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Abstract

We evaluated the long-term outcome of 148 patients with small cell lung cancer (SCLC) who had been entered into clinical trials of chemotherapy with or without thoracic and prophylactic cranial irradiation (PCI) between 1981 and 1987. Eighteen patients (12%) survived for 2 or more years. With a minimum follow-up of 4.5 years, 10 of the 18 patients who remained disease-free at 2 years are currently alive and free of SCLC. Seven of these 10 patients currently function as they did before diagnosis. However, three suffer from central nervous system changes of varying degrees in severity which appeared 2-3 years after PCI. Eight of the 18 patients who were disease-free at 2 years have died. Two died of isolated relapse in the brain at 3.6 and 4.2 years after initiation of chemotherapy. Five died of other malignancies while continuing their complete response to SCLC; two of non-small cell lung cancer, two of acute myelogenous leukemia, and one of hepatocellular carcinoma. Another patient died of an unrelated disease without any evidence of SCLC. A small but substantial proportion of patients who underwent intensive treatment will achieve long-term survival; however, these patients remain at higher risk for second cancers and late toxicities. Therefore, attention must be directed to defining the safest way to employ such treatment in the management of SCLC.

KEYWORDS: small cell lung cancer, long-term survivors, late relapse, toxicities, complications

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Mortality and Morbidity in Two-Year Disease-Free Survivors of Small Cell Lung Cancer after Treatment with Combination Chemotherapy with or without Irradiation

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We evaluated the long-term outcome of 148 patients with small cell lung cancer (SCLC) who had been entered into clinical trials of chemotherapy with or without thoracic and prophylactic cranial irradiation (PCI) between 1981 and 1987. Eighteen patients (12%) survived for 2 or more years. With a minimum follow-up of 4.5 years, 10 of the 18 patients who remained disease-free at 2 years are currently alive and free of SCLC. Seven of these 10 patients currently function as they did before diagnosis. However, three suffer from central nervous system changes of varying degrees in severity which appeared 2-3 years after PCI. Eight of the 18 patients who were disease-free at 2 years have died. Two died of isolated relapse in the brain at 3.6 and 4.2 years after initiation of chemotherapy. Five died of other malignancies while continuing their complete response to SCLC; two of non-small cell lung cancer, two of acute myelogenous leukemia, and one of hepatocellular carcinoma. Another patient died of an unrelated disease without any evidence of SCLC. A small but substantial proportion of patients who underwent intensive treatment will achieve long-term survival; however, these patients remain at hihger risk for second cancers and late toxicities. Therefore, attention must be directed to defining the safest way to employ such treatment in the management of SCLC.

Key words : **small cell lung cancer, long-term survivors, late relapse, toxicities, complications**

Introduction of intensive chemotherapy with or without thoracic irradiation (TRT) and prophylactic cranial irradiation (PCI) has resulted in a significant prolongation of survival in patients with small cell lung cancer (SCLC) (1). Despite this progress, only a small fraction of patients has a chance of long-term disease-free survival; a 15 to 20% chance for those with limited disease (LD) and a 1 to 3% chance for those with extensive disease (ED) (1-5). Moreover, long-term survivors became known to be at considerable risk for developing chronic morbidity due to complications of therapy, for recurrent disease (3-9), and for developing second malignancies (4-6). The objective of this study was to investigate late toxicities and complications developing in long-term disease-free survivors of SCLC who had received intensive combination chemotherapy with or without TRT and PCI.

Patients and Methods

From April 1981 to December 1987, a total of 148 newly diagnosed patients with histology- or cytology-proven SCLC

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Table 1 Treatment protocols used during study period

Protocol	Chemotherapy regimen	Thoracic irradiation	Prophylactic cranial irradiation
COMP-VAN [10]	CTX 260 mg/m², iv, days 1-5 VCR 1.4 mg/m², iv, day 1 MTX 6.5 mg/m², im, days 1-5 PCZ 65 mg/m², po, days 1-5 Alternating with: ETP 140 mg/m², po, days 29-32 ADM 40 mg/m², iv, day 29 NMT 40 mg/m², iv, day 29 Every 6-7 weeks(more than 5 cycles)	40 Gy only for patients with limited disease who were allocated to receive thorathic irradiation, between #1 and #2 cycle of COMP-VAN	40 Gy/20 fractions only for complete responders who were allocated to receive prophylactic cranial irradiation
CAV-EP Hybrid [11]	CTX 700 mg/m², iv, day 1 ADM 30 mg/m², iv, day 1 VCR 1.4 mg/m², iv, day 1 ETP 100 mg/m², iv, days 8-9 CDDP 60 mg/m², iv, day 8 Every 4 weeks (5-6 cycles)	50 Gy only for patients with LD, starting when they achieved a maximal response to CAV-EP	30 Gy/15 fractions only for patients with limited disease achiving a complete response

Abbreviations: CTX, cyclophosphamide; VCR, vincristine; MTX, methotrexate, PCZ, procarbazine; ETP, etoposide, ADM, Adriamycin; NMT, nimustine; CDDP, cisplatin; iv: intravenously; im: intramuscularly; po: orally.

