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INTERNAL MEDICINE

□ CASE REPORT □

Development of Cushing's Syndrome During Effective Chemotherapy for Small Cell Lung Cancer

Koichi Suyama, Yoichi Naito, Kiyotaka Yoh, Seiji Niho, Koichi Goto, Hironobu Ohmatsu, Yutaka Nishiwaki and Yuichiro Ohe

Abstract

Paraneoplastic Cushing's syndrome caused by ectopic adrenocorticotropin (ACTH) production has been reported. However, most cases of this syndrome are diagnosed before first-line chemotherapy or at the time of disease recurrence. Here, we present a 53-year-old man who gradually developed the symptoms of Cushing's syndrome during effective chemotherapy for small cell lung cancer. His symptoms were controlled using mitotane, but his primary cancer progressed and he died 5 months after the start of chemotherapy. This very rare case of Cushing's syndrome associated with small cell lung cancer during effective chemotherapy is presented here.

Key words: Cushing's syndrome, ACTH, lung cancer, chemotherapy

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Introduction

Paraneoplastic Cushing's syndrome caused by ectopic adrenocorticotropin (ACTH) production has been reported. However, most cases of this syndrome are diagnosed before first-line chemotherapy or at the time of disease recurrence. A few reports have described the gradual emergence of the symptoms of Cushing's syndrome during effective treatment for lung cancer. Identifying the symptoms of Cushing's syndrome at an early stage is important from the perspective of early diagnosis. Here, we present a case of paraneoplastic Cushing's syndrome that emerged gradually during effective chemotherapy for small cell lung cancer.

Case Report

A 53-year-old man presented with a cough, sputum, and dyspnea lasting for about two months. A plain chest radiograph at another hospital showed an abnormal shadow in a hilum of the left lung. A bronchoscopy revealed a small cell lung cancer (SCLC). He was referred to our hospital for treatment.

The patient had smoked 30 cigarettes a day for 32 years. Computed tomography (CT) of the chest revealed a mass in the left hilum of the lung and mediastinal lymph node swelling (Fig. 1A). No tumors other than those in the left thorax and no enlarged lymph nodes except those were found. His laboratory findings, including the serum potassium level, were almost normal. Regarding serum tumor markers, squamous cell carcinoma-related antigen and carcinoma-related antigen were not detected, but the serum neuron-specific enolase (NSE) level was 32.1 ng/mL (normal, <16.3 ng/mL) and the serum Pro-GRP level was 473 pg/mL (normal, <46 pg/mL). The clinical stage was T2N3M0, indicating limited SCLC.

At the time of hospitalization, the physical findings were not characteristic of a Cushingoid appearance. Because of the large radiation field, chemotherapy using cisplatin and etoposide was first performed (Fig. 2). After two cycles of chemotherapy, a tumor reduction was confirmed using CT (Fig. 1B). Thereafter, the patient began to complain of chest pain. We consulted a cardiologist, and three stenosed lesions were discovered in his coronary arteries. Percutaneus transluminal coronary angioplasty was performed for one lesion. Thereafter, we reinitiated chemotherapy after changing cisplatin to carboplatin to reduce the cardiac burden. Prior to the fourth round of chemotherapy, he developed hypoka-

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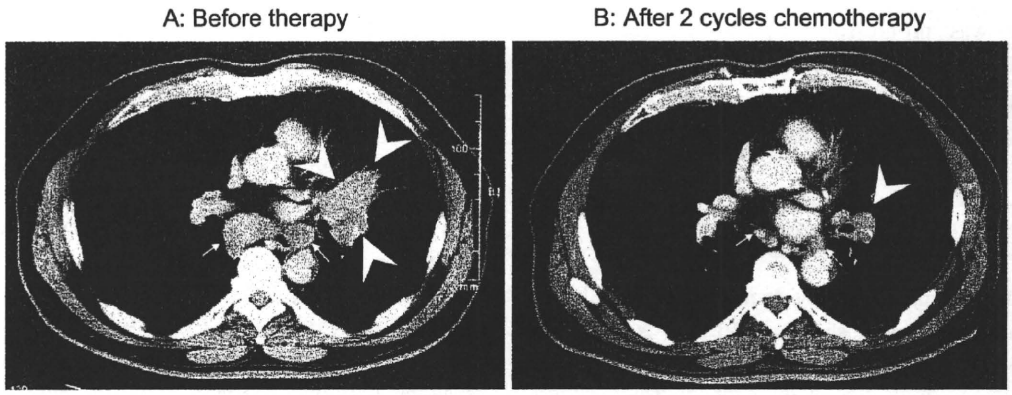

Figure 1. A: Computed tomography (CT) image obtained before chemotherapy. A chest CT revealed a mass in the left hilum of the lung (arrowhead) and mediastinal lymph node swelling (arrow). B: CT image obtained after 2 cycles of chemotherapy. The main tumor and swollen lymph node show signs of reduction.

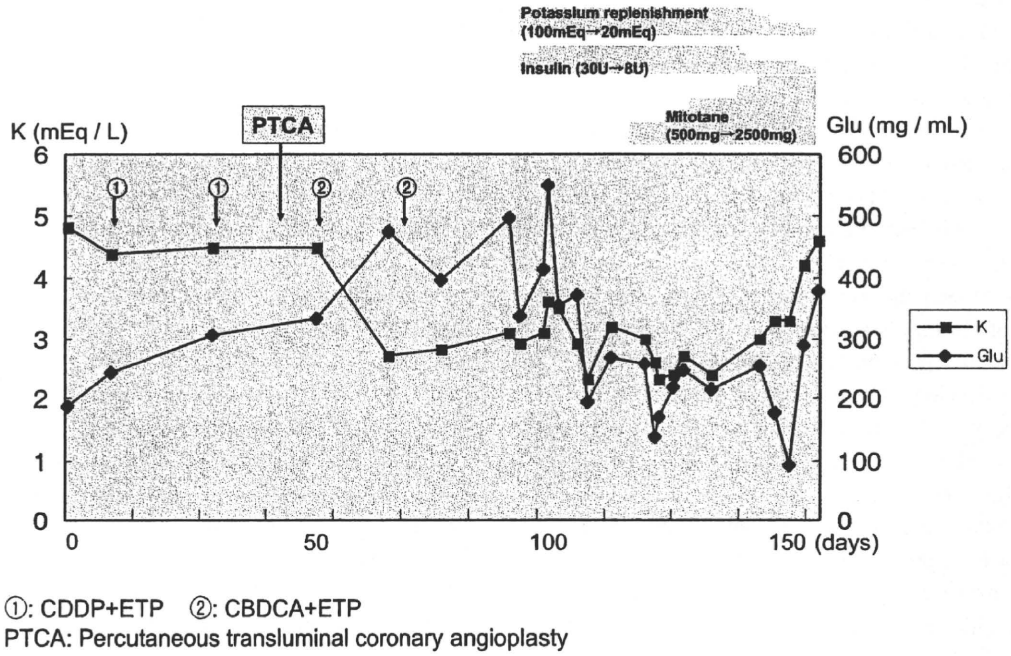

Figure 2. Clinical course.

lemia. His blood glucose level also gradually began to increase. Because these symptoms were not severe, we continued the chemotherapy. The serum tumor marker kept decreasing (NSE: max 50.3 ng/mL→21.5 ng/mL, Pro-GRP: max 1172 pg/mL→695 pg/mL) during the chemotherapy period. After completing 4 cycles of chemotherapy, he had developed severe hypokalemia, diabetes, hypertension and a depressive state (Fig. 2). He also exhibited centripetal obesity and a buffalo hump. We started the administration of potassium and insulin. However, no response to treatment was observed. The NSE and pro-GRP levels, which had been declining, began to rise. We speculated that these findings were consistent with Cushing's syndrome. The plasma ACTH concentration was 481.0 pg/mL (normal range, 7.2-63.3 pg/mL) and the plasma cortisol concentration was 144.0 μg/dL (normal range, 4.0-18.3 μg/dL). The serum ACTH concentration failed to be suppressed after treatment with 1 mg of dexamethasone overnight. It also was not suppressed after metyrapone loading. Magnetic resonance imaging (MRI) did not reveal a pituitary mass. These results suggested that the patient's Cushing's syndrome was caused by ectopic ACTH production associated with the SCLC.

