Phase II trial of postoperative adjuvant cisplatin and etoposide in patients with completely resected stage I-IIIa small cell lung cancer: The Japan Clinical Oncology Lung Cancer Study Group Trial (JCOG9101)

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Objective: Indications for surgical intervention for very limited small cell lung cancer have not yet been determined. The objective of this study is to determine whether resection followed by cisplatin and etoposide is feasible.

Methods: From September 1991 through December 1996, 62 patients with completely resected small cell lung cancer who were less than 76 years of age from 17 centers were entered in the trial. Of 62 patients, 61 were eligible, with a median follow-up of 65 months. Chemotherapy consisted of 4 cycles of cisplatin (100 mg/m², day 1) and etoposide (100 mg/m², days 1-3). There were 49 (80%) male patients, 44 with clinical stage I disease, 10 with stage II disease, and 6 with stage IIIa disease.

Results: Forty-two (69%) patients received 4 cycles of cisplatin and etoposide. No treatment-associated mortality was noted. Median survival time was not reached in patients with pathologic stage I disease, was 449 days in patients with stage II disease, and was 712 days in patients with stage IIIa disease. Three-year survival was 61% overall, 68% in patients with clinical stage I disease, 56% in patients with stage II disease, and 13% in patients with stage IIIa disease ($P = .02$). Recurrence was noted in 26 (43%) patients overall. Local failure was noted in 6 (10%) patients. Locoregional recurrence tends to be found more frequently in patients with stage IIIa disease. Distant failure was found in 21 (34%) patients overall. Brain metastasis was found in 15% of the patients.

Conclusion: Major lung resection followed by postoperative cisplatin and etoposide is feasible, with a favorable survival profile. Because nodal metastasis appears to be a major prognostic factor, preoperative evaluation of nodal status remains a major concern.

The prognosis of lung cancer remains poor, and this disease is the leading cause of cancer mortality worldwide. Small cell lung cancer (SCLC) comprises approximately 20% of lung cancer cases. Without treatment, SCLC has the most aggressive clinical course of any other type of lung cancer, resulting in a very short median survival time of approximately 2 to 4 months. Although surgical resection is generally indicated for early stage non-small cell lung cancer, this is not always the case with SCLC. This can be explained by the fact that

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dissemination to regional lymph nodes or distant organs would be found in most patients with SCLC at the time of initial presentation.¹ Therefore, localized forms of treatment, such as surgical resection or radiation therapy, rarely produce long-term survival, and systemic treatment with current chemotherapy regimens is usually incorporated into the treatment program.

Indications for surgical resection for SCLC have not yet been determined, although several authors have reported that a small minority of patients with limited-stage disease and adequate lung function might benefit from surgical resection.¹⁻⁹ According to these reports, the prognosis of resected SCLC was not so poor, especially when no pathologic nodal involvement was observed. The 5-year survival ranged from 26% to 61% in these trials if the tumor was stage I. Because SCLC tends to be disseminated and the results of surgical intervention alone for this disease have been reported to be poor,^{1,10} postoperative chemotherapy has been used in most studies. However, the chemotherapy was not standardized, and various chemotherapy protocols were often used. Furthermore, most previous studies were retrospective and thus suffered from the inherent weakness of any retrospective assessment of a given treatment.

Because the combination of cisplatin and etoposide has been considered to be standard in the treatment of SCLC,¹¹ this combination was selected as a postoperative adjuvant regimen. We conducted a prospective study of surgical resection plus adjuvant chemotherapy for stage I through IIIA SCLC to investigate the efficacy of this treatment strategy.