Table 2 Characteristics of patients who were fully evaluated in therapeutic trials conducted between 1981 and 1987

Total number of patients evaluated	148
Median age (range)	65 (28-80)
Sex	
Male	121
Female	27
Extent of disease	
Limited	76
Extensive	72
Performance status	
0-1	104
2-3	44
Chemotherapy	
COMP-VAN	112
CAV-EP hybrid	36
Thoracic irradiation	
Received	48
Not received	100
PCI	
Received	38
Not received	110

received their treatment in a series of our cooperative clinical trials (10, 11). These are outlined in Table 1. In the trial of COMP-VAN alternating chemotherapy (10), patients had to be 80 years of age or less, to have measurable disease, and to have a performance status (PS) of 0, 1, 2 or 3. Patients were considered to be ineligible if they had unrelated medical problems that would preclude chemotherapy and/or radiotherapy, *i. e.*, arrhythmias and/or congestive heart failure requiring daily medication, fresh myocardial infarction, intractable diabetes mellitus, uncontrolled infection, creatnine level greater than 1.5 mg/dl, or total bilirubin level greater than 1.5 mg/dl. Eligibility criteria in the pilot trial of CAV-EP hybrid chemotherapy (11) were almost identical to the above with the exclusion of those being 76 years or more, or those having a PS of 3. All cases underwent staging, which included fiberoptic bronchoscopy; chest radiographs including computerized tomography (CT) ; CT of the brain and upper abdomen; radionuclide bone scan; iliac crest bone marrow biopsy; complete blood count; and blood chemistry profile. Based on staging procedures, cases were divided into LD confined to the hemithorax or ED with metastases beyond the hemithorax. Cases with metastases in the supraclavicular lymph nodes were defined as LD, but those with cytology-positive unilateral pleural effusion were defined as ED. Characteristics of the 148 patients who were fully evaluated for tumor response and survival are listed in Table 2.

Patients who had completed the treatment were examined for disease status and late toxicity by careful history and physical examination; routine chest radiograph; and other examinations as indicated at intervals of 1-3 months. Brain metastases were routinely monitored by CT every 3-5 months.

Results

At restaging, 2 years after the initiation of chemotherapy, 18 (12 %) of 148 patients were found to be free of SCLC. These included 15 (20 %) of 76 patients with LD and three (4 %) of 72 patients with ED (Table 3). There were 13 men and five women with a median age of 64 years (range, 48 to 75). The majority of these patients

Table 3 List of 2-year disease-free survivors among 148 patients

Patient number	Age	Sex	PS	LD/ED	CT regimen	Irradiation		Time to progression in years	Survival in years	Cause of death
						Chest	PCI			
1	58	M	1	LD	COMP-VAN	R	NR	10.4+	10.4	NSCLC (Ad)
2	48	F	0	LD	COMP-VAN	R	NR	8.3+	8.3+	
3	55	M	1	LD	COMP-VAN	R	R	8.2+	8.2+	
4	66	M	1	LD	COMP-VAN	NR	R	6.0+	6.0	Cholecystitis
5	69	M	1	LD	COMP-VAN	R	R	5.8+	5.8+	
6	73	M	1	LD	COMP-VAN	R	NR	5.7+	5.7+	
7	66	F	0	LD	COMP-VAN	R	R	5.7+	5.7+	
8	67	M	2	LD	COMP-VAN	NR	R	5.5+	5.5	MDS/AML
9	75	F	0	ED	CAV-EP	NR	NR	5.4+	5.4+	
10	62	M	1	ED	CAV-EP	R	R	5.0+	5.0+	
11	75	M	1	LD	CAV-EP	R	R	4.9+	4.9+	
12	63	F	2	LD	CAV-EP	R	R	4.9+	4.9+	
13	58	M	2	ED	CAV-EP	NR	R	4.5+	4.5+	
14	58	M	1	LD	COMP-VAN	NR	NR	2.5	4.2	Relapse
15	67	M	2	ED	COMP-VAN	NR	NR	3.9+	3.9	NSCLC (Sq)
16	58	M	1	LD	CAV-EP	R	R	2.8	3.6	Relapse
17	52	F	1	LD	COMP-VAN	R	R	3.0+	3.0	MDS/AML
18	65	M	1	LD	CAV-EP	R	R	2.2+	2.2	HCC

