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Small-cell Carcinoma of the Lung: the Prognostic Significance of Stage on Survival

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Abstract—*Thirty-three patients (pts) with small cell carcinoma (SCC) were treated with combined modality therapy consisting of radiation therapy* (300 rad/15 *fractions*) *and cyclophosphamide, adriamycin, methotrexate and leucovorin (CAML). Thirty of* 33 *pts showed an objective response to therapy with a median survival of* 11.6 months *for all patients. When survival was determined by stage, pts with disease limited to the chest had a better median survival* (18.9 months) *than pts with metastases to supraclavicular nodes* (11.6 months, *median*) *or wide-spread metastatic disease* (8.0 months, *median*). *Not withstanding the routine use of chest irradiation, lung recurrences developed in* 7/33 *pts and were more frequent than CNS relapse,* 4/33. *If survival is to be increased in SCC, more aggressive means of local tumor control need to be pursued.*

INTRODUCTION

PRIOR to 1973, the clinical experience with small-cell carcinoma (SCC) of the lung was characterized by a poor cure rate after surgical resection. This poor cure rate was the result of rapidly progressive regional and metastatic disease causing death within 2–6 months of diagnosis [1]. Although a handful of patients had a long survival after radiation therapy (5%), the majority died from metastatic disease [2]. Studies of the biologic behavior of this tumor have demonstrated a large growth fraction and short doubling time; this rapid tumor growth has contributed to the aggressive clinical behavior, as well as the sensitivity of this tumor to cytotoxic therapy [3]. Clinical trials during the 1970's have established that significant tumor regression and improved survival are possible with the use of combination chemotherapy or combined radiation therapy and chemotherapy [4–7]. We wish to report our experience with combined-modality therapy for patients with small-cell carcinoma of the lung; we will show that survival of patients with SCC is clearly related to the extent of disease and that prolonged remission may be achieved in a subgroup of patients.

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MATERIALS AND METHODS

Patient population

Thirty-three consecutively untreated patients (pts) with biopsy proven small cell carcinoma (bronchial biopsy, 5 pts; mediastinoscopy, 13 pts; lymph node biopsy 10 pts; liver biopsy, 3 pts; and lung biopsy, 2 pts) were entered into a combined-modality program from October 1975 to May 1977 either at the University of Chicago (17 pts) or Michael Reese Medical Center (16 pts). There were 9 women and 24 men with a median age of 61 yr and a range of 47–86 yr. Performance status ranged from 20 to 100 with a median of 70 [7].

Staging

Initial studies included a complete history and physical examination, peripheral blood

counts, screening blood tests for renal function, liver function and electrolytes, electrocardiogram and chest X-ray. Studies to determine the extent of disease included technetium-99 bone and liver scans, either a nucleotide brain scan or computerized tomography of the brain, a gallium-67 scan, and a single bone marrow aspiration and biopsy (31 pts). Patients were staged according to the TNM system of the Task Force on Carcinoma of the Lung [8]. For study purposes, a modification of this system regarding metastases to the supraclavicular lymph nodes (SCN) or to distant sites was included. Stage III_{MO} patients had disease limited to one lung site, with or without hilar or mediastinal node metastases; stage III_{+SCN} patients had disease limited to one lung site, with or without hilar or mediastinal node metastases, but with supraclavicular node (SCN) metastases; stage III_{MI} had one or more distant metastases.

Combined chemotherapy and radiotherapy treatment program

The treatment protocol consisted of sequential combination chemotherapy and radiotherapy. The chemotherapy included cyclophosphamide, 1000 mg/m^2 i.v. on day 1; adriamycin, 40 mg/m^2 i.v. on day 1; methotrexate, 180 mg/m^2 i.v. on day 22; and leucovorin, 40 mg/m^2 p.o. q 6 hr × 4, beginning 24 hr after the methotrexate injection; the cycle was repeated every 28 days. High dose methotrexate with rescue was employed since a previous series of patients who progressed on conventional dose methotrexate showed response to high dose methotrexate with rescue (Bitran and Golomb, unpublished data). After two cycles of chemotherapy (day 57), radiation therapy to the lung was begun (17 pts, University of Chicago). Sixteen patients received radiation therapy initially followed by chemotherapy as a matter of institutional policy (Michael Reese Hospital). The radiation port encompassed the primary lesion in the lung, the hilar lymph nodes, and the mediastinum in all patients, and the supraclavicular area in patients with involved nodes (stage III_{SCN+}). The total dose was 3000 rad over 15 fractions, 200 rad per day. Radiation therapy was administered to all patients since it appears to delay pulmonary recurrence [7]. After a 7–10 day rest period, chemotherapy was started and continued every 4 weeks until a maximal dose of adriamycin (450 mg/m^2) was reached. Patients were then continued on chemotherapy with cyclophosphamide, 1500 mg/m^2 i.v. on day 1; vincristine 1.4 mg/m^2 i.v. on day 1; methotrexate and leucovorin as described above on days 22 and 23, respectively. Chemotherapy was begun within 3 weeks of diagnosis for 12 patients, within 4 weeks for 20 patients, and by 8 weeks for 1 patient.

