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Three-year Disease-free Survivors of Small Cell Lung Cancer Treated with Combination Chemotherapy With or Without Chest Irradiation

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Abstract—*One hundred and seventy-four patients with small cell lung cancer (SCLC) treated with combination chemotherapy, with or without chest radiation, were analyzed. Fourteen patients* (8%) *survived for* 3 *years or more. Three-year disease-free survival continued for* 12 *of the* 101 *patients* (12%) *with limited disease, and one of* 75 (1%) *with extensive disease* ($P < 0.05$). *Patients' sex and performance status were not important in achieving long-term survival. All disease-free survivors, except two who could not be evaluated, achieved a complete response. Although the treatment programs had some influence on the long-term survival rates* ($P < 0.05$), *thoracic radiation did not have significant impact on long-term survival. Three of the* 13 *patients* (23%) *developed second malignancies and died, and one of these patients also suffered from a progressive neurologic deterioration with dementia. Two other patients died free of SCLC.*

Consequently, eight have remained alive and free of disease. The last relapse was observed at 1.5 *years from beginning of treatment. The disease-free survival may offer the hope of cure of SCLC. However, the survivors are at an increased risk of developing late complications including second malignancies and neurologic abnormalities. Therefore, careful follow-up will be necessary.*

INTRODUCTION

WITH ADVANCES in the study of the biological and clinical properties of lung cancer, it has become apparent that small cell lung cancer (SCLC) differs from non-SCLC in its rapid growth, propensity for early and widespread metastases, and good responsiveness to both chemotherapy and radiation therapy [1–3]. Even patients with clinically localized SCLC are very rarely amenable to surgical resection or radiotherapy [4–6]. In recent years significant progress in the treatment of SCLC has been achieved using systemic combination chemotherapy. Chemotherapy with or without radiation therapy offers the best hope for survival in patients with SCLC. The results of many studies have demonstrated that up to 80% of patients with SCLC achieve a tumor response to combination chemotherapy, and 50% of the patients with limited disease (LD) and 25% of those with extensive disease (ED) achieve a complete response (CR) [7, 8]. In spite of high initial response rates, responses are often short in duration. As a result, the proportion of long-term disease-free survivors (>3 years) is reported to be only 2–24% for LD and 0–4% for ED [9–16].

In order to identify factors associated with favorable outcome, we have analyzed, in this study, actuarial survival of 174 previously untreated patients who received combination chemotherapy with or without radiation therapy for SCLC and for whom a minimum of 3-year follow-up information is now available. We have also evaluated the pretreatment characteristics of 3-year disease-free survivors and their treatment modality.

PATIENTS AND METHODS

From January 1978 to September 1984, 174 previously untreated patients with histologically or cytologically proven SCLC treated at the Osaka Prefectural Habikino Hospital were included in this study. The patients included 139 men (80%) and 35 women (20%). Patients had an average age of 64 years at the start of therapy (range 34–82 years). Of the 174 assigned a performance status (PS (ECOG scale), 74 (43%) had PS 0 or 1, 54 (31%) had PS 2 and 46 (26%) had PS 3.

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Although the initial diagnostic work varied depending on the year of examination, the staging was usually determined by physical examination, routine chest roentgenography, whole-lung tomography, fiberoptic bronchoscopy, computed tomography of the brain and abdomen, bone marrow aspiration and bone scintiscan as described previously [17]. One hundred and one patients (57%) presented with LD confined to one hemithorax including bilateral mediastinal and ipsilateral supraclavicular nodes and the remaining 73 patients (43%) had ED. Details are given in Table 1. Patients were treated with combination chemotherapy (Table 2). Two kinds of regimens were usually used simultaneously in our institute [CAV(P) vs. CONP and CONP vs. CONP-VAD]. A small number of patients was sometimes treated with the regimens used as a pilot study. From 1978 to 1982, chest radiation therapy following systemic chemotherapy was given to most patients with LD. From 1982 to 1984, no chest radiotherapy was employed in order to examine the efficacy of combination chemotherapy itself on SCLC. As a result, chest radiation therapy was also given to 34% of patients with LD, but prophylactic cranial irradiation (PCI) was not employed. Tumor response was evaluated according to the WHO guidelines [18] in the following manner. A CR was defined as the disappearance of all evidence of disease for more than 4 weeks without appearance of any new lesions. A partial response (PR) was defined as a greater than 50% decrease in the sum of the products of the two perpendicular diameters of all measurable lesions without an increase in any existing lesion lasting more than 4 weeks.