The patient was treated with mitotane (500 mg/day). We gradually increased the amount of mitotane, reaching a final dosage of 2500 mg/day. After the start of mitotane treatment, his hypokalemia and hyperglycemia gradually improved. The amount of required potassium and insulin also decreased (Fig. 2). The plasma ACTH and cortisol concentration also decreased (ACTH: 481 pg/mL→329.0 pg/mL, cortisol: 144.0 μg/dL→89.0 μg/dL). However, his primary

lung cancer was progressing. Second-line chemotherapy could not be started because of the patient's uncontrollable symptoms, poor performance status, and the refusal of the patient to undergo chemotherapy. He died 5 months after the start of the initial chemotherapy.

Discussion

A previous retrospective study demonstrated that the incidence of paraneoplastic Cushing's syndrome is 5% or less among all SCLC patients (1). In the recent literature, the incidence of SCLC associated with paraneoplastic syndrome has seemed to decrease (2). A possible explanation for this trend might be the recent improvements in diagnosis, chemotherapy, and radiotherapy. However, SCLC patients who develop paraneoplastic syndrome still have a poor prognosis because of various complications. Reportedly, 43% of SCLC patients with ectopic ACTH production experienced severe infections that contributed significantly to their eventual deaths (1). Another study reported a high rate of fatal infections (about 28%) and nonfatal infections in Cushing's syndrome (3). The cause of such infections might be hypercortisolism. The early diagnosis of Cushing's syndrome is very important for improving patient survival.

As shown in the case presentation, the chemotherapy was considered to have been effective. However, the patient gradually developed the symptoms of Cushing's syndrome. Most cases of Cushing's syndrome reportedly develop at the time of the initial presentation or the relapse of SCLC (1). Patients who develop Cushing's syndrome often have a poor outcome because of chemoresistance. The worsening of Cushing's syndrome during effective chemotherapy is thought to be very rare. One possible reason for the poor outcome in the present case is that chemoresistant cell clones might have produced the ACTH. In other words, cell clones that survived the chemotherapy might have begun to proliferate rapidly after chemotherapy. Thus, "the chemoresistant cancer cell clones that produced ACTH" might have contributed to the poor outcome of the present patient with SCLC who developed ectopic ACTH syndrome. Vanhees et al reported a case of syndrome of inappropriate antidiuretic hormone (SIADH) associated with effective chemotherapy in SCLC (4). They hypothesized that the release of ADH from the malignant cells during the early tumor breakdown from chemotherapy resulted in SIADH. As well as this hypothesis, the present case might have had the possibility of developing Cushing's syndrome from the release of ACTH from malignant cells in the period of rapid cell necrosis due to effective chemotherapy.

Once Cushing's syndrome is suspected, a differential diagnosis must be made by performing an overnight dexamethasone test and metyrapone test. If no ectopic ACTH production is present, the serum ACTH level should be greatly suppressed after the administration of 1 mg dexamethasone and should increase after the administration of metyrapone. If pituitary Cushing's disease is present, the serum ACTH level should also increase after the administration of metyrapone. The ACTH level in the present patient did not respond to the administration of dexamethasone and metyrapone. These results indicated that the patient had ectopic ACTH production; in this manner, a final diagnosis of Cushing's syndrome as a result of SCLC was confirmed. He was treated with mitotane to counteract the ectopic ACTH production. Mitotane, or o,p'DDD, can block the adrenocortical steroid synthesis by inhibition of cholesterol side-chain cleavage and 11β-hydroxylase. This inhibition affects extra-adrenal cortisol disposition by inducing its hepatic clearance, reducing hormone production, and ameliorating the symptoms of hormone excess (5). A recent study from a single center showed the ideal therapeutic control of the ectopic ACTH secretion syndrome by using mitotane (6). In that study, 20 of the 23 patients showed clinical improvement of Cushing's syndrome manifestations. The present patient's symptoms arising from Cushing's syndrome began to improve by using mitotane, but his SCLC also began to progress and could not be stopped, mainly because treatment of the cancer itself could not be resumed.

We could not perform an immunohistochemical study for ACTH using primary or metastatic tumor specimens for the diagnosis of ectopic ACTH secretion. ACTH produced from neoplasms is said to have a different structure than that of wild-type ACTH, and conventional immunohistochemical staining using a polyclonal anti-ACTH antibody may not be useful in tumor cells (7). The predominant form of ACTH in tumor extracts is reportedly a large ACTH molecule that cannot be detected using the usual immunohistochemical staining (8).

In summary, we have described a rare case of Cushing's syndrome that progressed even during effective chemotherapy for SCLC. The clinical symptoms of Cushing's syndrome must be kept in mind when treating patients with lung cancer, since early detection and appropriate treatment can overcome the otherwise poor prognosis.

The authors state that they have no Conflict of Interest (COI).

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Clinical Outcome of Small Cell Lung Cancer with Pericardial Effusion but without Distant Metastasis

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Background: Pericardial effusion is defined as M1a in the Union Internationale Contre le Cancer seventh tumor, node, metastasis edition for lung cancer. The clinical course of small cell lung cancer (SCLC) with pericardial effusion but without distant metastasis (M1a) has not been adequately investigated.

Methods: The medical records of patients with SCLC treated at the National Cancer Center Hospital East between July 1992 and December 2007 were reviewed. During this period, 766 patients were newly diagnosed as having SCLC. Thirty-three of the 416 patients with limited disease (LD) SCLC (8%) had pericardial effusion. Seventy-nine patients with LD-SCLC (19%) had ipsilateral pleural effusion or dissemination. Of these, 16 patients had both pericardial and ipsilateral pleural effusion. We divided the 96 M1a patients into two subgroups: group A ($n = 33$) included patients with pericardial effusion, and group B ($n = 63$) included patients with ipsilateral pleural effusion or disseminated pleural nodules but without pericardial effusion.

Results: The median survival time among the patients with LD-M1a was 13.4 months (95% confidence interval: 10.7–16.6 months), and the 1-, 2-, 3-, and 5-year survival rates were 56%, 18%, 9%, and 8%, respectively. The survival of the patients with LD-M1a was intermediate between those of the patients with LD-M0 and patients with extensive disease M1b ($p < 0.0001$). The overall survival period was not statistically different between groups A and B ($p = 0.5182$). Nineteen patients in group A received chemoradiotherapy, but only two patients survived for more than 2 years (2- and 5-year survival rate: 11% both). Twenty-six patients in group B received chemoradiotherapy, and four patients survived for more than 5 years (5-year survival rate: 18%).

Conclusions: Long-term survival was achieved among patients with SCLC with pericardial effusion but without distant metastasis who successfully underwent chemoradiotherapy, although 5-year survival rate in these patients was relatively lower than in patients with SCLC with ipsilateral pleural effusion but without pericardial effusion or distant metastasis.

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Disclosure: The authors declare no conflicts of interest.

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Key Words: Small cell lung cancer, Limited disease, Pericardial effusion.

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Lung cancer is the leading cause of cancer-related deaths worldwide. Small cell lung cancer (SCLC) accounts for approximately 15% of all forms of lung cancer. Compared with non-SCLC, SCLC grows rapidly, quickly disseminates to the regional lymph nodes and distant sites, and is sensitive to chemotherapy with a response rate of 70 to 80%. The Veterans Administration Lung Study Group proposed a clinical two-stage system for SCLC that distinguishes limited disease (LD) and extensive disease (ED). LD is defined as being limited to one hemithorax, including mediastinal, contralateral hilar, and ipsilateral supraclavicular lymph nodes, whereas ED represents tumor spread beyond these regions.[1] The current standard care for LD-SCLC is a combination of chemotherapy and thoracic radiotherapy (TRT). Conversely, ED-SCLC is treated with chemotherapy alone. The original definition of LD was a tumor volume that could be encompassed by a reasonable radiotherapy plan. According to the International Association for the Study of Lung Cancer (IASLC)'s consensus report, however, the classification of LD-SCLC includes bilateral hilar or supraclavicular nodal involvement and ipsilateral pleural effusion, regardless of whether the cytological findings are positive or negative.[2] Pericardial effusion has not been defined precisely.

In 2007, the IASLC proposed a new tumor, node, metastasis (TNM) classification for lung cancer,[3–6] and the Union Internationale Contre le Cancer (UICC) seventh TNM edition has been available since 2009. According to the UICC seventh TNM edition, malignant pleural or pericardial effusion and tumor with pleural nodules are defined as M1a, leading to stage IV. An analysis of 12,620 patients with SCLC in the IASLC database demonstrated that patients who have ipsilateral pleural effusion without extrathoracic metastases (M1a) have a survival that is intermediate between stages I and III without effusion and stage IV. Nevertheless, no information regarding the presence of pericardial effusion is available in the IASLC database.[7]

Our previous retrospective analysis also demonstrated that the survival of patients with LD-SCLC with ipsilateral pleural effusion was intermediate between those of patients with LD without ipsilateral pleural effusion and patients with

ED, and long-term survival was achieved by patients with LD-SCLC who successfully underwent definitive TRT after their ipsilateral pleural effusion had disappeared after induction chemotherapy.[8] In this retrospective study, we investigated the clinical course and overall survival among patients with LD-SCLC with pericardial effusion, compared with those among patients with ED-SCLC or LD-SCLC with or without ipsilateral pleural effusion.