Chemotherapy dose modifications for cyclophosphamide and adriamycin are shown below:

WBC > 4000, platelets > 150,000—100% dose; WBC > 3000, < 4000; platelets > 100,000 < 150,000—75% dose; WBC < 3000; platelets < 100,000—withhold chemotherapy.

Criteria for response

In the 17 patients receiving chemotherapy initially, response were determined at day 56 prior to radiation therapy and designated as follows: CR (complete response)—complete regression of tumor at all sites as determined by radiographic and scintigraphic studies (liver, bone and brain scans) for at least 2 months; PR (partial response)—regression of all measurable tumor by 50% or more as determined by radiographic and scintigraphic studies (liver, bone and brain scans) without the appearance of new disease for at least 2 months; regression of tumor by less than 50% or the appearance of new disease was graded as no response (NR).

Of the 16 patients initially treated with radiation therapy, 9 had disease confined to the chest or supraclavicular lymph nodes; response in these 9 patients was designated in the same fashion after completion of radiation therapy. The 7 remaining patients had responses determined in sites outside the radiation portal after 2 cycles of chemotherapy.

Follow-up studies

On the patient's first visit of each month, an interval history, physical examination, chest X-ray and blood counts were obtained. Blood counts were determined weekly for assessment of myelosuppression. The gallium tumor scan and other initially positive scans were repeated at 4–6 month intervals. Performance status was assessed at the start of therapy and during each subsequent visit [7].

Statistical methods

Survival was calculated from the first day of chemotherapy until death or up to the closing date of this study, 1 April 1978. Survival curves were compared by the Gehan modification of the generalized Wilcoxan [9].

RESULTS

The results of staging, response to therapy, and survival are shown in Tables 1 and 2 and Fig. 1. In 19 patients, the disease was confined to the primary lung tumor and regional lymph nodes; 14 patients had metastatic disease (Table 1). The complete and partial response rate was 90% to combined modality therapy. Eighteen of 19 patients with SCC, stage III_{MO} and stage III_{SCN+} had complete responses; whereas, of the 14 patients with stage III_{MI} SCC, there was only one complete response, 10 partial responses, and 3 no responses.

Survival

The median survival for all patients was 11.6 months. Median survival for the various stages are shown in Table 2 and Fig. 1. There was no difference in median survival between patients receiving radiation therapy initially (median 14 months) as opposed to those receiving it after 2 cycles of CAML (median 9.5 months). This difference in survival between patients receiving radiation therapy initially as opposed to those receiving chemotherapy initially could be explained by the higher proportion of stage III_{MO} patients in the former group (7/16 pts) as opposed to the latter (5/17 pts). There was a highly statistically significant difference in survival for patients with stage III_{MO} SCC (median 18.9 months) as opposed to those patients with supraclavicular node involvement (median 11.6 months), $[P>0.01<0.05]$. However, the differences in the survival curves between patients with stage III_{SCN+} SCC and stage III_{MI} were not statistically significant $P=0.21$.

Sites of relapse

As indicated in Table 3, of the 19 patients with complete response, relapse has occurred in 10 patients, 6 of these relapses have been in known sites of bulk disease (4 pulmonary, 1 each supraclavicular lymph nodes and liver). The remaining 4 patients experienced recurrent disease in the central nervous system (3 intracerebral, 1 spinal cord). There was an additional patient with a PR who developed CNS relapse within the spinal cord; thus, the incidence of CNS relapse in this series was 15%. Size of the chest lesion could not be correlated with the probability of local relapse in this series.

CNS irradiation was used to treat intracerebral and spinal cord recurrences, and a second line chemotherapy regimen CCNU +hexamethylmelamine (C-HEX) was used to treat recurrences elsewhere. Central nervous system irradiation was able to control disease in 3 patients for 10, 4 and 2+ months. The remaining 2 patients with CNS recurrence died within a month. None of the 9 patients with relapse or progression outside the central nervous system showed an objective response to C-HEX.

Toxicity

Although all patients experienced some degree of nausea and vomiting, usually starting within the first few hours after the injection of adriamycin and cyclophosphamide, most recovered by the following day. There was little nausea and vomiting following the methotrexate injection. No doses were tapered or withheld due to this complication. All patients developed partial or total alopecia. Body weight during therapy, prior to relapse, remained stable in 20 patients, increased in 4 patients, and decreased in 9 patients (by 4–11% of initial weight). At the time of relapse, one patient had a stable weight and 21 patients had lost 2–4% of their body weight.

