Eur J Cancer, Vol. 27, No. 4, pp. 427–430, 1991.
Printed in Great Britain

0277–5379/91 $3.00 + 0.00

Specialist Interest Articles

Late Toxicities and Complications in Three-year Survivors of Small Cell Lung Cancer

Fumihiro Oshita, Tomohide Tamura, Akira Kojima, Kohzo Yamada, Masaaki Fukuda, Kazuhiko Nakagawa, Yuichiro Ohe, Yasutsuna Sasaki, Kenji Eguchi, Tetsu Shinkai, Ryosuke Ono, Kohei Hara and Nagahiro Saijo

123 patients with small cell lung cancer (SCLC) presented to the National Cancer Center Hospital (Tokyo) between 1978 and 1986. 22 of 71 patients with limited stage disease (LD) and none of 52 patients with extensive disease (ED) survived for 3 years. 15 of the 22 three year survivors had significant late complications. All patients received chemotherapy and either thoracic irradiation, resection or both. No prophylactic cranial irradiation was given. 4 patients developed cardiac failure, 2 with a dilated cardiomyopathy, despite the fact that no patient received over 420 mg/m^2 of doxorubicin. 12 patients of the 17 who received thoracic irradiation developed radiation pneumonitis and 3 required hospitalisation for severe haemoptysis (2) or cavity formation (1). 1 patient who received nimustine developed a fatal myelodysplastic syndrome and 2 additional patients developed second primary tumours in the oesophagus (1) and stomach (1). Mild peripheral neuropathy (WHO grade 1) was persistent in 3 patients and asymptomatic azotemia (WHO grade 1) in 7. Despite advances in the treatment of SCLC there are very few asymptomatic long-term survivors.
Eur J Cancer, Vol. 27, No. 4, pp. 427–430, 1991

INTRODUCTION

SMALL CELL LUNG CANCER (SCLC) represents approximately 15–20% of all bronchogenic cancers and is usually disseminated at the time of diagnosis [1]. Advances in the systemic and local therapy of SCLC have resulted in a dramatic increase in responsiveness to treatment with long-term survival rates of 5–10% overall and 15–25% for patients with limited disease (LD) [2, 3]. As various centres have accumulated long term (3 years or longer) survivors it is clear that late toxicity and long-term complications are a significant problem, particularly in patients receiving prophylactic cranial irradiation [4–7].

This report analyses the experience of the National Cancer Center (Tokyo) for the period 1978–1986, during which 123 patients were treated for SCLC with diverse combinations of chemotherapy, chest irradiation (but not prophylactic cranial irradiation [PCI]) and surgery.

PATIENTS AND METHODS

123 patients with histologically or cytologically proven SCLC were initially treated with chemotherapy from 1978 to 1986 at the National Cancer Center Hospital (Table 1). 22 patients who survived more than 3 years were analysed for their incidence of respiratory, cardiac, haematological, neurological or other complications.

Before initial treatment, all patients underwent a standard staging evaluation including a unilateral bone marrow aspiration, isotopic bone scan, computed tomography of chest and brain and ultrasonography of the abdomen.

Following these staging procedures, limited disease (LD) was defined as tumour confined to one hemithorax, including mediastinal and/or bilateral supraclavicular lymph nodes. Disease beyond these confines was classified as extensive disease (ED) and during this period included patients with ipsilateral pleural effusion.

The criteria for performance status (PS) and response were

Table 1. Characteristics of patients with small cell lung cancer

No. of patients	123
Age (median)	34–82 (65)
Sex	
male	102
female	21
Stage	
LD	71
ED	52
PS (ECOG)	
0–1	92
2–4	31

PS = performance status, ECOG = Eastern Cooperative Oncology Group.

Correspondence to F. Oshita.
F. Oshita, T. Tamura, A. Kojima, K. Yamada, M. Fukuda, K. Nakagawa, Y. Ohe, Y. Sasaki, K. Eguchi and T. Shinkai are at the Department of Internal Medicine; R. Ono is at the Radiotherapy Division, National Cancer Center Hospital and N. Saijo is at the Pharmacology Division, National Cancer Center Research Institute, Tokyo; and K. Hara is at the Second Department of Internal Medicine, Nagasaki University School of Medicine, Nagasaki, Japan.
Revised 26 Nov. 1990; accepted 11 Jan. 1991.