Table 1. *Characteristics of patients with small cell lung cancer*

No. of patients treated	174
Sex	
Male/female	139/35
Ratio (M:F)	4:1
Mean age (range)	64 (34–82)
Performance status	
0–1	74 (43%)
2	54 (31%)
3	46 (26%)
Extent of disease	
Limited disease	101 (57%)
Extensive disease	73 (43%)

In this study all patients have been followed to death or for periods of at least 3 years. Survival was measured from first treatment to 1 September 1987. The survival curves were derived by the method of Kaplan and Meier [19] and analyzed by the generalized Wilcoxon test [20]. The chi-square test [21] was used to compare the response rates and the distribution of patient characteristics. Fisher's exact test [21] was used if fewer than five long-term survivors were expected in one of the categories. All *P* values correspond to a two-sided significance test.

RESULTS

Response to therapy

One hundred and sixty-two of the 174 patients were evaluable for response and all patients were

Table 2. *Chemotherapeutic regimens employed in therapy of small cell lung cancer* (1978–1984)

CAV(P):	
(C)	cyclophosphamide 600–700 mg/m^2, i.v. on day 2
(A)	adriamycin (doxorubicin) 40 mg/m^2, i.v. on day 1
(V)	vincristine 0.6–0.7 mg/m^2, i.v. on days 1, 4, 8 and 15
(P)	procarbazine 100 mg/body orally for 14 days
CONP:	
(C)	cyclophosphamide 700 mg/m^2, i.v. on day 2
(O)	vincristine 0.7 mg/m^2, i.v. on day 2
(N)	nimustine hydrochloride 70 mg/m^2 i.v. on day 1
(P)	procarbazine 100 mg/body orally for 7 days
CONP–AM: alternate CONP and AM every 28 days	
(A)	adriamycin (doxorubicin) 50 mg/m^2, i.v. on day 1
(M)	methotrexate 100 mg/body, i.v. on days 2 and 8
CONP–VAM: alternate CONP and VAM every 28 days	
(V)	etoposide (VP-16) 200 mg/body orally on days 1–4
(A)	adriamycin (doxorubicin) 40–50 mg/body, i.v. on day 1
(M)	methotrexate 50 mg/body, i.v. on day 1
CONP–VAD: alternate CONP and VAD every 28 days	
(V)	etoposide (VP-16) 60 mg/m^2, i.v. on days 1–4
(A)	adriamycin (doxorubicin) 30mg/m^2, i.v. on day 1
(D)	cisplatin (DDP) 60 mg/m^2, i.v. on day 1

i.v.: intravenously.

evaluable for survival (Table 3). In the 97 evaluable patients who initially presented with LD, 33 achieved a CR (23%) and 41 a PR (42%), with a response rate of 65%. In the 65 evaluable patients with ED, eight (12%) achieved a CR and 36 (55%) a PR, with a response rate of 68%. Thus, the overall response rate was 66%; the overall CR rate was 19%. There were no differences in response rates between patients with LD and those with ED. The response rates according to initial stage and chemotherapy program are also shown in Table 3. When chemotherapy programs were compared for response rates, the highest response rate was obtained with alternating regimen of CONP–VAD (response rates; 85% for LD, and 81% for ED).

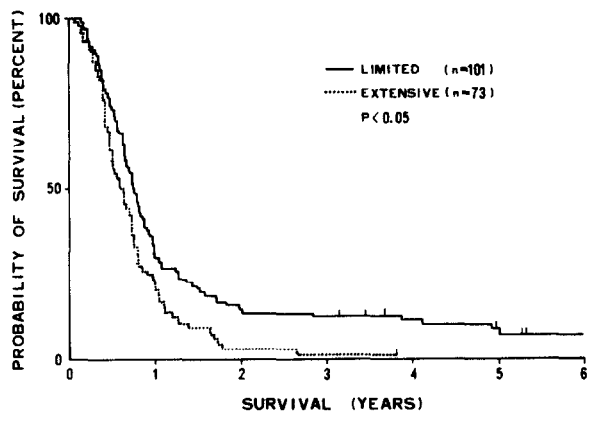

Fig. 1. Survival curves for patients with small cell lung cancer according to extent of disease. Vertical bars indicate the patients still alive.

Survival

Median survival for patients with LD was 8.7 months, compared to 7.1 months for those with ED (Fig. 1). There was a significant survival benefit for patients with LD ($P < 0.05$). The overall median survival was 8.3 months. The median survivals in the chemotherapy program with each stage are shown at each stage in Table 3. The alternating regimen (CONP–VAM or CONP–VAD) resulted in longer median survival.