The median nadir of white blood count and platelet count for the entire group of 33 patients was 1500 and 120,000 respectively. Myelosuppression occurred between days 7 and 10. There were 4 patients whose nadir white blood counts dropped below 1000 and required hospitalization for fever. Two of these four patients had bacterial pneumonia and all 4 recovered uneventfully. There were two episodes of methotrexate toxicity that resulted in one death (pt 29, Table 1). Death occurred in a patient who received 14 uneventful cycles of CAML. The methotrexate level was elevated $>10^6$ M on admission. One patient died of an aspiration pneumonia (pt 18, Table 1) during radiation therapy.

DISCUSSION

The results of treatment of patients with SCC employing either combination chemotherapy alone or combination chemotherapy and radiation have recently been summarized by Weiss [6]. Most of the combination chemotherapy regimens have employed combinations of cyclophosphamide, vincristine, adriamycin, methotrexate and a nitrosourea, and have shown significant activity (response rate 43–88% [6]. When one employs these combinations with radiation therapy, the results

Table 1. Patient characteristics and clinical course

Pt. No.	Age (yr)	Sex	Initial P.S.	Treatment	Response		Response: Post treatment P.S.	Response: Duration (months)	Response: Survival (months)	Site of initial relapse
Disease limited to the chest					After 2 cycles CAML	After RT				
1	52	M	90	B	CR	CR	100	10.5	20.7	Brain
2	47	F	100	B	CR	CR	100	20.0	20.3	Lung, within portal
3	58	M	90	B	CR	CR	90	12.2	14.7+	Lung, within portal
4	86	M	80	A	—	CR	80	9.1	10.0+	Lung, within portal
5	54	M	100	A		CR	100	14.0	18.0	Brain
6	62	M	70	A	—	CR	80	14.0	16.0+	Brain
7	59	M	100	A	—	CR	100	25.0+	25.0+	
8	60	M	90	A	—	CR	90	18.0+	18.0+	
9	61	M	80	B	CR	CR	100	11.5+	11.5+	
10	61	M	80	B	CR	CR	90	7.3+	7.3+	
11	56	M	90	A	—	CR	90	9.0+	9.0+	
12	55	M	70	A	—	CR	70	3.0++	3.0+	
Disease limited to the chest and supraclavicular nodes										
13	65	M	50	B	CR	CR	80	9.5+	9.5+	
14	56	F	70	B	CR	CR	90	7.8+	7.8+	
15	62	M	70	A	—	CR	90	9.0+	9.0+	
16	84	M	60	B	CR	CR	90	8.3	11.7	SCN
17	64	M	60	B	CR	CR	90	5.3	5.7	Spinal cord
18	65	F	60	B	PR	PR	90	2.7*	2.7	
19	48	F	80	A		CR	100	15.0	16.2	Lung, within portal

Metastatic disease

20	67	F	50	B	PR	60	4.7	11.8	Lung
21	48	F	70	B	CR	70	7.7	8.7	Liver
22	64	M	20	B	PR	20	2.4	2.4	
23	57	M	40	B	PR	60	3.8	3.8	
24	64	F	20	B	PR	90	7.5	9.7	Lung (pleura)
25	64	M	50	B	PR	90	9.0	10.0	Spinal cord
26	47	F	60	B	PR	80	5.6	5.6	
27	68	M	70	A	PR	70	12.0+	12.0+	
28	64	F	50	A	PR	70	6.0	8.1	Liver, bone
29	47	M	80	A	PR	90	16.0++	16.0	
30	52	M	60	A	PR	70	2.0	2.0	
31	48	M	40	A	NR	20		2.0	
32	58	M	30	A	NR	20		2.0	
33	47	F	70	A	NR	20		6.0	

Key: P.S. —Performance status.
SCN —supraclavicular lymph node involvement.
CR —complete response.
PR —partial response.
NR —no response.
RT —radiation therapy.
A —radiation therapy→CAML.
B —CAML × 2→radiation therapy.
\+ Patients still alive.

*Death due to bacterial pneumonia and aspiration.
++Methotrexate toxicity; one death (pt 29).

Table 2. Response to combined therapy

Stage	No. of patients by response CR	PR	NR	Duration of response Median (months)	Range (months)	Survival Median (months)	Range (months)	Number of patients still alive
III_{MO}	12	0	0	15.0	(3 –25+)	18.9	(3 –25+)	8
III_{SCN}	6	1	0	9.0	(2.7–9.5+)	11.6	(2.7–16.2)	3
III_{MI}	1	10	3	5.0	(2.4–9.0)	8.0	(2.4–16.0)	0

Key:
CR Complete response.
PR partial response.
NR no response.

