Eur J Cancer, Vol. 29A, No. 4, pp. 511–515, 1993.
Printed in Great Britain

0964–1947/93 $6.00 + 0.00
Pergamon Press Ltd

Combined Modality Therapy for Stage IIIA Non-small Cell Carcinoma of the Lung

Alan B. Weitberg, John Yashar, Arvin S. Glicksman, Marshall Posner, Frank Cummings, Marcia Browne, Jeffrey Clark, Paul Calabresi, Julie Beitz and Connie Murray

53 patients with stage IIIA non-small cell carcinoma of the lung (NSCCL) were treated with multimodality therapy consisting of induction radiotherapy (55.8 Gy) and two cycles of concurrent chemotherapy with cisplatin, 25 mg/m^2 for 4 days by continuous infusion and bolus etoposide, 100 mg/m^2 on days 2 and 4 of each cycle followed by surgery and adjuvant chemotherapy. Of 53 evaluable patients, 47 achieved clinical responses (9 complete response, 38 partial response) after induction therapy for a response rate of 89%. 47 patients were resectable after induction therapy, but 8 patients refused surgery and 6 patients were not eligible for surgery based on poor pulmonary function (medical contraindications). 33 patients underwent thoracotomy and in 6 patients, resection was technically unfeasible. Thus complete surgical resection was accomplished in 27 patients. After all therapy, 28 patients achieved a complete response (53%) and 19 patients a partial response (36%). Toxicities were mild. At a maximum of 75 months (median, 28 months) of follow-up, the median survival of the entire group is 24 months. The median survival of resected patients has not been reached; their 6-year survival rate is 55%. Unresected patients survived for a median of 11 months. This multimodality regimen is well-tolerated, induces a high response and resectability rate and prolongs survival in resected patients.
Eur J Cancer, Vol. 29A, No. 4, pp. 511–515, 1993.

INTRODUCTION

NON-SMALL CELL carcinoma of the lung (NSCCL) continues to pose a major international health care threat and will account for over 115 000 cases of lung cancer in the United States of America this year [1]. Of these, 30% will be locally advanced, inoperable and classified as stage III. This group of patients has been subclassified into stage IIIA, those patients with potentially resectable disease including tumours invading the chest wall or with ipsilateral mediastinal node involvement and stage IIIB, those patients with contralateral or neck nodal metastases, pleural effusion or more extensive extrapulmonary extension which is not amendable to surgery [2].

A generation ago, Fernando Bloedern suggested that local and regional disease in the chest in patients with carcinoma of the lung could be sterilised by radiotherapy and that subsequent surgery was potentially curative [3]. When this approach was tested in a prospective randomised trial conducted by the Veterans Administration, it failed to demonstrate an advantage for preoperative radiotherapy [4]. In fact, the irradiated patients had an increased mortality in the first 6 months but fared better thereafter.

Since that time, there has been significant improvement in the technical capabilities of both radiotherapy, thoracic surgery and supportive care. In addition, chemotherapeutic agents are now available which can minimise micrometastases as well as act as radiosensitisers [5]. Specifically, cisplatin can function in this manner. Accordingly, we believed we could develop an aggressive preoperative treatment program which would not only re-examine the Bloedern hypothesis for the chest, but also limit the early spread of disease outside of the chest with preoperative and postoperative chemotherapy, providing the potential for improved survival for patients with locally advanced lung cancer.

For patients with stage III, and particularly stage IIIA disease, recent trials employing a multimodal approach with conversion to resectability have yielded encouraging results. In a large randomised trial conducted by the CALGB comparing single agent radiotherapy to chemotherapy and sequential radiation therapy, a significant survival advantage was demonstrated for those patients treated with multimodality therapy (median survival, 16.5 months vs. 8.5 months) [6]. Response and resection rates generally greater than 50% have been documented in most trials employing induction regimens of cisplatin-based chemotherapy and radiotherapy [7–13] or cisplatin-based chemotherapy alone [14, 15]. Thus, patients with unresectable disease can be converted to resectability and resected patients, particularly those with negative surgical specimens, appear to enjoy a survival advantage. Local control rates are excellent, but systemic failures account for the vast majority of recurrences [16].

Although the long-term benefit of multimodality therapy over radiation therapy alone for locally advanced patients remains to be established definitively, results to date warrant continued clinical investigation of this approach with an emphasis on improved local control and reducing distant relapses. In this study, we present the results of a clinical trial employing induction chemotherapy and concurrent radiotherapy, surgery and adjuvant chemotherapy for patients with stage IIIA NSCCL and favourable clinical characteristics.