Abbreviations: CT, chemotherapy; PCI, prophylactic cranial irradiation; M, male; F, female; R, recieved; NR, not recieved; NSCLC, non-small cell lung cancer; Ad, adenocarcinoma; Sq, squamous cell carcinoma; MDS/AML, myelodysplastic syndrome terminated in acute myelogenous leukemia; HCC, hepatocellular carcinoma; COMP-VAN, CAV-EP, See Table 1.

had PS of 0 or 1 at the time of diagnosis. Irradiation had been delivered to the chest in 12 patients with LD, and to the brain in 12 patients as prophylaxis. Regarding chemotherapy regimen, these 18 patients comprised 11 (10%) of 112 patients who had received COMP-VAN, and seven (19%) of 36 patients who had received CAV-EP hybrid regimen.

With a minimum follow-up of 4.5 years, 10 (7%) of 148 patients continue to survive without evidence of SCLC. Seven of these 10 patients currently function at a level comparable with that before diagnosis. However, three patients receiving PCI suffered from central nervous system (CNS) changes of varying degrees in severity. A 63-year old woman (patient 12 in Table 3) who received CAV-EP and PCI of 30 Gy developed dementia and gait ataxia 2 years after PCI. She is debilitated with a gradual progression of symptoms. A 69-year old man (patient 5) who had received COMP-VAN and PCI of 40 Gy presented gait ataxia and mild impairment of recent memory 3 years after PCI. Another 62-year old man (patient 10) who had received CAV-EP and PCI of 30 Gy developed hand tremor and gait ataxia 2.3 years after completion of PCI. Symptoms in the latter two patients have remained stable, permitting them to care for themselves in the daily life. CT images of the brain in these patients revealed a various degree of cortical atrophy with or without ventricular dilatation. All 148 patients received Adriamycin as their initial treatment. None of the patients developed congestive heart failure due to cardiomyopathy. Although radiographically common, radiation fibrosis was generally not of clinical significance in those who received thoracic irradiation.

Eight of the 18 patients who were free of SCLC at 2 years have died. SCLC-related deaths were seen in only two patients, both of whom were diagnosed as having isolated brain relapse by a CT-based restaging at 2.5 and 2.8 years, and died of CNS metastases at 3.6 and 4.2 years, respectively, without developing any metastasis outside the brain. Of these two patients one had received PCI and the other had not. The relapse found in the brain of the latter patients at 2.8 years was identified as the last relapse seen in our series. Five patients have died of other malignancies while continuing their complete response to SCLC. Two patients who had received COMP-VAN died of myelodysplastic syndrome (MDS) terminating in acute myelogenous leukemia (AML): One who had received COMP-VAN plus TRT induction and COMP maintenance, which included nitrosourea and procarbazine, developed MDS at 1.9 years and died of AML at 3 years showing a typical chromosome abnormal-

ity seen in treatment-associated leukemia, a deletion of one chromosome 7; the other who had received 5 cycles of COMP-VAN and TRT suffered from MDS at 4.6 years and died of AML at 5.5 years. Two patients who continued to smoke developed non-small cell lung cancer (NSCLC). One developed squamous cell carcinoma at 2.3 years in the same lobe that was affected by SCLC. Histology of the tumor was confirmed twice by separate biopsies. He was not a candidate for surgical treatment because of his medical conditions, and died of the disease 3.9 years after diagnosis of SCLC. Adenocarcinoma stage I was diagnosed in the opposite lung of the other 7.9 years after diagnosis of SCLC, but he refused surgical treatment and died of the disease at 10.4 years. The fifth patient died of hepatocellular carcinoma at 2.2 years. In addition, one patient died of gangrenous cholecystitis at 6 years without clinical evidence of SCLC.

Discussion

In our series of patients with a 4.5 to 11-year follow-up, 8 (11 %) of 76 patients with LD, and two (3 %) of 72 with ED are currently alive and disease-free. These results seem to be comparable with other reported studies (1, 2, 12, 13). Seifter and Ihde compiled the results of 7 reports on 5-year disease-free survivors (1). Only 72 (4 %) of 2,006 patients survived beyond 5 years; 58 (7 %) of 862 with LD and 14 (1 %) of 1,144 with ED. Recent reports confirmed the results mentioned above (2. 12, 13).