PATIENTS AND METHODS

In this study, LD-SCLC was defined as disease limited to one hemithorax, including mediastinal, contralateral hilar, and supraclavicular lymph nodes, ipsilateral pleural effusion, and pericardial effusion; ED-SCLC was defined as tumor spread beyond these manifestations.

We retrospectively reviewed the medical records of patients with lung cancer treated at the National Cancer Center Hospital East between July 1992 and December 2007.

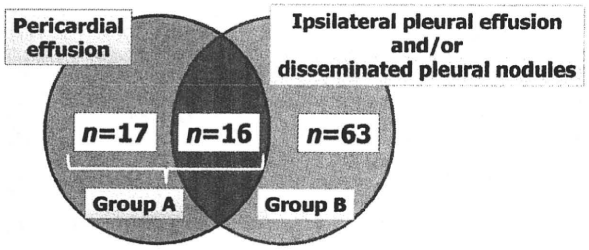

FIGURE 1. Patients with small cell lung cancer with M1a. Group A included patients with pericardial effusion, and group B included patients with ipsilateral pleural effusion or disseminated pleural nodules, but without pericardial effusion.

During this period, 766 patients were newly diagnosed as having SCLC. Four hundred sixteen patients were diagnosed as having LD-SCLC and 350 were diagnosed as having ED-SCLC using conventional staging procedures, including a medical history and physical examination, chest radiography, computed tomography (CT) scan of the chest, CT scan or ultrasound of the abdomen, bone scan, and CT scan or magnetic resonance imaging of the brain. Thirty-three of the 416 patients with LD-SCLC (8%, 95% confidence interval [CI]: 6–11%) had pericardial effusion and were included in this study. Seventy-nine of the 416 patients with LD-SCLC (19%, 95% CI: 15–23%) had ipsilateral pleural effusion or dissemination. Four patients had a disseminated mass without pleural effusion detected using CT scan. Sixteen patients with LD-SCLC had both pericardial and ipsilateral pleural effusion. Therefore, 63 patients with LD-SCLC had ipsilateral pleural effusion or dissemination without pericardial effusion. We divided the 96 M1a patients into two subgroups: group A included patients with pericardial effusion, and group B included patients without pericardial effusion. Group B patients had ipsilateral pleural effusion or disseminated pleural nodules (Figure 1).

The overall survival time was defined as the interval between the start of treatment and death or the final follow-up visit. The median overall survival time was estimated using the Kaplan-Meier analysis method.[9] Survival data were compared among the groups using a log-rank test. This study was approved by an institutional review board.

RESULTS

The patient characteristics are listed in Table 1. Eighty-three percent of the patients were male, and 81% had a performance status of 0 or 1. Fifty-four percent of the patients

TABLE 1. Patient Characteristics

	ED-SCLC (M1b)	LD-SCLC with Pericardial Effusion (M1a) (Group A)	LD-SCLC with Ipsilateral Pleural Effusion but without Pericardial Effusion (M1a) (Group B)	LD-SCLC (M0)
No. of patients	350	33	63	320
Sex				
Male	291	29	50	262
Female	59	4	13	58
Age (yr)				
Median	66	67	68	66
Range	28–85	37–82	46–83	22–87
Performance status				
0	22	0	4	108
1	224	25	47	190
2	63	6	9	15
3–4	41	2	3	7
Treatment delivered				
Chemotherapy	316	14	36	50
Chemoradiotherapy	25	19	26	224
Surgery + chemotherapy	0	0	0	33
Surgery alone	0	0	0	10
Best supportive care	9	0	1	3

LD, limited disease; SCLC, small cell lung cancer; ED, extensive disease.

TABLE 2. Timing of Thoracic Radiotherapy in Patients with M1a Small Cell Lung Cancer

Timing of Thoracic Radiotherapy	LD-SCLC with Pericardial Effusion (M1a) (Group A, $n = 19$)	LD-SCLC with Ipsilateral Pleural Effusion but without Pericardial Effusion (M1a) (Group B, $n = 26$)
Concurrently with the first course of chemotherapy	0	3
Concurrently with the second course of chemotherapy	0	4
Concurrently with the third course of chemotherapy	8	5
Concurrently with the fourth course of chemotherapy	4	0
Sequentially after chemotherapy	7	14

LD, limited disease; SCLC, small cell lung cancer.

received chemotherapy, and 38% received chemoradiotherapy. Six percent of the patients underwent surgical resection with or without adjuvant chemotherapy. Among the 96 patients with LD-M1a, all but one patient received chemotherapy ($n = 50$) or chemoradiotherapy ($n = 45$). Three patients underwent TRT (twice daily, 45 Gy in total) concurrently with the first course of chemotherapy. Four, 13, and four patients underwent TRT (once daily, 50 Gy in total) concurrently with the second, third, and fourth courses of chemotherapy, respectively. Twenty-one patients underwent TRT (once daily, 50 Gy in total) sequentially after chemotherapy. Among the group A patients, 12 patients underwent TRT concurrently with the third or fourth course of chemotherapy, and seven patients underwent TRT sequentially after chemotherapy. TRT was conducted if the pericardial effusion disappeared after induction chemotherapy. Among the group B patients, 12 patients underwent TRT concurrently with chemotherapy, and 14 patients underwent TRT sequentially (Table 2). Thirteen patients received prophylactic cranial irradiation of 25 Gy (seven patients in group A and six patients in group B).

Figure 2 shows the survival of all 766 patients with SCLC belonging to category M. The survival of patients with LD-M1a was intermediate between those of patients with LD-M0 and ED-M1b ($p < 0.0001$). Six hundred eighty-two patients have died. The median follow-up time was 65.8 months, ranging from 3.2 to 160.1 months. The median survival time among the patients with LD-M1a was 13.4 months (95% CI: 10.7–16.6 months), and the 1-, 2-, 3-, and 5-year survival rates were 56%, 18%, 9%, and 8%, respectively.

Survival analyses for the subgroup of patients with LD-M1a ($n = 96$) are shown in Figures 3, 4 and Table 3. Overall survival was not statistically different between groups A and B ($p = 0.5182$). All 14 patients who received chemotherapy in group A died within 3 years. One patient in group B who received chemotherapy as an initial treatment survived for more than 5 years, but this patient received chemoradiotherapy as a second-line treatment after a local

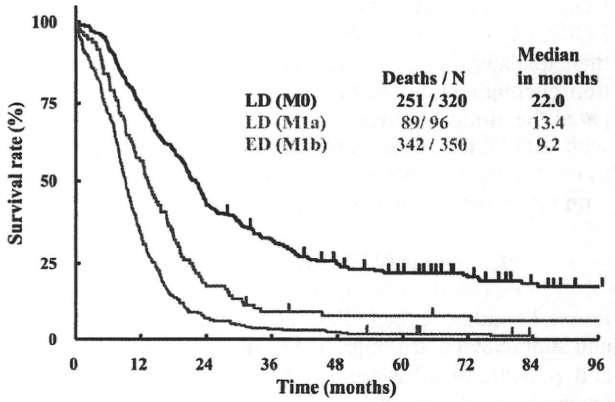

FIGURE 2. Overall survival among all 766 patients with M-category small cell lung cancer. LD, limited disease; ED, extensive disease.

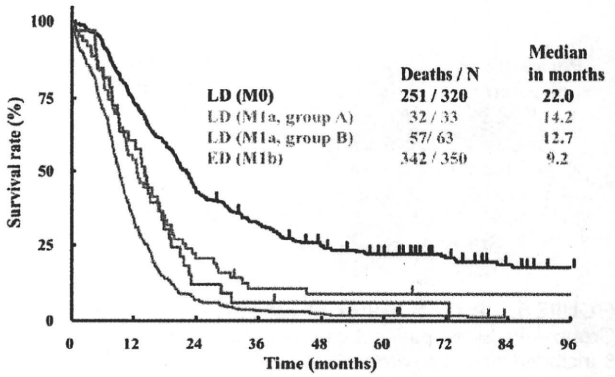

FIGURE 3. Overall survival among patients with M-category small cell lung cancer, subgroups A and B. LD, limited disease; ED, extensive disease.