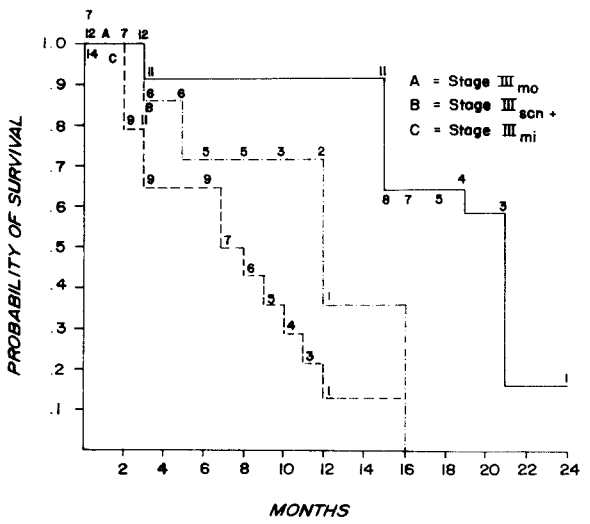

Fig. 1. Survival curve of pts treated with radiation therapy and CAML as stratified by stage. There was a statistically significant difference in survival between curves A (stage III_{MO}) and B (stage III_{SCN+}) $P>0.01$; <0.05. There was not a statistically significant difference between curves B (stage III_{SCN+}) and C (stage III_{MI}) $P=0.21$.

III_{MO}). Additionally, patients with involved supraclavicular lymph nodes fare only slightly better than patients with metastatic disease. The differences between the survival curves for patients with stage III_{SCN+} and stage III_{MI} SCC were not statistically significantly different ($P=0.21$). Thus, it may be better to classify these patients as having metastatic disease instead of limited disease as has been done in other series [11].

While much debate has centered about the value of prophylactic CNS irradiation in patients with SCC, no investigator or group has shown that prophylactic whole brain irradiation has influenced survival [12]. The incidence of CNS relapse in this series was 15% which is similar to the reports of others in patients with SCC not receiving prophylactic CNS irradiation [13]. While CNS relapse terminated a response in 5 patients (15%) local recurrence of tumor within irradiation portals either within the lung or supraclavicular lymph nodes was responsible for relapse in 7 patients (21%) in this series (Table 1). Of greater significance is the fact that local lung recurrence occurred in 3/12 patients with stage III_{MO} disease between 10 and 20 months. This occurred despite the routine use of radiation therapy to the chest primary. It is clear from our experience and that of Stanford [13] that more aggressive means of local control (higher doses of radiation therapy, surgical resection or neutron beam) appear warranted to prevent local relapse.

Table 3. Relapses in patients with small cell carcinoma and a complete response

Stage	No. of pts in CR	Relapse				
		CNS	Lung	Liver	Bone	Nodes
III_{MO}	12	3	3	0	0	0
III_{SCN}	6	1	1	0	0	1
III_{MI}	1	0	0	1	0	0

have been relatively uniform (median survival of 9–14 months for all pts) [4–7, 10]. Our results with combined radiation therapy and CAML in patients with SCC yield an excellent response rate (90% CR+PR; 57% CR) and a median survival (11.6 months) which is comparable to other series including a previously reported regimen from our institution [4–7, 10]. Although we did not randomize patients between initial radiation therapy or "sandwich" radiation therapy, our results indicate that one technique offers no advantage over the other.

Few previously reported studies have stratified patients in the manner that we have, and hence the significance of involved supraclavicular lymph nodes in patients with SCC has never been fully appreciated. Our results indicate that these patients have a more limited survival (Fig. 1) when compared to patients with truly localized disease (stage

The toxicity of therapy must be considered from the point of view of morbidity and mortality and with regard to changes in the quality of life while patients are undergoing therapy. Patients were treated according to this protocol, in an outpatient setting; most patients were able to lead relatively normal lives during the period of therapy. Myelosuppressive toxicity can be controlled

by careful monitoring of blood counts and appropriate dose reductions. A rather unique complication of radiation therapy combined with adriamycin chemotherapy has been severe radiation esophagitis, which had occasionally led to structure formation [14]. We have found that this complication can be prevented by maintenance of a rest period of 7 days between the completion of radiation therapy and the next adriamycin injection. The only patient in our study who developed esophagitis had inadvertently received adriamycin after only a 2-day rest period. Our observations are thus consistent with those of Wittes regarding the importance of the 7-day delay [15].

The success of this combined modality regimen for treatment in oat cell carcinoma is encouraging; but the subsequent relapse rate is of serious concern. Approaches to yield more durable remissions would include the use of alternating non-cross resistant regimens which can be utilized along with CAML, or more aggressive means of local control, which may prevent the emergence of resistant tumor cells and ultimately lead to cure.

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