The major cause of deaths in the 2-year disease-free survivors was not relapsing disease, but second malignancies. Only two patients died of relapsing disease which developed solely in the brain. Investigators reporting long-term follow-up of SCLC patients have identified the last relapse at 1.5 (2), 3.3 (14), 5 (4, 15), 6.2 (16) and 8.1 years (3) after initiation of treatment. In all of the reported series including our own, relapses after 5 years appear to be a rare event. We believe that our patients surviving free of SCLC beyond 4.5 years have probably been cured of the disease. Although brain relapses are not so uncommon among long-term survivors of SCLC (4, 14, 17, 18), late relapses in our series occurred solely in the brain. This finding indicates that the incidence of such brain metastasis would increase as the number of long-term survivors increases in the future.

Long-term survivors of SCLC appear to remain at high risk for the development of other malignancies such as MDS, usually terminating in AML (4, 6, 19), and NSCLC (4, 5, 13). Among the 18 2-year disease-free survivors, two patients each developed acute non-lymphocytic leukemia (ANLL) and NSCLC. The incidence of ANLL in our series was lower when compared with Volk's series (20), but was higher than that in the Danish series where three cases of leukemia among 72 long-term survivors have been reported (4). The National Cancer Institute (NCI) series documented only one erythroleukemia among 28 such patients (16). The cause of ANLL occurring in survivors of SCLC is assumed to be the treatment. Dang *et al* reported a case of ANLL and reviewed 14 such cases in the literature (19). They speculated that long-term maintenance chemotherapy, use of alkylating agents, nitrosoureas, and/or procarbazine, and TRT were the factors contributing to the development of secondary leukemia. Indeed, the development of ANLL in our series was restricted to those receiving COMP-VAN (10) which included cyclophosphamide, nitrosourea and procarbazine.

NSCLC has been another concern in the long-term survivors of SCLC (4, 5, 13, 21). In our series, one patient each has developed squamous cell carcinoma and adenocarcinoma. Since the former patient developed his second tumor in the same lobe that had been affected by SCLC, we made the diagnosis with caution. Johnson *et al.* suggested criteria for the diagnosis of metachronous NSCLC after treatment of SCLC including (a) a 2-year disease-free interval; (b) histological proof of the absence of SCLC component; (c) origin in a different lobe to the original SCLC; and (d) no extrapulmonary SCLC metastasis (21). The patient fulfilled all of the criteria but the third. However, his clinical course was typical for squamous cell lung cancer, showing a dominant local growth with a minimal extrathoracic progression, and terminating in respiratory failure. The development of a second malignancy in the lung is probably less likely to be related to chemotherapy and/or TRT because a similar risk for occurrence of second lung cancer has bees seen in patients with NSCLC being resected surgically (22, 23). Including the present study, the incidence of NSCLC which occurs in long-term survivors of SCLC seems to be less frequent in Japan (2, 24) than in the Western countries (4, 5, 13). This may reflect a difference in the incidence of lung cancer in the general population of these countries.

Late toxicities developing in long-term survivors of SCLC is another concern. A frequent occurrence of

treatment related fatal cardiomyopathy and debilitating pulmonary fibrosis has been reported (4, 7, 24), but no patient in our series has presented with such symptoms of clinical significance. This may be related to the mode of treatment we had used. The cumulative dose of Adriamycin was limited to 360 mg/m^2 in patients receiving COMP-VAN as well as CAV-EP hybrid regimen, which was much less than in Frytak's series (7). The sequence of chemotherapy and TRT may represent another explanation; all the patients in the former trial received TRT sequentially between cycles 1 and 2 of the chemotherapy, and those in the latter trial received it after they achieved a maximal response to chemotherapy. Late CNS toxicity was seen in three patients who had received PCI; it was debilitating in one, and mild and non-progressive in the two other patients. This toxicity is of particular concern because it is very distressing for previously functioning patients. Armstrong showed that CNS toxicities of varying degrees in severity occurred in a rang of 13% to 73% of patients by compiling the literature, and indicated a close interaction of cranial irradiation and such drungs as nitrosourea, methotrexate and procarbazine in the development of CNS toxicity (25). However, the toxicity in our series appears to be less frequent and less serious in COMP-VAN that includes all such drugs compared to CAV-EP that includes none of such drugs. Recent studies also have indicated that CNS toxicity in long-term survivors receiving PCI occurred in 19% to 63% of the cases (9, 26, 27). The incidence in our series seems to be less frequent than the NCI (26) and the Indiana series (27), and more frequent than the Toronto series (9).

Although improvement of the long-term disease-free survival rate in SCLC patients remains a priority concern in designing new strategies, the late toxicities and complications seen in long-term survivors should be of concern. Thus, modifications that may potentially avoid such troubles should be taken into consideration when designing future treatment regimens.

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