Patients and Methods

Eligibility

Patients who were given postoperative diagnoses of SCLC histologically or cytologically were eligible for enrollment in the study. The patients had to have completely resected pathologic stage I, II, or IIIA disease according to the TNM classification of the International Union Against Cancer.¹² Histologic typing was determined according to the World Health Organization classification.¹³ Inclusion criteria included an Eastern Cooperative Oncology Group performance score of 0 or 1, age between 20 and 75 years, no prior treatment for lung cancer, no other concurrent or previous malignancies, a leukocyte count of greater than 3500/ μ L, a platelet count of greater than 100,000/ μ L, a hemoglobin level of greater than 9.5 g/dL, a serum creatinine level of less than 1.5 mg/dL, and aspartate aminotransferase–alanine aminotransferase values of less than twice the institutional upper limit of normal. Exclusion criteria included a history of myocardial infarction within the past 3 months, hepatic cirrhosis, and/or severe cardiopulmonary dysfunction that required oxygen therapy. The following preoperative investigations were performed before entry into the study: computed tomographic (CT) scanning of the chest, upper abdomen, and brain; bronchoscopy; chest plain film; radionuclide bone scanning; complete blood cell count and serum chemistry; and physical examination. Preoperative mediastinoscopy was performed in

some cases. All patients provided written informed consent before entering the study.

Treatment Schedule

Major lung resection, such as pulmonary lobectomy or pneumonectomy, was required as a surgical procedure for SCLC. Complete hilar and mediastinal lymph node dissections were recommended on the basis of the lymph node map defined by Naruke and colleagues.¹⁴ After confirming complete resection and histologic typing of SCLC histologically, eligible patients were registered in the study.

Chemotherapy consisted of cisplatin (100 mg/m² on day 1) and etoposide (100 mg/m² on days 1-3; PE regimen). This regimen was repeated every 4 weeks and was administered in 4 courses. The dose was modified according to the blood cell count and renal function on the day of chemotherapy. Chemotherapy was administered unless the leukocyte count was less than 3000/ μ L or the platelet count was less than 75,000/ μ L. Chemotherapy was withheld until the counts recovered. If grade 4 hematologic toxicity, according to World Health Organization (WHO) criteria,¹⁵ was seen, the dose of etoposide was reduced to 75%. Chemotherapy was permanently discontinued at any time when the serum creatinine level was 2.0 mg/dL or greater or the blood urea nitrogen level was 30 mg/dL or greater. To assess toxicity, we subjected all patients to complete blood cell counts and blood chemistry evaluations, such as for aspartate aminotransferase–alanine aminotransferase, blood urea nitrogen, and serum creatinine, as well as chest plain film and urinalyses at least once per week during treatment. Toxicity criteria were evaluated on the basis of the WHO criteria.¹⁵

Patients were followed up at the outpatient department every 3 months postoperatively and underwent CT scans of the chest, upper abdomen, and brain, as well as radionuclide bone scanning every 6 months, even when they were asymptomatic. No postoperative radiotherapy was applied until relapse was apparent.

Sites of relapse were determined by clinical, radiologic, or histologic criteria at initial recurrence. Local failure was defined as recurrence at the primary lung site or hilar-mediastinal lymph nodes. Distant failure was defined as recurrence in the contralateral lung, bone, brain, liver, or other extrathoracic regions.

Statistical Analysis

The trial was designed as a prospective phase II trial. The primary goal of the study was to estimate the survival. A sample size of 30 was considered to provide a power of 90% for detecting a significant improvement in the 3-year survival (from 20% to 50%) in a 1-sided test with an α value of .025 and a β value of .10. The median follow-up period for 35 surviving patients was 65 months. The length of survival was defined as the interval in months between the day of surgical resection of lung cancer and the date of death from any cause or the last follow-up. The survival curves were constructed by using the Kaplan-Meier method,¹⁶ and curves were compared with the log-rank test.

Results

Patient Characteristics

Between September 1991 and December 1996, 62 patients were entered in this phase II trial at the 16 institutions that

TABLE 1. Patient characteristics

Total	61
Sex	
Male	49
Female	12
Age (y)	
Range	22-74
Median	64
Histologic subtype defined by WHO*	
Oat cell type	9
Intermediate type	45
Combined type	7
Clinical stage	
I	44
II	9
IIIA	8
Side of primary tumor	
Right	32
Left	29
Operative procedure	
Lobectomy	57
Pneumonectomy	4
Extent of lymph node dissection†	
Complete hilar and mediastinum	59
Only hilar	2
Pathologic stage	
I	35
II	8
IIIA	18
Performance status	
0	32
1	29