Table 2. Clinical and treatment characteristics of the 22 3-year survivors of SCLC

No. of patients	22
No. of disease free patients	20
Age (median)	37–74 (58)
Sex	
Male	16
Female	6
PS (ECOG)	
0	7
1	14
2	1
Stage	
LD*	22
Treatment (primary)	
No. of chemotherapy courses (median)	1–13 (6)
Response to initial chemotherapy	
CR	8
PR	7
NC	1
NE†	6
Chest irradiation*	17
Surgery (after chemotherapy/ radiotherapy)	10
Pneumonectomy	3
Lobectomy	7
Follow-up (months)	39–118

*1 patient had extension of disease into the cervical lymph-nodes with radiotherapy added to the primary treatment course.
†Bronchial artery infusion (1) or no response to first chemotherapy followed by second regimen.
CR = complete response, PR = partial response, NC = no change, NE = not evaluable.

given as part of a series of protocol trials. Only 8 of the 22 patients received doxorubicin. 17 patients received chest radiotherapy, 1 with an extension to cervical nodes. An additional patient had neck irradiation for local progression. 10 patients underwent resection of responding (6) or stable (4) disease following chemotherapy with or without radiotherapy.

Pulmonary complications

Radiation fibrosis was radiographically evident on chest X-ray in 12 of 16 patients receiving radiotherapy, but was not of clinical significance. 3 of the 12 patients had significant haemoptysis requiring hospitalisation in 2, including 1 patient with cavity formation requiring bronchial artery embolisation. The onset of severe haemoptysis occurred 49–59 months follow-

Table 3. Chemotherapy regimens

Initial chemotherapy	No. of patients	No. of courses (median)
CPA+VCR+ACNU	7	5
VCR+ACNU	2	2
VCR+MMC	1	7
CPA+DOX+VCR	5	6
CDDP+VP−16	3	6
CPA+DOX+VCR alternating CDDP+VP−16	3	6
MMC (BAI)	1	6

CPA = cyclophosphamide, VCR = vincristine, ACNU = nimustine, MMC = mitomycin, DOX = doxorubicin, CDDP = cisplatin, VP-16 = etoposide, BAI = bronchial artery infusion.

Table 4. Cardiac toxicity in 3-year survivors

Age/sex	Dyspnoea (NYHA)	PH	ST-T change (ECG)	Ultrasound	Doxorubicin (mg/m²)	Operation	Radiation (Gy)
64/M	3	−	Diffuse	DCM pattern	−	−	52.7
57/M*	3	+	Diffuse	DCM pattern	420	lt pneumonectomy	44
44/F	2	−	Lateral and inferior	−	120	lt pneumonectomy	60
68/M	2	+	Anterior	−	100	−	−

*Died of myocardial infarction.
PH = past history of cardiac disease, DCM = dilated cardiomyopathy, NYHA = New York Heart Association classification.

defined by the Eastern Cooperative Oncology Group (ECOG) scale [8].

RESULTS

Patients' characteristics

Table 2 displays the clinical and treatment characteristics of the 3 year survivors. Their median age was 58 (range 37–74), 16 were male and 6 female and all were found to have limited disease with the exception of 1 patient with cervical extension of supraclavicular disease. All but 1 patient were PS 0–1 at start of therapy. Follow-up ranged from 39–118 months with 11 patients still alive at 5 years (6 alive but not for 5 years). Treatment consisted of various combination of chemotherapy (Table 3)

Table 5. Other toxicities and complications of 3-year survivors

	No. of patients
Neurological	
Cerebral infarction	1
Peripheral neuropathy	3
Infection	
Herpes zoster	2
Renal	
Elevation of serum creatinine (<2.0 mg/dl)	7
Myelodysplastic syndrome	1

Table 6. Association of clinical and treatment characteristics with extent of complications

Patient no.	Age	Sex	PS	Prior heart disease	No. of chemo-therapy	Type of chemo-therapy	Chest RT (Gy)	Surgery	Complication				Survival (mo)	Deaths		
									Cardiac	Pulmonary	Neuro-pathy	Renal		Recurrence	2nd primary tumour	Disease
1.	54	M	2	–	4	CVA, PVP	60	–	–	+	–	+	89+	–	–	–
2.	64	M	0	–	3	CVA	59.4	–	–	f	–	+	102+	–	–	–
3.	70	F	1	–	2	VA	50	–	–	f	–	–	113	–	–	Accident
4.	41	M	0	–	6	MMC(BAI)	–	P	–	f*	–	–	118+	–	–	–
5.	50	F	0	–	2	CVA	60	–	–	f	+	–	95+	–	–	–
6	64	M	0	–	7	VA, MMC	52.7	–	+	+	–	+	116+	–	–	–
7.	57	M	1	–	5	CVA, PVP	40	–	–	+	–	–	83+	–	–	–
8.	53	M	0	–	7	CVA, PVP	48	L	–	–	–	–	89+	–	–	–
9.	44	F	1	–	13	CVA, PVP, ADR	60	P	+	–	–	–	94+	–	–	–
10.	58	F	1	–	8	CAV	40	–	–	+	+	–	59+	–	–	–
11.	57	M	1	–	11	CAV, PVP	44	P	+	–	–	+	50	–	–	MI
12.	71	F	1		9	CAV, PVP	–	L	–	–	–	+	39+	–	–	–
13.	37	M	1	–	4	PVP	42	L	–	–	–	–	51+	–	–	–
14.	71	M	0	–	4	CAV, PVP	–	–	–	–	–	–	40+	–	–	–
15.	73	M	1	–	5	CAV, PVP	50	–	–	f	–	–	50+	–	–	–
16.	48	M	1	–	11	CAV, PVP	–	L	–	–	–	–	47+	–	–	–
17.	60	M	1	–	6	CAV, PVP	50	L	–	f	+	–	41+	(+)	–	–
18.	74	F	0	+	6	PVP	40	–	–	f	–	+	41+	(+)	Stomach	–
19.	68	M	1	+	7	CAV, PVP	–	–	+	–	–	+	33+	–	–	–
20.	59	M	1	+ –	9	CVA, PVP, CAV	44	L	–	–	–	–	59	–	–	MDS
21.	72	M	1	–	1	VA	60	–	–	+	–	–	90	–	Oesphagus	–
22.	50	M	1	–	10	PVP, CAV	–	L	–	–	–	–	62+	–	–	–

