, and I wonder if postoperative therapy would give similar results. What is the evidence that chemotherapy plus radiation therapy is superior when given before rather than after a complete mediastinal node dissection?

Dr. Sugarbaker. The use of adjuvant radiation and chemotherapy has been studied in a number of single-institutional trials and was also actually looked at by the Lung Cancer Study Group separately, using chemother-

apy in the adjuvant setting and then radiation, and no benefit to survival was noted. There are some theoretical advantages to giving neoadjuvant therapy. The intact blood supply maximizes drug delivery to the tumor and nodal metastases. The actual intervention or the administration of chemotherapy comes much earlier in the natural history of a disease, which has a very *short* natural history, with a life cycle that almost many times spans 18 to 20 months from diagnosis to death. So by intervening earlier with chemotherapy, we may be getting to the disease when there is lower tumor bulk. And almost regardless of the malignancy that has been studied, the lower the stage or the lower the tumor bulk, the higher the response rate to chemotherapy. In addition, there may be some advantage to giving chemotherapy while micrometastatic disease in the lymph nodes with the highest mitotic index has an intact blood supply, thereby maximizing drug delivery and effectiveness of therapy.

Dr. Fry. Eastern Cooperative Oncology Group protocol 3590, which is available through Intergroup, wherein everybody gets radiation and half the subjects get chemotherapy, is maturing. I think that the question that you pose will be answered by that multiinstitutional clinical trial.

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