*Histologic subtyping was determined on the basis of the World Health Organization (WHO) classification. †The extent of lymph node dissection was defined by Naruke and associates.¹⁴

participated in the study. One patient was excluded because his final histologic category was changed from SCLC to large cell carcinoma. Thus, 61 patients were eligible for assessment of survival data, and their characteristics are shown in Table 1. The median age was 64 years (range, 22-74 years). According to histologic typing defined by the WHO, oat cell, intermediate, and combined types were found in 9, 45, and 7 patients, respectively. Forty-four patients had clinical stage I disease, 9 had stage II disease, and 8 had stage IIIA disease. Pathologically, stage I, II, and IIIA disease was found in 35, 8, and 18 patients, respectively.

Treatment Administration

As a surgical procedure, pulmonary lobectomy was performed in 57 (93%) patients, and pneumonectomy was performed in the other 4 patients. Among 4 pneumonectomies, 3 were on the left side, and 1 was on the right side. Complete hilar and mediastinal lymph node dissection was performed in 59 (97%) patients.

TABLE 2. Treatment delivery

Total no. of patients	61
No. of chemotherapy courses	
0	1 (2%)
1	5 (8%)
2	8 (13%)
3	5 (8%)
4	42 (69%)

A total of 204 courses were administered (Table 2). Forty-two (69%) patients underwent a full course of chemotherapy. The other 19 patients did not complete postoperative chemotherapy because of progressive disease in 3 patients, adverse effects in 7 patients, refusal of chemotherapy in 8 patients, and death from pneumonia in 1 patient.

Treatment-Related Toxicity

No treatment-associated deaths were found. Postoperative bronchopulmonary fistula was found in 1 (2%) patient who underwent pulmonary lobectomy after completion of the first cycle of chemotherapy. Chemotherapy-related toxicity is shown in Table 3. Grade 4 toxicity was found in 9 (15%) patients: leukopenia in 4 patients, thrombocytopenia in 2 patients, nausea in 2 patients, and cardiac failure in 1 patient. One patient died of pneumonia 2 months after the first course of chemotherapy, but this was not considered to be chemotherapy related.

Survival

Survival data are shown in Table 4. Among the 61 eligible patients, 35 were still alive after a median follow-up of 65

TABLE 3. Chemotherapy-related toxicity in 60 eligible patients treated for resected stage I to IIIA SCLC

Toxicity	WHO grade				
	1	2	3	4	4 (%)
Anemia	9	29	16	0	0
Leukocytopenia	7	17	26	4	6.5
Thrombocytopenia	11	8	14	2	3.2
Infection	2	1	0	0	0
Nausea	24	13	13	2	3.3
Diarrhea	8	2	2	0	0
Azotemia	35	0	0	0	0
Renal failure	18	0	0	0	0
Stomatitis	14	1	1	0	0
Dyspnea	5	0	0	0	0
Fever	10	7	0	0	0
Skin	4	2	0	0	0
Alopecia	13	23	11	0	0
Cardiac dysfunction	5	2	1	1	1.7
CNS	1	1	1	0	0
Peripheral neuropathy	5	1	0	0	0

WHO, World Health Organization; CNS, central nervous system.

TABLE 4. Survival in patients with resected SCLC who underwent postoperative chemotherapy

		Survival	
		3 y	5 y
Median survival time (d)			
Clinical stage			
IA	Not reached	70%	66%
IB	Not reached	65%	65%
II	Not reached	56%	56%
IIIA	530	13%	13%
Pathologic stage			
IA	Not reached	78%	73%
IB	Not reached	67%	67%
II	449	38%	38%
IIIA	712	39%	39%

months. The overall estimated 3- and 5-year survivals were 61% and 57%, respectively (Figure 1). The 5-year survival was 66%, 56%, and 13% in patients with clinical stage I, II, and IIIA disease, respectively (Figure 2). Among the 44 patients with clinical stage I disease, 27 were classified as having clinical stage IA disease, and the other 17 were classified as having clinical stage IB disease. There was no significant difference in prognosis between clinical stage IA and IB disease. Similar results were obtained regarding the pathologic stage. Pathologic stage I disease showed a significantly better prognosis (Figure 3). The 5-year survivals in the 23 patients with pathologic stage IA disease and the 12 patients with stage

IB disease were 73% and 67%, respectively. No significant differences in survival were observed between patients with pathologic stage IA and IB disease.