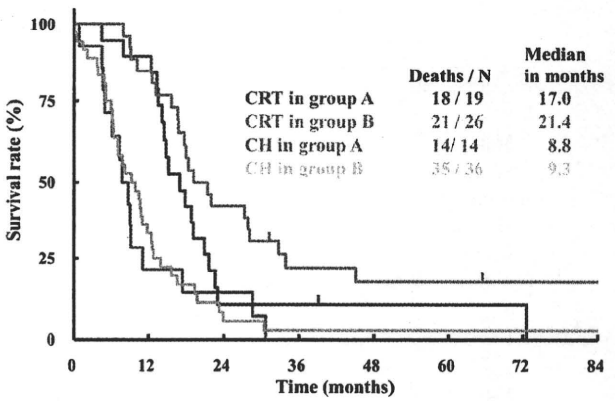

FIGURE 4. Overall survival among M1a patients with small cell lung cancer according to subgroups A, B, and initial treatment delivered. CRT, chemoradiotherapy; CH, chemotherapy.

TABLE 3. Survival Data

Subgroup	No. of Patients	Median Survival Time (mo) (95% CI)	1-yr Survival Rate (%)	2-yr Survival Rate (%)	3-yr Survival Rate (%)	5-yr Survival Rate (%)
ED (M1b)	350	9.2 (8.5–10.0)	34	7	3	2
LD (M0)	320	22.0 (20.0–23.5)	74	43	33	22
LD with pericardial effusion (group A)	33	14.2 (9.1–17.5)	61	12	6	6
Receiving CRT	19	17.0 (13.6–21.0)	89	11	11	11
Receiving Chemotherapy	14	8.8 (4.7–11.1)	21	14	0	0
LD with ipsilateral pleural effusion but without pericardial effusion (group B)	63	12.7 (10.2–16.7)	54	21	11	9
Receiving CRT	26	21.4 (16.7–28.2)	85	42	22	18
Receiving chemotherapy	36	9.3 (6.3–11.8)	33	6	3	3

CI, confidence interval; ED, extensive disease; LD, limited disease; CRT, chemoradiotherapy.

TABLE 4. Six Patients with M1a Small Cell Lung Cancer who Survived for More Than 5 yr

Age (yr)	Sex	Group	Initial Treatment	Survival Time (mo)	State
64	M	A	Chemoradiotherapy	72.6	Dead
70	F	B	Chemoradiotherapy	146.5	Alive
53	M	B	Chemotherapy[a]	140.4	Alive
73	F	B	Chemoradiotherapy	138.0	Alive
72	M	B	Chemoradiotherapy	117.0	Alive
68	M	B	Chemoradiotherapy	65.5	Alive

[a] This patient received chemoradiotherapy as a second-line treatment after a local recurrence. Therefore, all six patients received chemoradiotherapy and achieved long-term survival for more than 5 yr.

M, male; F, female.

recurrence. Four of the 26 patients who received chemoradiotherapy in group B survived for more than 5 years (Table 4). Conversely, only 2 of the 19 patients who received chemoradiotherapy in group A survived for more than 2 years. One patient developed a local recurrence at 4 years and 10 months after the initiation of first-line chemoradiotherapy and died of lung cancer 14 months later. The remaining patient also developed a local recurrence at 2 years and 9 months after the initiation of first-line chemoradiotherapy and received second-line chemotherapy. This patient was still alive at the time of the data cutoff.

DISCUSSION

This retrospective analysis demonstrated that the survival of patients with SCLC and ipsilateral pleural or pericardial effusion (M1a) was intermediate between those of M0 and M1b patients. It is suitable that patients with ipsilateral pleural effusion or pericardial effusion belong to M1a category in the UICC seventh TNM edition. No statistically significant difference in the overall survival between M1a patients with pericardial effusion (group A) and those with ipsilateral pleural effusion but without pericardial effusion (group B) was observed. Among the patients who successfully underwent chemoradiotherapy, the patients in group B had 2-, 3-, and 5-year survival rates of 42%, 22%, and 18%, respectively, whereas the patients in group A had a 2-year survival rate of only 11%. Our previous retrospective analyses demonstrated that the median survival time of patients with cytologically positive and cytologically negative pleural effusion were 9.3 and 12.7 months, respectively. Furthermore, all 11 patients with cytologically positive pleural effusion died within 3 years.[8] Long-term survival for more than 5 years was achieved only by patients with cytologically negative pleural effusion. We speculate that an inflammatory process, such as atelectasis, causes ipsilateral pleural effusion in some patients. Conversely, most pericardial effusion is believed to be malignant. Therefore, long-term survival was seldom achieved by patients with pericardial effusion, even if they received chemoradiotherapy.

Recently, the applicability of the UICC seventh TNM edition for SCLC was investigated using the California Cancer Registry database. This database included 108 and 1518 M1a patients with pericardial effusion and pleural dissemination, respectively. No significant difference in overall survival was observed among patients with pleural or pericardial effusion (median survival time: 7 versus 7 months, 2-year survival rate: 16.7% versus 9.7%, respectively).[10] These data were comparable with our results. Nevertheless, no information regarding the treatment performed for the M1a patients was included in the previous article.

Our retrospective analysis has several limitations. First, the number of M1a patients with pericardial effusion was only 33, because only 8% of the patients with LD-SCLC exhibited pericardial effusion. Second, we did not conduct a cytological examination of the pericardial effusion. Pericardial puncture or drainage is usually performed in patients with cardiac tamponade. None of the patients in group A had cardiac tamponade; therefore, a pericardial puncture was technically difficult. Third, examination period was more than 15 years, from 1992 to 2007. Irinotecan, active for SCLC, has been commonly used from 2000 in Japan. Patients in this study were treated with a potential range of different chemotherapeutic agents during the period, which was not controlled.

Only 2 of 19 patients (11%) who received chemoradiotherapy in group A survived for more than 3 years. Con-

versely, all 14 patients who did not receive chemoradiotherapy in group A died within 3 years. TRT probably improves local control and achieves long-term survival in some patients. Definitive TRT is recommended in M1a patients with SCLC, if ipsilateral pleural or pericardial effusion has disappeared after induction chemotherapy.

In conclusion, the survival of patients with SCLC and ipsilateral pleural or pericardial effusion (M1a) is intermediate between those of M0 and M1b patients. No statistically significant difference in the overall survival of M1a patients with pericardial effusion and those with ipsilateral pleural effusion but without pericardial effusion was observed. Long-term survival was achieved among M1a patients with pericardial effusion who successfully underwent chemoradiotherapy, although 5-year survival rate in these patients was relatively lower than in M1a patients with ipsilateral pleural effusion but without pericardial effusion.

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Clinical Implication of the Antidiuretic Hormone (ADH) Receptor Antagonist Mozavaptan Hydrochloride in Patients with Ectopic ADH Syndrome

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Ectopic antidiuretic hormone syndrome is a medical emergency characterized by dilutional hyponatremia. Clinical effectiveness of the vasopressin V2 receptor antagonist mozavaptan was evaluated in 16 patients. In short-term (7-day) treatment with the drug, serum sodium concentration (mean ± standard deviation) significantly ($P = 0.002$) increased from 122.8 ± 6.7 to 133.3 ± 8.3 mEq/l, and symptoms due to hyponatremia were improved. On the basis of these results, mozavaptan (Physuline®) was approved as an orphan drug for the treatment of the syndrome in 2006 in Japan. During the 43 months following its launch, 100 patients have been treated with the drug; overall clinical effects of the drug were found similar to those of this clinical trial. Clinically, mozavaptan may allow hyponatremic patients to be treated by aggressive cancer chemotherapy with platinum-containing drugs. Moreover, the drug may free patients from strict fluid-intake restrictions and thereby improve their quality of life.

Key words: SIADH – ectopic ADH syndrome – small cell lung carcinoma – hyponatremia – antagonist

INTRODUCTION

The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is divided into two categories; one is the ectopic ADH syndrome induced by abnormally secreted ADH (arginine vasopressin) from cancer cells, and another is the morbidity caused by inappropriately secreted ADH from the pituitary gland in various benign diseases. In both situations of SIADH, ADH binds to vasopressin V2 receptors (V2Rs) in renal tubules and thereby increasing water reabsorption. Clinically, SIADH is characterized by elevated fluid retention in the body, resulting in dilutional hyponatremia and subsequent manifestations of various central nervous system (CNS) symptoms.