PATIENTS AND METHODS

Histologically or cytologically confirmed stage IIIA NSCCL (T3 and/or N2 lesions) was required for entry into this trial.

Correspondence to A. B. Weitberg, Division of Hematology/Oncology, Roger Williams Cancer Center, 825 Chalkstone Avenue, Providence, Rhode Island 02908, U.S.A.
Revised 23 June 1992; accepted 1 July 1992.

Patients who had previously received chemotherapy or radiotherapy were excluded. Other eligibility requirements included: a creatinine clearance of 50 ml/min or greater, normal bone marrow function, ECOG performance status (PS) of three or less and measurable disease. Informed written consent was obtained from each patient participating in this trial which was approved by our Institutional Review Board.

Study design and treatment

Pretreatment staging studies included a complete history and physical examination, urinalysis, complete blood count with platelets, 24-h urine creatinine clearance, serum electrolytes and chemistries, chest X-ray and computerised tomography (CT) of the chest to the adrenals. A ^{99}Tc bone scane and/or liver–spleen scan was performed if indicated clinically. CT of the brain was not done routinely in the absence of neurological deficits. Mediastinoscopy was performed on all but 3 patients who had large T3 lesions and no evidence of mediastinal adenopathy radiographically.

Treatment protocol. Induction chemotherapy consisted of cisplatin 25 mg/m^2/day for 4 days (days 1–4) intravenously by continuous infusion with 3 l of normal saline daily and etoposide 100 mg/m^2 intravenously by infusion over 30 min on days 2 and 4. A second cycle of chemotherapy was initiated on day 28. Radiation was administered concurrently with chemotherapy beginning on day 1. The initial field arrangement was an anterior/posterior parallel opposed port, which included the tumour, the hilum and the mediastinum. The contralateral hilum and the supraclavicular fossae were not included in the field. These portals were carried to no higher than 39.6 Gy at 180 cGy per day for 22 sessions. The volume includes the entire mediastinum superiorly to the thoracic inlet, interiorly 5 cm below the carina for upper lobe lesions and to the diaphragm for lower lobe lesions. A 2 cm margin around the identified tumour was allowed in all directions. After 39.6 Gy treatment portals were modified to come off cord carrying the mediastinum and tumour to 54 Gy, limiting the spinal cord dose to 46 Gy. We found it useful to consider coming off cord earlier than 39.6 Gy in many cases, because we would have been limited in our dose to the mediastinum by the spinal cord restriction. We carefully chose our off-cord fields to restrict the dose to the contralateral lung. A boost of 5.4 Gy (180 cGy × 3) was given directly to the tumour-bearing volume whenever possible without adding to the spinal cord dose.

Two weeks after the completion of radiotherapy, restaging studies were performed and consisted of a history and physical examination, chest X-ray, CT of the brain, chest and abdomen, ^{99}Tc bone scan, split pulmonary function studies and repeat serum chemistries. Mediastinoscopy was performed on all patients prior to thoracotomy and sites of prior mediastinal disease were biopsied. Patients deemed resectable underwent thoracotomy 4–6 weeks after the completion of radiotherapy. A radical pulmonary resection was the surgical procedure of choice. This included a dissection of the mediastinal fat pad starting at the thoracic inlet and dissected down to the level of the hilum. The pericardium was opened to approach major vascular and lymphatic structures. A lobectomy or pneumonectomy was performed as needed to extirpate all disease with negative margins.

Three weeks after surgery, chemotherapy was administered as follows: cisplatin, 25 mg/m^2 day for 5 days intravenously by continuous infusion with 3 l of normal saline daily and etoposide, 100 mg/m^2 intravenously by infusion over 30 min on days 2 and 4 of each cycles. Two cycles of adjuvant chemotherapy were given at 28-day intervals. Patients who did not undergo surgical resection after induction therapy received the same adjuvant chemotherapy as above until progression. In addition, 14.4 Gy of radiation was administered in eight sessions to the tumour and mediastinum in these unresected patients concurrent with the inception of additional chemotherapy.