Patterns of failure. Recurrence was noted in 26 (43%) patients, and the sites of initial relapse at a median follow-up time of 65 months are shown according to the pathologic stage in Table 5. Recurrence was found in 30% of patients with stage IA disease, 25% of patients with stage IB disease, 50% of patients with stage II disease, and 67% of patients with stage IIIA disease.

Local failure was noted in 6 (10%) patients: 4 in the mediastinal lymph nodes and 2 in the bronchial stump. Locoregional recurrence tended to be found more frequently in patients with stage IIIA disease (22%) than in patients with stage I or II disease. Relapse at the bronchial stump was only seen in patients with stage IIIA disease.

Distant failure was found in 22 (36%) patients overall: 6 (26%) with stage IA disease, 2 (17%) with stage IB disease, 4 (50%) with stage II disease, and 9 (50%) with stage IIIA disease. Distant failure was most frequently noted in the brain, followed by the liver. The incidence of brain metastasis was 15% overall, 17% in patients with stage IA disease, and 11% in patients with stage IIIA disease. Bone metastasis was noted exclusively in patients with stage IIIA disease.

Discrepancy between clinical and pathologic stages. Table 6 shows the relationship between the clinical stage and the pathologic stage. Among 44 patients with clinical stage I disease, only 33 (75%) had pathologic stage I disease, and

Figure 1. Survival curve for overall patients with resected SCLC.

Figure 2. Survival curves for patients with resected SCLC by clinical stages.

6 had stage IIIA disease. Five patients with clinical stage IA disease had mediastinal lymph node metastasis. According to the Bowker test of symmetry, these differences were statistically significant.

Discussion

This phase II trial showed that postoperative PE for patients who underwent surgical resection of stage I to IIIA SCLC was feasible, and the outcome was acceptable. Survival was excellent in patients with stage I disease and did not appear

to be inferior to that with chemoradiotherapy in patients with stage II or IIIa disease.

On the basis of the results of the British Medical Research Council, radical radiotherapy has been preferable to surgical intervention for SCLC,^{17,18} and the indications for surgical resection for SCLC are still controversial. An operation would be indicated for limited SCLC because the most common relapse site after radiotherapy was locoregional, and surgical intervention might improve local control.¹⁹ Several authors have reported that a small minority of

Figure 3. Survival curves for patients with resected SCLC by pathologic stage.

TABLE 5. Site of the first relapse by pathologic stages*

Variables	Overall	Stage IA	Stage IB	Stage II	Stage IIIA
No. of patients	61	23	12	8	18
No. of recurrence	26 (43%)	7 (30%)	3 (25%)	4 (50%)	12 (67%)
Recurrence					
Local					
Overall	6 (10%)	1 (4%)	1 (8%)	0 (0%)	4 (22%)
Mediastinum	4	1	1	0	2
Bronchial stump	2	0	0	0	2
Distant					
Overall	22 (36%)	6 (26%)	2 (17%)	4 (50%)	9 (50%)
Brain	9 (15%)	4 (17%)	0 (0%)	3 (38%)	2 (11%)
Bone	3	0	0	0	3
Liver	7	1	1	1	4
Lung	2	0	1	0	1
Small intestine	2	1	0	0	1

