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ORIGINAL ARTICLE

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Combined-modality treatment for stage IIIa (N_2) non-small cell lung cancer: A National Cancer Institute Intergroup study

Abstract Induction chemotherapy plus radiotherapy followed by surgery, evaluated in a number of phase II studies, is an effective treatment for patients with stage III A non-small cell lung cancer (NSCLC). The ongoing phase III National Cancer Institute Intergroup study is evaluating concurrent chemotherapy (cisplatin + etoposide)/radiotherapy followed by either surgery or additional radiotherapy followed by 2 additional cycles of chemotherapy in patients with stage III A disease. This study will help define the role of surgery and radiotherapy as part of the multimodality therapy of locoregional advanced NSCLC.

Key words Combined-modality treatment · Stage III A · NSCLC

Introduction

This report presents preliminary data from the ongoing National Cancer Institute Intergroup phase III study evaluating concurrent cisplatin/etoposide plus chest radiation therapy followed by either surgery or additional radiation therapy as well as additional chemotherapy for stage III A (N_2) non-small cell lung cancer (NSCLC). In the USA, NSCLC is the most common cause of cancer-related deaths [9], and approximately 15% of NSCLC patients have stage IIIA disease.

Patients with stage III NSCLC represent a heterogenous group with survival rates ranging from 5–40% [5]. In the staging classification adopted in 1985, stage III was divided into stage IIIA and stage III B [7]. Stage III A ($T_3N_{0-1}M_0$ or $T_{1-3}N_2M_0$) is considered to be a surgical disease in selected patients, while stage IIIB (any T, N_3, M_0 or T_4, any N, M_0) is not. Despite this change in the staging system, the 5-year survival rates still ranged from $<10\%$ to 40% in patients with stage IIIA disease [4], with the variation depending on the extent of mediastinal nodal involvement: patients with bulky N_2 lesions had a 5-year survival rate of $<10\%$ while those surgically staged with a $T_3N_0M_0$ lesion had a 40% 5-year survival rate.

In 1996, the American Joint Committee on Cancer and the International Union Against Cancer approved revisions to the international staging of lung cancer. End-result studies for patients with both clinical and surgical-pathologic stage III A disease supported grouping patients with $T_3N_0M_0$ disease in stage II B rather than stage III A in the revised international staging system [8].

The optimal treatment for stage III A (N_2) NSCLC has not been established. Treatment strategies involving surgery have included the use of 2 or 3 treatment modalities: surgery and radiation therapy; surgery and chemotherapy; and surgery, radiation therapy, and chemotherapy. In these strategies, radiation therapy and/or chemotherapy could be administered pre- or postoperatively while combined chemotherapy and radiation therapy could be given concurrently or sequentially.

Even in locally advanced (stage III) NSCLC, it is believed that including surgery as part of a treatment plan offers patients the best chance for cure. In an attempt to enhance the effectiveness of surgery, cytoreductive therapy (induction therapy) has been employed to reduce bulky disease before the patient undergoes a definitive surgical resection. Such therapy could include chemotherapy, radiation therapy, or both.

A number of phase II studies of induction chemotherapy with and without radiation therapy before surgical resection for patients with stage III NSCLC have been conducted (Table 1) [1–3, 6, 11, 14–16]. In all of these studies, the response to induction therapy was approximately 50–75%, the surgical resection rate was high, and the survival at 3 years was approximately 25–30%. Unfortunately, despite

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Table 1 Induction chemotherapy ± radiotherapy followed by surgery in stage III NSCLC (*RTX* radiotherapy; *CT* chemotherapy; *MVP* mitomycin C, vinblastine, and cisplatin; *PEF* cisplatin, etoposide, and 5-fluorouracil; *PF* cisplatin and 5-fluorouracil; *CAP* cyclophosphamide, doxorubicin, and cisplatin; *PVF* cisplatin, vinblastine, and 5-fluorouracil; *PE* cisplatin and etoposide; *NS* not stated

No. of patients	CT	RTX	Response Rate (%)	Resection Rate (%)	3-year survival Rate (%)	Reference
85	PEF, PF	Yes	NS	73	31	3
41	CAP	Yes	72	90	31	14
64	PF	Yes	84	61	30	11
85	PF	Yes	56	52	20	16
39	MVP	No	64	56	26	2
41	PVF	Yes	51	61	28	15
136	MVP	No	77	65	28	6
126	PF	Yes	59	83	26	1

Table 2 Induction chemotherapy followed by surgery compared to surgery alone in stage III NSCLC (*S* surgery, *CT* chemotherapy)

Therapy	No. of patients	CT response (%)	Resection Rate (%)	3-year Survival (%)	Reference
S	14		86	23	10
CT→S	13	62	85	50	
S	30		90	0	12
CT→S	29	60	85	29	
S	32		65	15	13
CT→S	28	35	61	56	

the aggressive therapy, recurrence of tumor occurs both locally and in distant sites.