P = pneumonectomy, L = lobectomy, MI = myocardial infarction, MDS = myelodysplastic syndrome, f = radiation fibrosis only without pulmonary complication (f* = fibrosis after chemotherapy only).

Chemotherapy regimens: CVA = cyclophosphamide plus vincristine plus nimustine; VA = cyclophosphamide plus nimustine; PVP = cisplatin plus etoposide; CAV = cyclophosphamide plus doxorubicin plus vincristine.

ing completion of radiotherapy. 1 patient developed fibrosis after chemotherapy only.

Cardiac complications

4 patients developed clinically significant heart failure (New York Heart Association class 2 or 3) requiring digitilisation. 1 patient went on to suffer a fatal myocardial infarction. All of the patients had evidence of ST-T wave flattening and 2 had evidence of a dilated cardiomyopathy on ultrasound (Table 4). There was no apparent relationship to doxorubicin dosage with only 1 patient receiving a traditionally significant dose (420 mg/m^2).

Other toxicities

Table 5 displays the non-cardiopulmonary complications seen in the 3 year survivors. 1 patient had a stroke, 3 had residual peripheral neuropathy (WHO grade 1), 2 developed herpes zoster (painful, WHO grade 1) and 7 had asymptomatic azotemia (WHO grade 1). PCI was not given to any of these patients and there were no episodes of confusion or accelerated dementia. 1 patient developed a myelodysplastic syndrome 65 months after completing therapy containing ACNU (nimustine).

Second primary cancers

2 patients developed second primaries, 1 oesophageal (outside of the prior radiation port at 80 months) and the other gastric, at 33 months. The oesophageal cancer was fatal despite further radiation and the gastric cancer was cured by laser therapy.

DISCUSSION

Although response rate and median survival for patients with SCLC have improved over the past decade the overall outlook remains poor, even for those patients with limited disease [1]. Recent reports have focused on the long-term complications of treatment, in particular those associated with PCI [4–7]. This report summarises our experience in an institution that did not employ PCI and serves as a reminder that a 18% 3 year survival (22 of 123) is not accomplished without cost.

Pulmonary complications were significant. Virtually all patients were dyspnoeic but the relative contributions of underlying pulmonary disease, radiation and surgery could not be elucidated. Although radiographically common, radiation fibrosis was not generally of clinical significance [9]. The late onset of haemoptysis appeared to be a result of inflammation due to radiation with or without chemotherapy. 2 cases required hospitalisation including the 1 case with cavity formation in the radiation field (Table 6). The 4 cases of cardiac failure are again likely to be multifactorial in origin. Feld reported a 1.5% incidence of cardiomyopathy in 881 patients treated with combined modality therapy, similar to the 3% (4/123) here [3]. Only 1 case had a significant dose of doxorubicin (420 mg/m^2) but 1 patient had a combined total of 60 Gy of radiation in addition to 120 mg/m^2 of doxorubicin. However, 1 patient had only chest irradiation to 52.7 Gy and 1 patient had only 100 mg/m^2 of doxorubicin. It is clear that many combinations of prior smoking, surgery, radiation and doxorubicin may result in significant cardiac injury (Table 6).

The mild peripheral neuropathies and azotemia were likely related to vincristine and cisplatin respectively. The single cerebral infarct might have been expected in this group. None of the accelerated dementia seen by others was obvious in this group of patients not receiving PCI. The single case of myelodysplasia was not unusual, given the use of nitrosoureas in his management [10–14].