In the present study, clinical effectiveness of a newly developed vasopressin V2R antagonist was evaluated in patients with ectopic ADH syndrome. This morbidity is frequently observed in patients with small cell lung carcinoma (SCLC) and makes it to be difficult to aggressive cancer chemotherapy with platinum-containing drugs. Patients with SIADH often require severe water restriction, worsening their quality of life.

Mozavaptan, the world's first non-peptide V2R antagonist with aquaretic action, was developed by Otsuka Pharmaceutical, Japan, in 1989 (1). Its potent effect was first demonstrated by clinical pharmacological trials involving healthy adult male subjects in 1992 (2). To understand

whether mozavaptan might play an important role in the treatment of ectopic ADH syndrome, the Ectopic ADH Syndrome Therapeutic Research Group conducted an open-label multicenter clinical trial at Japanese hospitals from December 1994 to December 1997. This paper describes the study results and their implication for mozavaptan's potential usefulness in the treatment of cancer-related ectopic ADH syndrome.

PATIENTS AND METHODS

This open-label, multicenter study protocol was approved by the Institutional Review Board of each participating medical institution prior to its inception; written informed consent was obtained from all patients.

Recruited were inpatients aged 20 to <75 years who had malignant tumors that might cause ectopic ADH syndrome as well as the diagnostic criteria of ectopic ADH syndrome as defined by Bartter and Schwartz (3) such as serum sodium concentration ≤124 mEq/l, persistent urinary sodium excretion, normal renal, adrenal, and thyroid function, and no evidence of edema or dehydration.

Following a ≤2-day placebo administration period during which baseline data were collected, patients were given orally mozavaptan (single 30 mg tablet) once daily for 7 days, or where this was difficult, 3 days was allowed. Fluid restriction was used throughout the study period only for patients in whom it had already begun. Treatment of hyponatremia with demeclocycline, lithium chloride, or urea was not permitted.

The primary endpoint was serum sodium concentration. Blood samples were collected immediately before dosing on each test day. Clinical symptoms associated with hyponatremia such as anorexia, nausea/vomiting, headache, and CNS symptoms were recorded. Urine volume, urinary osmolality, urinary electrolyte (sodium, potassium, chloride) excretion, serum electrolyte (potassium, chloride) concentration, serum osmolality, and plasma ADH concentration were measured. New medical problems or exacerbations of those already existing were reported as adverse events.

In each case, the serum sodium level after the final administration of the study drug was compared with baseline value. The patients are divided into three groups: (i) the serum sodium level is improved to normal range; (ii) the level is still low, but increase is ≥6 mEq/l and (iii) the level is still low, and increase is <6 mEq/l. And mean sodium concentration after the final administration of the study drug was compared with that of baseline value by paired *t*-test.

RESULTS

Sixteen patients [M/F: 10/6; mean age: 63.9 (range: 48–78) years] who received at least one dose of the study drug were included in the efficacy and safety evaluation. All patients received mozavaptan 30 mg once daily for 7 days, except two individuals who received treatment for 3 days.

Underlying diseases were SCLC ($n = 14$), thymic small cell carcinoma ($n = 1$) and cervical cancer ($n = 1$). Fluid intake was restricted in 5 of the 16 patients (Table 1).

Serum sodium concentration (mean ± SD) at the time of diagnosis of the ectopic ADH syndrome was 117.3 ± 4.3 (range: 110–124) mEq/l. Plasma ADH concentration was 4.9 ± 5.8 (median: 2.3; range: 0.4–18.9) pg/ml immediately before treatment.

At baseline and at the end of study, mean serum sodium concentration was 122.8 ± 6.7 and 133.3 ± 8.3 mEq/l, respectively, a statistically significant difference ($P = 0.002$; Fig. 1). Serum sodium concentration increased at 24 h after the first administration of mozavaptan and remained elevated ≤24 h after administration for 7 days. Serum osmolality gradually increased starting from 24 h after first administration till the study end. Cumulative urine volume over 24 h increased on the first treatment day, whereas urine osmolality decreased in the first two treatment days.

A total of 16 patients were evaluated for the serum sodium level. The serum sodium level was improved to normal range in eight patients, still below normal range but increased by at least 6 mEq/l in four patients and increased by <6 mEq/l in four patients (Table 1).

Symptoms associated with ectopic ADH syndrome such as anorexia, nausea/vomiting, headache and CNS symptoms improved or disappeared in seven of eight patients who had at least one of these symptoms at baseline. By symptom, anorexia disappeared in three and improved in two among eight patients who had the symptom at baseline, whereas nausea/vomiting, headache and CNS symptoms disappeared by the completion of treatment in all patients who had at least one of the symptoms at baseline. On the other hand, however, new anorexia and headache developed in one patient each.

Although some patients showed slight increases or decreases of plasma ADH concentration after receiving mozavaptan, overall there were no obvious changes.

There were 35 adverse events in 11 of the 16 patients; none was serious. The most common adverse event was dry mouth developing in five patients. Fifteen adverse drug reactions occurred in six patients (dry mouth, $n = 5$; increased blood potassium, $n = 2$; malaise, increased AST, increased ALT, decreased blood calcium, increased blood lactate dehydrogenase, increased blood urea, decreased appetite and nocturia, $n = 1$ each).

One patient was withdrawn after administration of the study drug for 3 days because of anorexia. After completion of administration of mozavaptan, one cancer-related death occurred 30 days post-treatment (ID 1 in Table 1); the patient had small cell lung cancer, and had myasthenia gravis, diabetes, pneumonia and hypertension. Chemotherapy (carboplatin and etoposide) was given from 146 to 144 days before treatment with mozavaptan, which reduced the tumor size and improved SIADH. However, the chemotherapy was

Table 1. Clinical characteristics of each patient at baseline and changes in serum sodium concentration/clinical symptoms

ID	Sex (M/F)	Age (years)	Disease	Tx duration (days)	Fluid-intake restriction	Data at baseline			Changes in serum sodium concentration (mEq/l)				Clinical symptoms
						Plasma ADH concentration (pg/ml)	Serum osmolality (mOsm/kg)	Urine osmolality (mOsm/kg)	At the time of diagnosis	At baseline	24 h after the first administration	24 h after the last administration	
1	F	64	SCLC	7	Yes	12.5	274	712	115	129	136	139	ANRX improved, NV disappeared, HA disappeared
2	F	64	Thymic SCC	3	Yes	3.3	256	----	110	122	133	140	ANRX improved, NV disappeared, HA disappeared, CNSS disappeared
3	M	54	SCLC	7	Yes	0.8	254	754	115	123	130	139	ANRX disappeared, HA disappeared, CNSS disappeared
4	M	76	SCLC	7	No	2.1	254	657	119	111	121	119	ANRX disappeared, NV disappeared
5	M	65	SCLC	3	Yes	2.4	300	753	121	130	134	142	ANRX developed
6	M	66	SCLC	7	No	18.9	256	461	119	123	----	128	None
7	M	78	SCLC	7	No	0.5	279	590	124	127	128	133	None
8	F	75	SCLC	7	No	0.4	254	465	124	120	125	122	None
9	M	66	SCLC	7	No	7.8	261	492	115	117	123	127	ANRX continued, NV disappeared, HA developed
10	M	48	SCLC	7	Yes	2.1	283	730	110	132	129	127	None
11	M	66	SCLC	7	No	1.4	241	450	116	107	117	130	ANRX disappeared, NV disappeared, HA disappeared, CNSS disappeared
12	F	53	SCLC	7	No	1.5	241	465	117	127	138	148	n/a
13	F	60	SCLC	7	No	2.8	245	406	123	122	128	142	None
14	M	65	SCLC	7	No	5.2	263	370	114	123	130	139	None
15	M	63	SCLC	7	No	15.7	275	755	116	129	133	133	ANRX continued
16	F	60	Cervical cancer	7	No	1.0	268	349	119	123	132	140	ANRX continued, HA disappeared, CNSS disappeared

SCLC, small cell lung carcinoma; Thymic SCC, thymic small cell carcinoma; ANRX, anorexia; NV, nausea/vomiting; HA, headache; CNSS, central nervous system symptom; n/a, not available.