limited-stage SCLCs could be managed with an operation and postoperative chemotherapy.¹⁻⁹ According to those reports, the 5-year survivals were 28% to 36% overall and 26% to 61% in patients with stage I disease. However, most of those reports were retrospective and used various combinations of chemotherapy. Therefore, a prospective trial of adjuvant chemotherapy for patients with resected SCLC using standardized chemotherapy has been needed. Our survival data suggest that postoperative PE after major lung resection and hilar and mediastinal lymph node dissection is a feasible and promising treatment, especially for patients with stage I SCLC. The 3- and 5-year survivals for patients with stage I disease were 78% and 73%, respectively, and the median survival time was not reached. As for patients with stage II or IIIA disease, the results were not definitive, and a further prospective study is needed. This study dealt with postoperatively proved SCLC. As to the indication for surgical intervention for preoperatively diagnosed SCLC, controversies still remain. Our recommendation is as follows. When a patient has SCLC of clinical N1 or N2 status, chemoradiotherapy should be considered because a survival after an operation alone would not be good enough. Surgical intervention should be considered, however, for patients with clinical stage I disease because an operation followed by chemotherapy offers a good prognosis, as shown in this

study, and because such SCLC sometimes turns out to be non-SCLC postoperatively. A phase III trial comparing chemoradiotherapy with surgical intervention followed by chemotherapy is interesting. However, the number of patients with SCLC with clinical stage I or II disease is very small, and we do not think it is possible to perform the phase III trial in this population.

Because clinical stage and pathologic stage were significant prognostic factors in our trial, preoperative staging, intraoperative staging, or both should be a major concern for the treatment of very limited SCLC. Actually, the following preoperative investigations were performed before entry into the study in this cohort: CT scans of the chest, upper abdomen, and brain; bronchoscopy; chest plain film; radio-nuclide bone scans; complete blood cell count and serum chemistry; and physical examination. If the diagnosis of SCLC was made preoperatively, we recommend the same preoperative workup as done by us in this study. Furthermore, if swollen lymph nodes are detected on thoracic CT scans, we absolutely recommend mediastinoscopy for such cases. As for positron emission tomography, we have no recommendation thus far because this modality has recently begun to be evaluated, although it could be useful for staging N1 disease. Intraoperatively, hilar and mediastinal lymph node sampling or dissection was performed in 59 (97%) patients. This intraoperative staging is also important for deciding on the treatment strategy.

The site of the first relapse was another fruit of our study. This clinical trial did not use postoperative mediastinal irradiation or prophylactic cranial irradiation (PCI). We should discuss the importance of these strategies for very limited SCLC. As to locoregional recurrence, approximately 10% of the patients showed relapse in the mediastinal lymph nodes, bronchial stump, or both. Five percent of patients with stage I or II disease eventually have locore-

TABLE 6. Relationship between clinical and pathologic stages

Clinical stage	Pathologic stage			P value*
	I	II	IIIA	
I	33	5	6	.011
II	1	3	5	
IIIA	1	0	7	

*P value in Bowker's test of symmetry.

gional recurrence, whereas this is seen in 22% of patients with stage IIIA disease. These results suggest that patients with stage IIIA disease, at least, could benefit from postoperative mediastinal irradiation, whereas those with stage I or II disease might not need to undergo radiotherapy. Thus, postoperative chemoradiotherapy might be used in a future trial for stage IIIA disease.

Auperin and associates²⁰ reported that PCI improved both overall survival and disease-free survival among patients with SCLC in complete remission. Surgically resected SCLC would be considered SCLC in complete remission, and PCI would be indicated. Overall, 15% of the patients in our study showed brain metastasis. Even among patients with stage IA disease, more than 10% of the patients had brain metastasis. Therefore, PCI might be necessary for all patients with completely resected SCLC, whereas some authors have insisted that patients with pathologic stage IA SCLC can be cured without any adjuvant treatment.¹⁹

Noda and coworkers²¹ reported that combination chemotherapy consisting of irinotecan (CPT-11) and cisplatin was superior to PE for extensive SCLC. Although concurrent radiotherapy with CPT-11 would be harmful, we would use the new regimen for very limited SCLC, especially for stage II or IIIA SCLC.

Major lung resection with complete hilar and mediastinal lymph node dissection followed by postoperative PE is a feasible treatment and results in a favorable survival profile. Survival was especially good for patients with stage I disease. Our strategy could be used as a standard treatment arm in a future trial for very limited SCLC.

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