Long-term survival

By September 1987, 14 of 174 (8%) survived for 3 years or more. Thirteen of 174 (7.5%) remained alive and free of disease at 3 or more than 8 years of follow-up; 12 of the 101 patients (11.9%) presented with LD and one of 73 (1.4%) with ED restricted to only one metastatic site of the contralateral cervical node. The results in patients with ED were very disappointing. The difference between the long-term survival rates in LD and ED was statistically significant ($P < 0.05$). Only one patient with apparent disease is alive after 3 years at the time of this report and he has never been disease-free. Patient characteristics, type and duration of treatment and outcome of the 13 disease-free long-term survivors are summarized in Table 4. Of these 13 patients, 10 were men (7.2%) and three were women (8.6%) ($P > 0.1$), with an average age of 62 years (range, 36–77 years). In addition to the

Table 3. Response rates and survival in chemotherapy programs and extent of disease

Regimen*	Stage	No. of patients	Response			Median survival (months)	No. of 3-year disease-free survivors	
			CR	PR	CR + PR			
CAV(P)	LD	16	4	4	(57)	9.7	4	(25)
	ED	5	0	2	(40)	5.1	0	(0)
CONP	LD	57	9	29	(69)	8.6	2	(4)
	ED	38	5	18	(66)	6.1	0	(0)
CONP–AM	LD	2	0	1	(50)	2.3	0	(0)
	ED	7	0	5	(71)	6.3	0	(0)
CONP–VAM	LD	4	2	1	(75)	17.1	2	(50)
	ED	0						
CONP–VAD	LD	13	6	5	(85)	15.7	4	(31)
	ED	21	4	9	(81)	8.5	1	(5)
Others	LD	9	0	2	(22)	6.6	0	(0)
	ED	2	0	1	(50)	2.5	0	(0)
Total	LD	101	22	41	(65)	8.7	12	(12)
	ED	73	8	36	(68)	7.1	1	(1)
Overall		174	30	77	(66)	8.3	13	(8)

*See Table 2 for details of the chemotherapy program.
Figures in parentheses are percentages.
CR: complete response; PR: partial response; LD: limited disease; ED: extensive disease.

Table 4. Three-year disease-free survivors of small cell lung cancer

Patient No.	Age* (years)	Sex	PS	Stage	Induction chemotherapy	Chest radiation (Gy)	Duration of therapy (months)	Response	Survival (years)	Cause of death
1	68	M	2	LD	CAV	30	6	NE	8.1	Pneumonia
2	58	M	3	LD	CAVP	30	14	CR	6.8†	
3	63	M	1	LD	CAVP	30	16	CR	6.7†	
4	60	M	1	LD	CONP–VAD	40	9	CR	5.3†	
5	57	M	1	LD	CONP–VAD	0	11	CR	5.3†	
6	59	M	3	LD	CONP–VAM	0	14	CR	5.0†	
7	77	F	1	LD	CONP	30	3	CR	5.0	Squamous cell carcinoma of the lung
8	68	F	2	LD	CONP	0	5	CR	4.9	Cancer of the stomach and gallbladder
9	72	M	1	LD	CAV	60	12	NE	4.1	Cardiac arrest
10	60	M	1	ED	CONP–VAD	0	4	CR	3.8†	
11	70	M	2	LD	CONP–VAM	0	20	CR	3.8	Squamous cell carcinoma of the lung
12	52	F	1	LD	CONP–VAD	0	4	CR	3.7†	
13	36	M	1	LD	CONP–VAD	0	17	CR	3.4†	

*At induction chemotherapy.
†Alive and disease-free as of 1 September 1987.
PS: performance status; NE: nonevaluable; CR: complete response.
Other abbreviations as in Table 2.

patients' sex, performance status had statistically no difference on the probability of 3-year disease-free survival. Six of 13 (46%) received chest radiation therapy following systemic chemotherapy. Three-year disease-free survival rates were 18% vs. 10% for chemotherapy + thoracic radiotherapy vs. chemotherapy alone ($P > 0.05$). Of the 13 patients, 11 achieved a CR with the initial chemotherapy or subsequent radiation therapy. The remaining two patients who could not be evaluated had radiation fibrosis, making interpretation of the tumor response impossible on a chest roentgenogram. However, we believe that they have achieved a CR. To date, eight of the 13 patients have remained alive and disease-free, and have returned to their previous life-style. Five died free of disease from unrelated causes. Three (23%) (patients 7, 8 and 11) developed second malignancies. Patients 7 and 11 developed squamous cell carcinoma of the contralateral lung 3.3 and 2.3 years after starting of SCLC therapy, and died 1.7 and 1.5 years after the second malignancy was found. Patient 8 was found to have adenocarcinoma of the stomach and gall bladder 4.8 years after beginning of therapy, and died 2 months after the second cancer was detected. As a whole, the number of second cancers was 4.9 times larger than its expected value calculated from the cancer incidence rate of Osaka Cancer Registry [22] ($P < 0.05$). It was statistically significant although the 95% confidence interval was 1.02–14.5. Patient 1 died of pneumonia and patient 9 died of a sudden cardiac arrest. Autopsies, performed on three (patients 1, 7 and 8) of the five who died, revealed no evidence of SCLC. With regard to neurologic abnormalities, patient 1 suffered from a paraplegia due to radiation myelopathy 4.3 years after he had received radiation therapy to the chest (30 Gy). Patient 11 developed progressive neurologic deterioration with dementia 2 years after starting chemotherapy. Other complications of therapy including pulmonary dysfunction secondary to radiation therapy and hematologic abnormalities were not observed in our series.