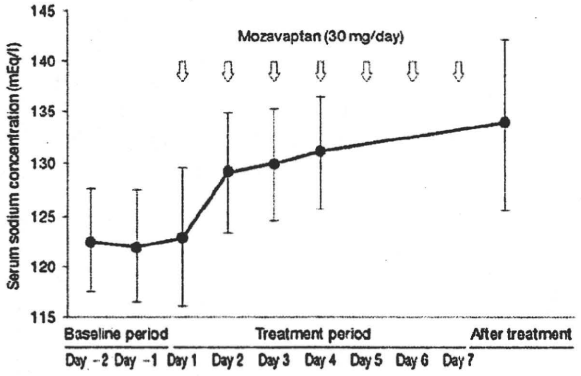

Figure 1. Time-course of serum sodium concentration (mean ± SD) in 16 cancer patients with ectopic ADH syndrome. Baseline serum sodium concentration was 122.8 ± 6.7 mEq/l. At 24 h after the first dose, serum sodium increased to 129.1 ± 5.7 mEq/l; at 24 h after completion of treatment, the value was 133.3 ± 8.3 mEq/l.

terminated due to marked myelosuppression, and then this led to marked tumor growth. The serum sodium concentration was 132 mEq/l 29 days before the mozavaptan treatment, but gradually decreased to 119 mEq/l 14 days before treatment. At that time, the patient's condition did not permit chemotherapy, and mozavaptan therapy was performed. Although mozavaptan was effective, the condition became worse due to rapid tumor progression. The patient died 30 days after completion of the mozavaptan therapy, and the autopsy demonstrated direct invasion to heart and thoracic vertebra, indicating that the patient had died of cancer. No other serious adverse events were reported.

DISCUSSION

Since the ectopic ADH syndrome is the morbidity induced by inappropriately secreted ADH from cancer cells, V2R antagonist rationally might be expected to exert pharmacological effects in the syndrome. During Phase I pharmacological evaluation, mozavaptan 30 mg/day exerted potent V2R antagonistic activity. Therefore, we plan to evaluate the clinical efficacy and safety of this agent at a dose of 30 mg/day in cancer patients with ectopic ADH syndrome defined by Bartter and Schwartz (3).

We found that the drug increased the mean serum sodium level; 10 patients at 24 h after the first dose and 12 patients at 24 h after the last dose showed a $\geq$6 mEq/l increase in serum sodium concentration from baseline.

Of 12 patients who showed an increase in serum sodium concentration of $\geq$6 mEq/l from baseline at 24 h after the last dose, 7 had anorexia, nausea/vomiting, headache and/or CNS symptoms before treatment. Anorexia ($n = 7$) disappeared in three, was alleviated in two and remained unchanged in two patients; all other symptoms (nausea/vomiting in five, headache in five and CNS symptoms in four patients) disappeared following therapy. However, new anorexia and headache developed in one patient each. Of the remaining four subjects who showed an increase in serum sodium concentration of <6 mEq/l, three had no symptoms and one complained of anorexia that remained unchanged 24 h after the last dose.

Since SCLC is the chemo-sensitive tumor and SIADH is the condition of oncologic emergency, urgent treatment is always required. However, in the cases of SIADH, hyponatremia makes it difficult to perform chemotherapy; hydration is necessary for the therapy with cisplatin-based chemotherapy. Mozavaptan improved compliance to chemotherapy in patients with ectopic ADH syndrome.

The present study did not plan to give chemotherapy during the study period. Thus, information on chemotherapy was not designed to be collected from patients. However, we evaluated present cases whether they received chemotherapy after the mozavaptan treatment. Information was obtained from 14 patients of the 16 subjects, 9 were administered mozavaptan prior to scheduled chemotherapy, and 8 of these underwent chemotherapy with the regimen including cisplatin or carboplatin after successful correction of hyponatremia.

With regard to safety, the treatment was discontinued in one patient due to adverse drug reaction, and two patients required treatment for adverse effects but recovered after appropriate treatment. There was no excessively rapid increase in serum sodium concentration or central pontine myelinolysis, suggesting that mozavaptan can be safely used in the target patient population.

On the basis of these results, mozavaptan (Physuline®) was approved in Japan as an orphan drug for the treatment of ectopic ADH syndrome, in 2006. It is worth noting that until now demeclocycline, lithium chloride or urea was reported effective for the ectopic ADH syndrome, although clinical experiences revealed that the effects of these drugs are limited (4).

In the USA and EU, there are two V2R antagonists available on the market—conivaptan (injection formulation) (5) and tolvaptan (oral tablet) (6). Conivaptan, a dual V1a receptor and V2R antagonist, is marketed in the USA with the indication of 'treatment of euvolemic and hypervolemic hyponatremia in hospitalized patients'. Tolvaptan, which by structural modification has a higher affinity for the V2R than does its parent drug, mozavaptan, is marketed in the USA with the indication of 'treatment of clinically significant hypervolemic and euvolemic hyponatremia, including patients with heart failure, cirrhosis and SIADH' and in the EU with the indication of 'treatment of adult patients with hyponatremia secondary to syndrome of inappropriate antidiuretic hormone secretion (SIADH)'. Mozavaptan is currently the only approved drug available for treatment of patients with ectopic ADH syndrome (7) in Japan but is neither approved nor under development outside Japan.

During the 43 months following its launch, 100 patients have been treated with the drug. On the basis of the post-marketing drug use results survey, overall clinical effects of the drug have been found similar to those of the

clinical trial. Mozavaptan provides two important contributions for the treatment of ectopic ADH syndrome. First, short-term treatment with mozavaptan may allow hyponatremic patients who might otherwise be contraindicated to receive aggressive cancer chemotherapy with platinum-containing drugs. Second, mozavaptan may free patients from strict fluid-intake restrictions and thereby improve their quality of life. Thus, mozavaptan provides new treatment options for aggressive chemotherapy as well as for palliative care in patients with ectopic ADH syndrome.

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Conflict of interest statement

None declared.

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Appendix

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Long-Term Administration of Second-Line Chemotherapy with S-1 and Gemcitabine for Platinum-Resistant Non-small Cell Lung Cancer

A Phase II Study

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Background: Standard second-line chemotherapies for non-small cell lung cancer (NSCLC) have been established but have limited clinical relevance. S-1 is a recently developed agent with potential activity against NSCLC.

Methods: Patients with confirmed NSCLC recurrence after previous single- or two-regimen chemotherapy with platinum, performance status of 0 to 1, adequate organ functions, and measurable lesions were treated with S-1 (60 mg/m^2/d, twice a day) on days 1 to 14 and gemcitabine (1000 mg/m^2) on days 8 and 15, which were repeated every 3 weeks until tumor progression.

Results: Treatment was administered for a median of 4 courses (range, 1–13) over a median of 125-day period in 34 patients. The overall response rate was 23.5% (no complete response and eight partial response; 95% confidence interval: 9.1–38.0%). The median progression-free and overall survival times were 6.6 and 19.9 months, respectively. The 1- and 2-year survival rates were 58.8 and 30.9%, respectively. Toxicity was mild during the entire treatment period, except for three grade 3 interstitial pneumonia.

Conclusion: The primary end point was met with the relatively high overall response rate. Randomized phase III studies for elucidating survival outcome of the regimen are warranted.

Key Words: Gemcitabine, Maintenance, Non-small cell lung cancer, S-1, Second-line therapy.

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The standard first-line chemotherapies for advanced non-small cell lung cancer (NSCLC) are four to six courses of platinum-based combination chemotherapy with or without bevacizumab.[1] Despite the relevance of first-line chemotherapy, tumors in due time will recur in the most cases. On the other hand, second-line chemotherapy has been proven to prolong the survival time of patients who had progressive disease (PD) after first-line chemotherapy. The current standard second-line chemotherapy includes monotherapy with docetaxel,[2] pemetrexed,[3] erlotinib,[4] or gefitinib.[5] Of these agents, erlotinib and gefitinib are specifically effective for patients with tumors harboring some specific types of mutation in the epidermal growth factor receptor (*EGFR*).[6] Subset analysis has suggested that pemetrexed is active for prolonging survival time only in patients with nonsquamous NSCLC.[7] In addition, the use of docetaxel and pemetrexed in second-line chemotherapy is not efficacious in patients who had already been treated with those agents in the first-line chemotherapy. Therefore, more options for second-line chemotherapy are required, and more effective regimens are sought.