Response and toxicity criteria. After restaging, responses to induction therapy were determined and classified as complete (CR) if there was complete disappearance of disease as determined by physical examination and radiological studies. Partial response (PR) was defined as a greater than 50% reduction of the product of the greatest perpendicular diameters of all lesions. Patients with stable or progressive disease were classified as having no response (NR). Patients achieving a CR or PR were considered resectable. Toxicity was graded using ECOG criteria. After surgery, a CR was achieved if all sites of disease were resected. A pathological CR (pCR) was noted if the resection specimen was histologically free of disease. Survival was calculated from day 1 of induction therapy and actuarial survival with 95% confidence intervals was analysed by the method of Kaplan and Meier [17].

RESULTS

Patients' characteristics

From March 1985 to March 1991, 53 patients were entered on this study and all are evaluable for response and survival. Patients' characteristics are summarised in Table 1. The median age was 61.5 years and the majority of patients were male and ambulatory.

Analysis of response

Response data are shown in Table 2. After completion of induction therapy, 9 patients (17%) achieved a CR and 38 patients (72%) achieved a PR. 6 patients (11%) were non-

Table 1. Patients' characteristics

Number of patients	53	
Patients evaluable for response	53	
Sex (M:F)	30:15	
Median age (range)	61.5 years (39–79)	
Histology		
Squamous	28	
Adenocarcinoma	13	
Large cell	12	
Performance status (ECOG)		
0	8	
1	42	
2	3	
Weight loss		
None	25	
≤ 5%	24	
5–10%	4	
< 10%	0	
TNM		
T3N0M0	2	Classification (1 dead) (1 alive)
T3N1M0	1	
T2N2M0	18	
T3N2M0	32	

Table 2. Responses

	After induction therapy (%)	After all therapy (%)
CR	9 (17)	28 (53)
PR	38 (72)	19 (36)
NR	6 (11)	6 (11)
Total	47 (89)	47 (89)

responders. The total response rate (CR and PR) was 89%. After the completion of all therapy (induction therapy, surgery and adjuvant chemotherapy), the CR rate increased to 53% and the PR rate was 36%.

47 patients were considered resectable after the completion of induction therapy (Table 3). 8 patients refused surgery and 6 patients were considered inoperable based on their pulmonary function determined preoperatively. A thoracotomy was performed on 33 patients, but in 6 patients resection was not feasible due to extensive fibrosis. Thus, of the 47 patients considered resectable, 27 patients (57%) were resected.

Twelve (44%) of the 27 resection specimens were free of tumour and in 3 of the 5 patients unresected due to fibrosis, multiple biopsies performed at the time of thoracotomy were negative for tumour.

Analysis of survival

With a median follow-up of 28 months (range, 3–75 months), the median survival of the entire group is 24 months. The median survival of the resected patients has not been reached, but their 6-year survival rate is 55% ($P < 0.001$ vs. all others) (Fig. 1). The median survival of the unresected patients was 11 months.

Of the 27 resected patients, 10 have died and 17 patients remain free of disease from 21+ to 75+ months. Of the 6 patients not resected due to technical difficulties, 1 has died at 6 months, 2 have relapsed, but remain alive with disease at 29+ and 45+ months and 3 are free of disease at 3+, 51+ and 41+ months. 8 of the 12 patients with histologically negative resection specimens are alive and free of disease from 23+ to 60+ months. 2 of these patients have died with distant metastases and 1 died of a myocardial infarction at 39+ months with no evidence of disease at autopsy.

Of the 28 patients in complete remission at the completion of all therapy, one has relapsed locally only. There have been 10 distant only relapses, 2 of which were in the brain. 1 of the brain relapses was the only site of distant disease. 1 patient relapsed

Table 3. Conversion to resectability

	Number (%)
Total	53 (100)
Excluded	20 (43)
Refused	8 (17)
Medical contraindications	6 (13)
Technically unfeasible	6 (13)
Resected	27 (57)
Lobectomy	14 (29)
Pneumonectomy	13 (28)

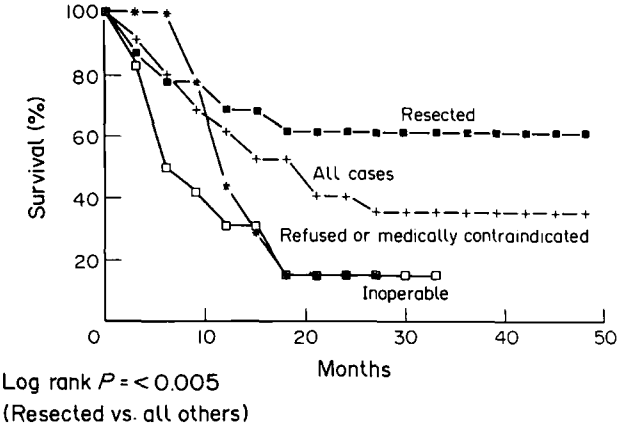

Fig. 1. Survival of 53 evaluable patients registered on study.