Although our patients achieved prolonged survival at a rate similar to other centres, there were only 7 patients (5.7%) who were alive and free of significant complications at 3 years (10% of limited disease patients). Therapy for this disease remains suboptimal particularly for those patients with extensive disease or those who present with poor performance status, who have virtually no chance of long-term remission.

1. Morstyn G, Ihde DC, Lichter AS, *et al.* Small cell lung cancer 1973–1983: early progress and recent obstacles. *Int J Radiat Oncol Biol Phys* 1984, **10**, 515–539.
2. Aisner J, Alberto P, Bitran J, *et al.* Role of chemotherapy in small cell lung cancer: a consensus report of the International Association for the Study of Lung Cancer Workshop. *Cancer Treat Rep* 1983, **67**, 37–43.
3. Feld R. Combinations in the treatment of small cell carcinoma of the lung. *Cancer Treat Rev* 1981, **8**, 5–25.
4. Lee JS, Umsawasdi T, Lee YY, *et al.* Neurotoxicity in long-term survivors of small cell lung cancer. *Int J Radiat Oncol Biol Phys* 1986, **12**, 313–321.
5. Pedersen AG, Kristjansen PEJ, Hansen HH. Prophylactic cranial irradiation for small cell lung cancer. *Cancer Treat Rev* 1988, **15**, 85–103.
6. So NK, O'Neill BP, Frytak S, Eagan RT, Earnest FIV, Lee RE. Delayed leukoencephalopathy in survivors with small cell lung cancer. *Neurology* 1987, **37**, 1198–1201.
7. Johnson BE, Becker B, Goff WB, *et al.* Neurologic, neurosychologic, and computed cranial tomography scan abnormalities in 2 to 10 year survivors of small cell lung cancer. *J Clin Oncol* 1985, **3**, 1659–1667.
8. Zubrod CG, Schneiderman M, Frei E, *et al.* Appraisal of methods for the study of chemotherapy of cancer in man: comparative therapeutic trial of nitrogen mustard and triethylene thiophosphoride. *J Chron Dis* 1960, **11**, 7–33.
9. Hellman S, Kligermann MM, von Essen CF, *et al.* Sequelae of radical radiotherapy of carcinoma of the lung. *Radiology* 1964, **82**, 1055–1061.
10. Saijo N, Niitani H. Experimental and clinical effect of ACNU in Japan, with emphasis on small-cell carcinoma of the lung. *Cancer Chemother Pharmacol* 1980, **4**, 165–171.
11. Pedersen-Bjergaad J, Østerlind K, Hansen M, Philip P, Pedersen AG, Hansen HH. Acute nonlymphocytic leukemia, preleukemia, and solid tumors following intensive chemotherapy of small cell carcinoma of the lung. *Blood* 1985, **66**, 1393–1397.
12. Spiegelman L, Maurer H, Ware JH, *et al.* Prognostic factors in small-cell carcinoma of the lung: ann analysis of 1521 patients. *J Clin Oncol* 1989, **17**, 44–354.
13. Chak LY, Sikic BI, Tucker MA, Horns RC, Cox RS. Increased incidence of acute non lymphocytic leukemia following therapy in patients with small cell carcinoma of the lung. *J Clin Oncol* 1984, **2**, 385–390.
14. Lee JS, Umsawasdi T, Lee YY, *et al.* Neurotoxicity in long-term survivors of small cell lung cancer. *Int J Radiat Oncol Biol Phys* 1986, **12**, 313–321.
15. Suga J, Saijo N, Shinkai T, *et al.* Long-term survival in patients with small cell lung cancer. *Jpn Clin Oncol* 1986, **16**, 309–315.
16. Shinkai T, Sakurai M, Eguchi K, *et al.* Prognostic factors in small cell lung cancer: multivariate analysis in the National Cancer Center Hospital (Japan). *Jpn J Clin Oncol* 1989, **19**, 135–141.
17. Vogelsang GB, Abeloff M, Ettinger DS, Booker SV. Long-term survivors of small cell carcinoma of the lung. *Am J Med* 1985, **79**, 49–56.
18. Livingston RB, Stephens RL, Bonnet JD, Grozea PN, Lehane DE. Long-term survival and toxicity in small cell lung cancer. Southwest Oncol Group Study. *Am J Med* 1984, **77**, 415–417.

Acknowledgments—This work was supported in part by Grants-in-Aid for Cancer Research and by the Comprehensive 10-Year Strategy for Cancer Control from the Ministry of Health and Welfare. We thank Dr John C. Ruckdeschel for valuable advice. Dr Ruckdeschel's visit was supported by the Visiting Scientist Program of the Foundation for Promotion of Cancer Research based on the Comprehensive 10-Year Strategy for Cancer Control.