S-1 is a recently developed orally administered agent consisting of 5-chloro-2,4-dihydoroxypyrimidine, potassium oxonate, and tegafur, a prodrug of 5-fluorouracil (5-FU).[8] Tegafur is converted to 5-FU by hepatic microsomal P450 followed by phosphorylated activation in various tissues and tumors.[9] Potassium oxonate inhibits this phosphorylation step in the intestine to decrease intestinal toxicity,[10] and 5-chloro-2,4-dihydoroxypyrimidine inhibits 5-FU degradation to neurotoxic F-β-Alα, reducing neurotoxicity.[11] Thus, the combination of these three compounds renders intracapsular biologic modulations to enhance cancer cell killing capability

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as well as minimize toxicity. Since S-1 was first approved for NSCLC in July 2007 in Japan, a number of studies of S-1 for NSCLC patients have recently been published. They include studies of front-line chemotherapy combined with cisplatin,[12,13] carboplatin[14,15] or nonplatinum agents[16–18]; second-line chemotherapy[19–22]; chemoradiotherapy for locally advanced disease[23–25]; chemotherapy for elderly patients[26]; and postoperative adjuvant setting.[27] Although they were all phase I/II or II studies, they reproducibly suggested a potential activity of S-1 in treating NSCLC patients in various situations. Gemcitabine is one of the most powerful agents against NSCLC,[28] and its relevance in the second-line setting is also suggested by phase II studies with overall response rate (ORR) ranging from 6 to 20%.[29–34] In addition, combination of S-1 and gemcitabine is potentially synergistic. They inhibit DNA synthesis via different pathways. 5-FU recruits cell surface human equilibrative nucleoside transporter 1,[35,36] and its increase potentially augment the effect of gemcitabine that enters the cell via human equilibrative nucleoside transporter 1.[37] These preclinical data suggest that the combination of the two agents potentially exert synergism. Based on the rationale, we conducted a phase I/II study of combination chemotherapy consisting of S-1 and gemcitabine for elderly patients with chemotherapy-naive NSCLC. The study established the recommended doses of combination chemotherapy, with S-1 at 60 mg/m^2/d (daily, in two fractions) on days 1 to 14 and gemcitabine at 1,000 mg/m^2 on days 8 and 15 repeated every 3 weeks, and suggested mild toxicity and potential efficacy, with the median progression-free survival (PFS) and overall survival (OS) of 4.2 and 12.9 months, respectively.[26]

Based on these facts, a phase II study of S-1 and gemcitabine as second-line chemotherapy for previously treated NSCLC patients was conducted.

PATIENTS AND METHODS

Eligibility

Patients meeting all the following criteria were eligible: proven NSCLC refractory or recurrent after previous single- or two-regimen chemotherapy consisting of platinum in at least one regimen, a performance status (PS, Eastern Cooperative Oncology Group) of 0 or 1, adequate organ functions (neutrophils $\geq$2000/mm^3, hemoglobin $\geq$9.0 g/dl, platelets $\geq$100,000/mm^3, total bilirubin $\leq$2.0 g/dl, aspartate transaminases (AST)/alanine aminotransferase (ALT) <2.5 fold of the normal value, creatinine $\leq$1.5 mg/dl, creatinine clearance $\geq$50 ml/min, and PaO_2 $\geq$70 Torr), measurable lesions by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0, life expectancy exceeding 3 months, and written informed consent. Patients with any of the following conditions were ineligible: use of any pyrimidine analog in the previous treatment; resected primary site; requirement of thoracic irradiation; interstitial lung disease; pleural, pericardial effusion or ascites requiring treatment; symptomatic brain metastasis; concomitant malignancy; or other inadequate conditions.

Pretreatment Evaluation

The baseline evaluation included history with a complete record regarding the front-line treatment and concomitant medical conditions, physical examinations, PS, complete blood counts, serum chemistries and electrolytes, urinalysis, chest radiogram, chest computed tomography (CT), abdominal CT, brain magnetic resonance imaging with contrast medium enhancement otherwise contraindicated, and bone scintigram. These examinations were to be performed within 1 month before the enrollment.

Drug Administration

S-1 (60 mg/m^2/d; twice a day, PO, on days 1–14) and gemcitabine (1000 mg/m^2; on days 8 and 15) were administered every 3 weeks for at least three courses and until disease progression unless termination criteria defined below are encountered. As S-1 is available in a capsule form containing either 20 or 25 mg, the daily dosing according to body surface area was approximated to be 60 to 130 mg/d by rounding off to less than 10 mg. For example, when a daily dose of 110 mg is required, 60 mg in three 20-mg capsules in the mornings and 50 mg in two 25-mg capsules in the evenings were administered. Post-treatment was withheld until evidence of disease progression, followed by no restriction afterward.

Evaluation During Chemotherapy

Symptoms, physical examination, complete blood counts, serum chemistries, and chest radiogram were checked every week or every other week. Chest CT and other radiographic modalities necessary for evaluating target lesions by RECIST version 1.0 were repeated every month until disease progression.

Dose Modification, Postponement, Skipping, and Termination Criteria of Chemotherapy

The dose of gemcitabine was reduced to 800 mg/m^2 when any of the following criteria were encountered: grade 4 neutropenia lasting for more than 7 days, grade 4 thrombocytopenia, febrile neutropenia, and skipping of gemcitabine on day 15 according to the following postponement criteria. The dose of S-1 was not reduced. Gemcitabine administration on days 8 and 15 was postponed until recovery when any of the following criteria were encountered: fever (axillary) $\geq$grade 1, neutropenia, thrombocytopenia and elevated total bilirubin $\geq$grade 2, AST and ALT >2.5 fold of the normal value, and any other nonhematological toxicity $\geq$grade 2. If gemcitabine on day 15 was not administered within a 7-day delay because of toxicities, it was skipped. S-1 administration in a course was withheld until improvement when skin rash $\geq$grade 2 or neutropenia $\geq$grade 3 was encountered. The next course was postponed until recovery when any of the following criteria were encountered: PS $\geq$2, neutropenia, thrombocytopenia and elevation of total bilirubin $\geq$grade 2, serum creatinine >1.3 mg/dl, AST and ALT >2.5 fold of the normal value, and infection of any grade. If the next course was not started because of toxicities within a 14-day delay, then chemotherapy was terminated.

Response and Toxicity Criteria

Tumor response was evaluated according to RECIST version 1.0 and was classified into five categories: complete response (CR), partial response (PR), stable disease (SD), PD, and not evaluable (NE). All target lesions were re-evaluated with the same imaging studies as used in the

pretreatment evaluation. A minimum of 6-week interval from the start of therapy was required for establishing SD. All evaluations were confirmed or corrected by external reviews. Toxicity during the entire therapy course was evaluated, and the worst event was scored according to the National Cancer Institute Common Toxicity Criteria version 3.0.

Statistical Analysis and Ethical Considerations

The primary end point was to assess the ORR, and the secondary endpoints were to evaluate toxicity and survival data consisting of PFS and OS. The calculated minimum sample size was 29 based on the Simon two-stage optimal design, with a target and threshold response rate of 20 and 5% and α and β errors of 0.05 and 0.20, respectively. The final determined sample size was 32. The first stage required at least one responder among the first 10 patients before proceeding to the second stage. Survival time was measured from enrollment into the study and was analyzed by Kaplan-Meier's method. The Institutional Review Board of each participating institute approved the study. It was registered to the clinical trial registration system of University Hospital Medical Information Network-Clinical Trial Registry with the identification number UMIN000000896 on November 15, 2007.

RESULTS

Treatment Delivery, Tumor Response, and Toxicity

A total of 34 patients were enrolled from November 2007 to September 2008, and their characteristics are summarized in Table 1. Twenty-three patients were pretreated with a single regimen and 11 were treated with two regimens including gefitinib in two patients, resulting in 13 PR, 16 SD, and 5 PD in prior chemotherapy. All patients were eligible for the evaluation of response rate, toxicity, and survival.

Chemotherapy was administered for a median of 4 courses (range, 1–13) or a median of 125 days (range, 4–360 days). Thus, six courses or more were administered in as many as 41% patients. Among the total 171 courses administered, skipping or dose reduction of gemcitabine was observed in five courses. S-1 was administered for more than 90% of the scheduled dose in 166 courses. The ORR and disease control rate were 23.5% (8/34; 95% confidence interval [CI]: 9.1–38.0%) and 64.7% (22/34; 95% CI: 48.4–81.0%), respectively, with no CR, 8 PR, 14 SD, 9 PD, and 3 NE. The ORRs of patients who responded (CR + PR) to the previous chemotherapy and those who did not (SD + PD + NE) were 38.5% (5/13) and 14.3% (3/21), respectively ($p = 0.11$, χ^2 test).