Table 4. Sites of failure in 26 complete responders

Site	Number
Local disease	1
Distant disease (brain only)	10 (2)
Both	1

both locally and distantly (Table 4). Sites of relapse included contralateral lung, bone and brain.

Analysis of toxicities

As shown in Table 5, myelosuppression was mild with only 4% of patients evidencing grade 4 leukopenia, although one death related to nadir sepsis occurred during induction therapy. No patient experienced grade 2 or greater mucositis or oesophagitis. As noted previously, there were 2 perioperative mortalities, one from sepsis and one from a vascular event.

Table 5. Toxicities (ECOG criteria)

	Number (%)
Leukopenia	
Grade 1, 2	15 (28)
Grade 3, 4	6 (12)
Thrombocytopenia	
Grade 1, 2	8 (15)
Grade 3	1 (2)
Nausea	
Grade 1	8 (15)
Grade 2	7 (13)
Vomiting	
Grade 1, 2	18 (34)
Grade 3	2 (4)
Oesophagitis	
Grade 1	11 (21)
Mucositis	
Grade 1	3 (6)

DISCUSSION

A variety of combined modality trials for patients with locally advanced NSCCL have been evaluated in an attempt to improve the survival rate achieved with radiation alone. Although a comparison of these studies is difficult due to variation in patient characteristics, dosing and sequencing of therapies, some general conclusions can be drawn from published data.

In a large, randomised trial conducted by CALGB comparing single-agent radiotherapy (60.0 Gy) to chemotherapy (cisplatin/vinblastine) sequentially followed by radiation therapy, the median survival time of the patients treated with chemo/radiotherapy was significantly longer than those treated with radiotherapy alone, 13.8 months vs. 9.7 months [6]. 3-year survival rates also were higher in the group treated with combined modalities (23% vs. 11%). Without any surgery, the CALGB figures reflect less survival in either of their arms as compared with this study.

Most phase II studies have employed cisplatin-based chemotherapy in combination with radiotherapy (30.0 Gy—60.0 Gy), which consistently induces a high response and resection rate of greater than 50% [7–13]. A trial conducted by the Lung Cancer Study Group evaluated cisplatin, 5-fluorouracil and concurrent radiotherapy (30.0 Gy) in 76 patients with stage IIIA disease. The response rate was 57% (all partial) and 80% of patients deemed resectable were resected at thoracotomy. There were 23% of the resection specimens pathologically free from tumour and the median survival of all patients in the trial was 10.5 months. Toxicity was mild to moderate [10]. In another CALGB study of cisplatin, 5-fluorouracil, vinblastine and concurrent radiotherapy (30.0 Gy) for patients with stage IIIA disease, 26 of 41 patients achieved a PR and 81% were resectable at thoracotomy. Pathology was negative in 16% of the resected patients. The median survival time was 16.5 months and the 1-year survival rate was 58%, but haematological toxicity was severe [7]. The best arm of this study does not achieve the control rates seen with intensive preoperative programmes.

Similar results have been observed in trials of induction regimens using combination chemotherapy alone [14, 15] preoperatively. In a trial by Gralla *et al.* induction chemotherapy consisting of mitomycin, a vinca alkaloid and cisplatin as administered to 47 patients with clinically apparent mediastinal node involvement. The response rate was 69% and 77% of the patients were resected. Of the resection specimens 25% were free from tumour and the 1-year and 3-year survival rates were 68 and 31%, respectively [14]. In general, median survival times in the 15–20 month rate are noted and local recurrence rates are low. Of significance, survival rates are improved in completely resected patients. The resection specimen is free of histologically demonstrable tumour in 15–30% of patients. It appears that these latter patients have a survival advantage [16].

The response rate of 89% in our study is consistent with the somewhat higher responses observed in similar phase II trials discussed above. Our results also support an aggressive attitude towards surgery in these patients. Only 5/47 patients could not be resected at thoracotomy due to technical difficulties stemming from an extensive fibrotic reaction produced by the induction therapy. In one of these patients, however, surgery was delayed beyond 6 weeks following the completion of radiotherapy due to an exacerbation of chronic active hepatitis. The importance of performing surgery within a 4–6 week "window" following induction therapy cannot be overemphasised. Beyond 6 weeks, the chances for resection are diminished as fibrosis develops in the surgical field.