Three randomized trials have compared the use of induction chemotherapy followed by surgery to surgery alone in patients with stage III NSCLC (Table 2) [10, 12, 13]. Unfortunately, each of the studies had problems relating to the inclusion of too few patients or early termination of the study. Despite their shortcomings, each demonstrated a survival advantage (approximately ≥30%) for induction therapy followed by surgery over surgery alone.

Phase II Southwest Oncology Group study

The forerunner to the high-priority intergroup phase III study evaluating concurrent chemotherapy plus chest irradiation followed by either surgery or additional radiotherapy for stage IIIA (N_2) NSCLC was Southwest Oncology Group (SWOG) phase II study 8805 [1]. This study was activated in July 1988 and closed in March 1992 and was a feasibility trial of 2 cycles of concurrent cisplatin/etoposide plus chest radiotherapy (4500 cGy) followed by surgical resection of stage III A (N_2) or stage III B (N_3 or T_4) disease if there was no disease progression following induction therapy. Two more cycles of chemotherapy were given and radiotherapy was completed (total of 5940 cGy) if either unresectable disease, incomplete resection, or positive mediastinal lymph nodes was found at surgery.

A total of 126 eligible patients were evaluated, of which 75 had stage III A (N_2) and 51 stage III B disease. The objective response rate to the induction therapy (concurrent chemotherapy/radiotherapy) was 59%, while 29% of patients had stable disease. For stage IIIA and IIIB disease, surgical resection was possible in 85% and 80% of patients, respectively. There were 13 treatment-related deaths (10%). At the time of the report, 65 patients had relapsed; 11% of these patients had only locoregional disease while 61% had only distant site recurrence, with 26 having recurrence in the brain. For stage III A and stage III B disease, median survival times were 13 and 17 months, 2-year survival rates 37% and 39%, and 3-year survival rates 27% and 24%, respectively. Absence of tumor in the mediastinal lymph nodes at the time of surgery was the strongest predictor of long-term survival.

Intergroup study

To define the role of surgery in controlling locoregional NSCLC following induction therapy (chemotherapy plus radiotherapy) in patients with stage III A (N_2) disease as promptly as possible, an intergroup study was initiated. One of the arms of the intergroup study employed the treatment program used in the phase II SWOG study (8805) with minor modifications. The minor modifications included: 1) ineligibility of stage III B patients; 2) uniform radiation ports in both arms; 3) deletion of the small dose of postoperative radiotherapy; and 4) use of 2 cycles of postoperative chemotherapy for all patients.

The intergroup phase III study compares the modified SWOG combined modality treatment program to nonsurgical therapy consisting of the same induction therapy with additional radiation therapy and a total of 4 cycles of chemotherapy. The study is being coordinated by the Radiation Therapy Oncology Group (RTOG) and was activated in March 1994. In addition to the RTOG, other participating groups include the Eastern Cooperative Oncology Group, SWOG, Cancer and Acute Leukemia Group B, North Central Cancer Treatment Group, and NCI-Navy and National Cancer Institute-Canada. Figure 1 shows the treatment schema. Induction therapy for both arms consists of 2 cycles of cisplatin and etoposide with concurrent continuous radiation therapy beginning on day 1 of chemotherapy. The patients are reevaluated after completion of induction therapy. With no evidence of disease progression, patients randomized to the surgery arm receive 2 additional