Finally, the last relapse that we observed was at 1.5 years from the beginning of combination chemotherapy.

DISCUSSION

Aisner *et al.* [7] have stressed that the best measurement of any regimen's efficacy is survival for 2 or preferably 3 years. Therefore, the present study was designed to evaluate the survival of patients with SCLC treated with multiple intensive combination chemotherapy at a single institution, the Osaka Prefectural Habikino Hospital in Japan. Of particular interest was to identify 3-year disease-free survivors with specific factors of prognostic importance. Overall, out of the 174 patients with SCLC, 13 (7.5%) have remained disease-free for more than 3 years (range, 3.4–8.1 years) (Table 4). This figure is within the range of the expected rate of 5–10% 3-year disease-free survival rate from a highly active treatment program [7]. With regard to extent of disease, the 3-year disease-free survival rate of patients with LD (12%) was significantly better than that of those with ED (1%) ($P < 0.05$) (Table 3). One patient with ED who survived 3

years or longer had only one metastatic site (cervical node). Østerlind *et al.* [23] suggested that tumor spread is more critical than the initial amount of tumor in determining the possibility of cure. The present study confirms the well-established survival benefit for patients with LD [9–12, 15]. A CR is generally believed to be an essential prerequisite for long-term survival [9, 14, 15]. However, Vogelsang *et al.* [12] reported that eight of the 104 patients (7.7%) with a PR survived for 2 years and some patients in whom a CR did not occur survived longer than traditionally expected.

Indeed, in the present study one patient who has never achieved a CR survived 3 years or more although all disease-free long-term survivors, except the two patients who could not be evaluated, achieved a CR (Table 4). Increased long-term survival in women compared to men has been observed [15, 22, 24], while Souhami *et al.* [25] reported no differences in survival between male and female patients. Choi *et al.* [16] stated that there was a trend of better survival for female patients up to 2 years, but this difference of survival between male and female patients disappeared thereafter. In this study, the patients' sex has had no influence on 3-year survival (Table 4). In agreement with the findings of Johnson *et al.* [11] and Suga *et al.* [15], we did not find any statistical significance of performance status in long-term survival (Table 4). Although the exact role of chest radiation and its impact on long-term survival remain unclear [16, 26, 27], we did not recognize a statistically significant benefit in the 3-year disease-free survival rate with the combined modality treatment (10% for chemotherapy alone vs. 18% for chemotherapy plus thoracic radiation).

Second malignancies have been reported after successful treatment of SCLC. Most of them are therapy-related acute nonlymphocytic leukemias [10, 12, 28–31]. Dang *et al.* [30] hypothesized that patients with SCLC given radiotherapy and multiple cycles of chemotherapy might be at increased risk for development of multiple karyotypic abnormalities and that these in turn might predispose patients to an increased risk of second leukemia. In our study, no hematologic abnormalities were observed. To date, there were 25 reported cases of second non-SCLC in long-term survivors of SCLC [11, 31–33]. In the present study, patients 7 and 11 developed squamous cell carcinoma of the contralateral lung 3.3 and 2.3 years after the beginning of initial therapy (Table 4). Three of 13 (23%) developed second malignancies. For these patients, the number of second cancers was 4.9 times higher than the expected rates in the Osaka Cancer Registry [22]. This increased risk suggests that their entire epithelium has still remained at risk for subsequent development of neoplasms. This may be due to a genetic predisposition or to previous increased carcinogenic exposure (smoking or the prolonged use of anticancer agents).

Neurologic abnormalities have been noted by several investigators especially when PCI had been given [10, 11, 16, 29–31]. Some of them [11] reported that neurologic abnormalities were the most prevalent findings in the follow-up of the long-term survivors. Livingston *et al.* [10] believed that co-administration of a nitrosourea and methotrexate during the induction chemotherapy may account for these complications. One of our patients (patient 11), who received both a nitrosourea and methotrexate, manifested a progressive neurologic deterioration with dementia. In addition, patient 1 suffered from a paraplegia due to radiation myelopathy.

Although the proportion of long-term disease-free survivors is still low, there are many late complications including second malignancies and neurologic abnormalities after the successful treatment of SCLC. Therefore, it is necessary that these long-term survivors of SCLC should be kept under careful supervision to detect these complications as early as possible.

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