Table 6. Histological documentation of tumours in resection specimens

Preoperative response rate in resected patients (no.)	Histologically negative	Histologically positive
PR (23)	8	15
CR (4)	4	0

In 12/27 (44%) of the resection specimens, no tumour was demonstrable histologically. As shown in Table 6, 8 of the patients clinically classified as a partial responders had in fact achieved a complete histological response not predicted by CT scan. Of the 12 patients with negative histologies, 8 remain alive and free of disease from 23+ to 60+ months. Thus, response to induction therapy at surgery is higher than can be determined radiographically preoperatively. In support of this observation, there is at least one report of complete histological responses in patients with no clinical response radiographically [13]. Without evidence, distant spread or medical contraindications, all patients should be re-explored.

When sites of failure were analysed in patients having undergone complete surgical resection, distant relapses were most frequent. Only one of our patients relapsed locally and there were two relapses in the brain, one of which was associated with a local occurrence as well. Although the numbers are small, relapses restricted to the brain were rare in this study.

Toxicities were mild in this study and well tolerated. There were two perioperative mortalities and one death due to nadir sepsis for an overall treatment-related death rate of 6% which is lower or comparable with other multimodality studies in which surgery is employed [7–13]. The toxicities described are similar to those observed at this institution using continuous infusions of cisplatinum [19, 20] with the exception of an additional mild oesophagitis induced by the concomitant administration of radiotherapy, but without 5-fluorouracil the oesophagitis was tolerable and no patient had to discontinue radiotherapy due to toxicity.

With a long period of follow-up, our 6-year survival rate of 55% in resected patients is higher than reported in other published studies. Based on these data and the collective experience of other authors, multimodality therapy offers significant promise in the treatment of patients with stage IIIA NSCCL. Future efforts should be directed at the development of more intensive systemic therapies particularly postoperatively in an effort to reduce distant recurrences and thereby improve overall survival. In addition, a randomised trial comparing chemo/radiotherapy to chemo/radiotherapy followed by surgery is now justified.

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Acknowledgements—This study was supported by NCI grant CA13943.

Eur J Cancer, Vol. 29A, No. 4, pp. 515–518, 1993.
Printed in Great Britain

0964–1947/93 $6.00 + 0.00

Control of Nausea and Vomiting with Ondansetron in Patients Treated with Intensive Non-cisplatin Chemotherapy for Acute Myeloid Leukaemia

J. Bart Braken, John M. M. Raemaekers, Peter P. Koopmans and Ben E. de Pauw

18 consecutive patients with acute myeloid leukaemia (AML) treated with 34 cycles of intensive chemotherapy received ondansetron as antiemetic treatment. 14 patients were chemotherapy-naive, while 4 patients were treated for relapsed leukaemia. All patients received at least one cycle of chemotherapy, 11 patients (61%) received two cycles and 5 patients (28%) received three cycles. The remission induction regimen consisted of cytarabin 200 mg/m^2 daily from day 1 to day 7, in combination with an anthracycline or amsacrin on 3 days. During the second and third cycle the dose of cytarabin was increased. Ondansetron was administered as follows: 8 mg intravenously before the start of chemotherapy, followed by 8 mg orally three times daily for 10 days. 50% of patients had no episodes of vomiting during the first cycle of chemotherapy and 78% had less than five episodes of vomiting over 10 days. 72% of patients had no or only mild nausea. These high response rates were maintained during the subsequent cycles. No side-effects due to ondansetron were registered. These data indicate that ondansetron is efficacious in preventing nausea and vomiting in patients with AML treated with intensive chemotherapy.
Eur J Cancer, Vol. 29A, No. 4, pp. 515–518, 1993.

INTRODUCTION

SEVERE NAUSEA and vomiting are common side-effects of treatment with antineoplastic agents. Recent studies suggest that serotonine, released from enterochromaffine cells in the intestinal tract, stimulating 5-hydroxytryptamine-type 3 ($5HT_3$) receptors located in the area postrema in the medulla oblongata and on vagal afferent fibres of the upper gastrointestinal tract, play a major role in the development of nausea and vomiting [1–3]. High-dose metoclopramide is the most frequently used antiemetic drug in patients treated with chemotherapy, but it has, apart from anti-$5HT_3$ receptor properties, antidopaminergic activity, causing unpleasant and unpredictable extrapyramidal