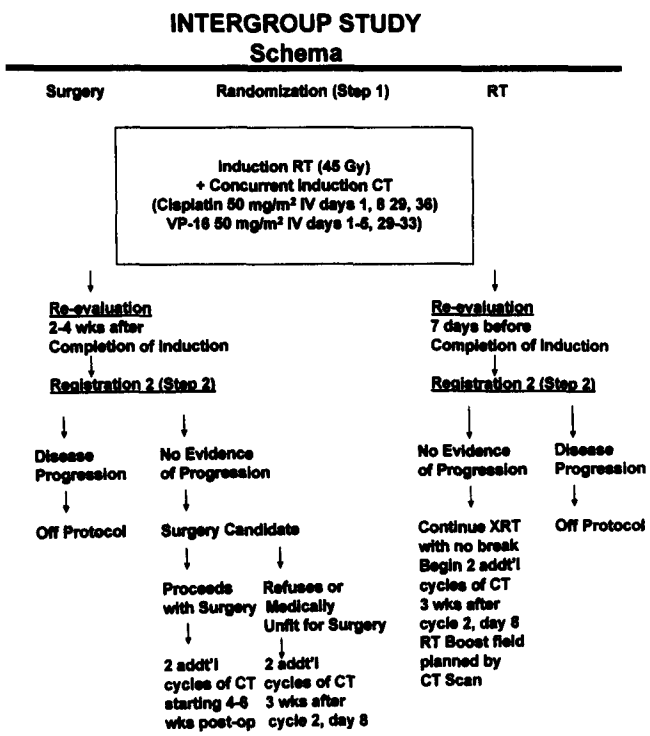

Fig. 1 Intergroup study schema

cycles of chemotherapy starting 4–6 weeks postoperatively; patients randomized to the radiation therapy arm continue radiation therapy without a break, with 2 additional cycles of chemotherapy beginning 3 weeks after cycle 2.

The objectives of the intergroup study are twofold. First, it will assess whether concurrent chemotherapy and radiotherapy followed by surgical resection results in a significant improvement in progression-free, median, and long-term (2-year and 5-year) survival compared to the same chemotherapy plus standard radiotherapy alone for patients with stage IIIA (N_2-positive) NSCLC. Second, the patterns of local and distant failure will be evaluated to assess the impact of therapy on local control and distant metastases.

Patients eligible for the intergroup study must have stage IIIA NSCLC with ipsilateral positive mediastinal lymph nodes (N_2) which has not been treated with chemotherapy or radiotherapy. They must be a candidate for potential future pulmonary resection as determined by the attending thoracic surgeon. Patients must have a Karnofsky performance status (KPS) ≥70% and a forced expiratory volume (FEV_1) ≥2.0 L or, if less than 2.0 L, a predicted postresection FEV_1 of ≥800 cc based on a formula using the quantitative V/Q scan. Diffusion capacity should be measured and if a pneumonectomy is a consideration, the diffuse capacity (as corrected for hemoglobin) should be ≥50% of predicted. A normal complete blood count and measured or calculated creatinine clearance of ≥50 mL/min are required.

The total number of patients entered into the study as of September 1, 1997, was 201; the study requires 510 patients. The recent average monthly accrual is 5.7 patients.

Table 3 Pretreatment characteristics (*CT* chemotherapy, *RT* radiotherapy, *S* surgery)

	Treatment group	
Patient characteristic	CT + RT + S (n = 66)	CT + RT (n = 65)
Age (years)		
<60	31 (47)	36 (55)
≥60	35 (53)	29 (45)
Gender		
Male	43 (67)	39 (60)
Female	23 (33)	26 (40)
KPS		
70–80	7 (11)	7 (11)
90–100	59 (89)	58 (89)
Weight loss		
<5%	56 (85)	48 (74)
≥5%	9 (13)	11 (17)
Not recorded	1 (2)	6 (9)
Histology		
Squamous	23 (34)	21 (32)
Adenocarcinoma	21 (31)	31 (48)
Large cell	10 (15)	4 (6)
Adenosquamous	2 (3)	1 (2)
Carcinoma NOS	2 (3)	4 (6)
Other	8 (12)	3 (4)
Missing	0	1 (2)
Lobar location		
Right upper	35 (53)	30 (46)
Right middle	3 (5)	3 (5)
Right lower	3 (5)	8 (12)
Right multiple	1 (1)	0
Left upper	14 (21)	18 (28)
Left lower	2 (3)	5 (8)
Lingula	3 (5)	1 (1)
Main bronchus	5 (7)	0
FEV (L)		
<2	15 (22)	13 (20)
2–3	38 (58)	35 (54)
3–4	12 (18)	14 (22)
>4	1 (2)	3 (4)
Pleural effusion		
No	59 (90)	56 (85)
Prior	2 (3)	1 (2)
After	4 (6)	4 (6)
Before/After	1 (1)	3 (5)
Unknown	0	1 (2)

Figures in parentheses are percentages

At this rate the projected completion date of this intergroup study will be April 2002. Table 3 gives the pretreatment characteristics of the first 131 patients randomized to the intergroup study. To date there have been no unexpected toxicities and at present no response or survival data are available.

Conclusions

Concurrent chemotherapy and radiotherapy as induction therapy prior to surgery are feasible in the treatment of stage IIIA NSCLC. Moreover, in a number of phase II studies such therapy appears effective in prolonging the survival of patients with this disease. The National Cancer Institute Intergroup study is focusing on the role of surgery

versus radiotherapy in controlling locoregional disease in a multimodality treatment program to treat patients with stage III A NSCLC.

The curability of stage III A NSCLC patients depends on the effectiveness of the combined-modality treatment of the disease. Refinement of both surgical and radiotherapy techniques as well as the use of new drug combinations should aid in the endeavor to cure stage III A NSCLC.

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