Toxicities including grade 3 or 4 are listed in Table 2. The most frequent grade 3 or 4 toxicities were neutropenia, leukocytopenia, and anemia. No nausea/vomiting with grade 3 or 4 was observed. Grade 3 interstitial pneumonia was observed in three patients. That is, it emerged at the end of the first course for a 63-year-old ex-smoker man and required treatment consisting of 1000 mg/d of methylprednisolone for 3 days followed by 40 mg/d of prednisolone, which was tapered off in 2 months. It also emerged in the second course for a 70-year-old ex-smoker man and required treatment consisting of 500 mg/d of methylprednisolone for 3 days followed by 50 mg/d prednisolone for 12 days. It developed in the third course for a 73-year-old ex-smoker man and required treatment consisting of 30 mg/d of prednisolone, which was tapered off in 4 months. Although they were all improved by the therapy stated above, two patients, except for the last patient described above, required home oxygen therapy. There was no treatment-related death.

TABLE 1. Patient Characteristics ($n = 34$)

Characteristic	No. of Patients (%)
Sex	
Male	22 (66)
Female	12 (35)
Age (yr)	
Median	61.5
Range	30–84
PS	
0	20 (59)
1	14 (41)
Histology	
Adeno	29 (85)
Squamous	3 (9)
Large	1 (3)
NSCLC, NOS	1 (3)
Smoking status	
Never smoker	12 (35)
Ex-smoker	11 (32)
Current smoker	11 (32)
Prior chemotherapy[a]	
1 regimen	23 (68)
2 regimens	11 (32)
Cisplatin-containing	16 (47)
Carboplatin-containing	18 (53)
Nedaplatin-containing	1 (3)
Tumor response to prior chemotherapy	
CR	0 (0)
PR	13 (38)
SD	16 (47)
PD	5 (15)
Prior radiotherapy	
Thoracic, curative intent	5 (15)
Thoracic, palliative	3 (9)
Other than thoracic	4 (12)

[a] One patient received both cisplatin- and carboplatin-containing regimens as prior chemotherapy, resulting in 35 platinum regimens for the 34 patients.

NSCLC, non-small cell lung carcinoma; NOS, not otherwise specified; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Post-Treatment and Survival

Twenty-four patients of the 34 (70.6%) underwent postchemotherapy, with a median regimen number of 1 (range, 0–4). The regimens included a platinum-containing regimen in 5 patients, EGFR-tyrosine kinase inhibitors in 13, taxanes in 10, and pemetrexed in 7. Three patients were retreated with a combination of S-1 and gemcitabine. Aside from chemotherapy, palliative thoracic irradiation and irradiation of metastatic lesions were performed in 4 and 10 patients, respectively. At the

TABLE 2. Toxicity Profile (n = 34)

	Grade[a]				
Toxicity	1	2	3	4	% (3 and 4)
Hematological					
Leucocytopenia	5	14	7	0	21
Neutropenia	2	7	13	4	50
Neutropenic fever	—	—	1	0	3
Hypohemoglobinemia	9	11	5	1	18
Thrombocytopenia	6	6	2	2	12
Nonhematological[b]					
ALP elevation	9	0	1	0	3
Appetite loss	12	5	1	0	3
Fatigue	10	4	1	0	3
Rash	6	2	2	0	6
Stomatitis	3	0	1	0	3
Interstitial pneumonia	0	1	3	0	9
Deep venous thrombosis	0	0	1	0	3

[a] The worst grade during the entire chemotherapeutic courses in each patient.
[b] Only nonhematological toxicities including grade 3 and/or 4 are listed.
ALP, alkaline phosphatase.

time of a median follow-up interval of 18 months, 12 patients were still alive and censored; the median OS and PFS were 19.9 (95% CI: 9.3–22.2) and 6.6 (95% CI: 4.2–7.8) months, respectively, and the 1- and 2-year survival rates were 58.8 and 30.9%, respectively (Figure 1).

DISCUSSION

In this study, a combination chemotherapy of S-1 with gemcitabine for second-line setting was evaluated for the first time. The treatment schedule included S-1 on days 1 to 14 and gemcitabine on days 8 and 15, which was repeated every 3 weeks until disease progression. Satouchi et al. compared two schedules: S-1 for 14 days combined with gemcitabine either on days 1 and 8 or days 8 and 15, which were repeated every 3 weeks for chemotherapy-naive NSCLC patients. They selected the latter schedule because it showed a tendency of better ORR, OS, and PFS than the former schedule although not statistically significant.[18]

The ORR of 23.5% and disease control rate of 64.7% in this study seem excellent for second-line therapy for NSCLC. The ORR exceeded the predefined target ORR of 20%, and the lowest end of the 95% CI of 9.1% also exceeded the predefined threshold ORR of 5%. Therefore, the primary end point of the study was met. Toxicity was mild with neutropenia (≥grade 3) as the most prevalent toxicity observed in 50% of the patients during the entire treatment course. Notably, gastrointestinal toxicities were very rare; appetite loss and stomatitis (≥grade 3) were observed in only one patient each, and nausea/vomiting (≥grade 3) was not observed. Grade 2 and 3 interstitial pneumonia was observed in one and three patients, respectively. Although improved in every case, special attention should be paid to this adverse event with this regimen. As the protocol required the treatment being repeated until disease progression, this mild toxicity profile at large lead to prolonged treatment for a median of 4 courses

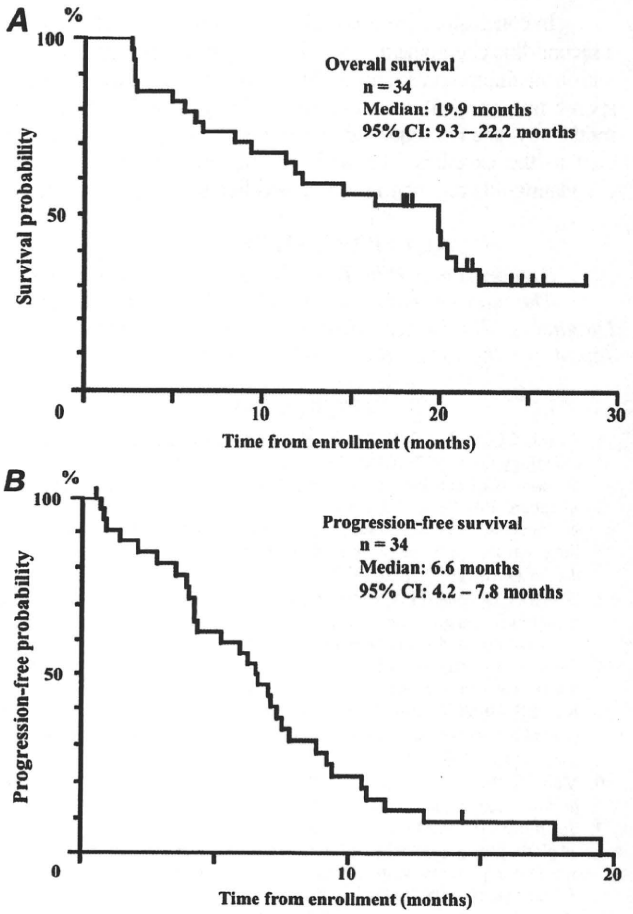

FIGURE 1. Kaplan-Meier survival curves of the 34 patients treated with second-line chemotherapy consisting of S-1 and gemcitabine for overall survival (*A*) and progression-free survival (*B*) times starting from study enrollment. Vertical lines indicate censored cases.

(range, 1–13 courses) or for a median of 125 days (range, 4–360 days). Although the current standard regimen for recurrent NSCLC is monotherapy, this combination chemotherapy with potential synergism was easily repeated for a prolonged period, presumably as long as or longer than the current standard monotherapy, because of its mild toxicity. Resulting survival data were also excellent with median OS and PFS of 19.9 (95% CI: 9.3–22.2) and 6.6 (95% CI: 4.2–7.8) months, respectively, and 1- and 2-year survival rates of 58.8 and 30.9%, respectively. In this research, extensive poststudy chemotherapy that included platinum, EGFR-tyrosine kinase inhibitors, taxans, and pemetrexed possibly resulted in good OS; however, the excellent PFS might be attributed to the combination chemotherapy of S-1 and gemcitabine. Recent studies addressed the clinical relevance of maintenance chemotherapy for NSCLC and suggested its potential benefits.[38,39] Although they were for the front-line chemotherapy, the excellent PFS in this second-line study is possibly affected by the prolonged administration of chemotherapy with relatively mild toxicity.

In conclusion, this phase II trial with S-1 and gemcitabine as a second-line chemotherapy for NSCLC patients previously treated with a platinum-containing regimen provided an encouraging response rate, survival data, and mild safety profile. Long-term chemotherapy as a consequence of the mild toxicity possibly contributed to the excellent PFS and OS. Randomized studies further elucidating this regimen in the second-line setting are warranted.

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